Coordinated by / Scientific editor
Amal BOURQUIA

African Pediatric Nephrology
Guidebook
To Leila
To Salma
for all African children
Paediatric Nephrology (PN) has in recent years impressive progress in health care, however, the greatest challenges in our continent is to provide children with kidney disease access to specialized care by paediatric nephrologists having a good education and the opportunity to have affordable access to the use of modern techniques, effective drugs and prevention strategies.

The development of paediatric nephrology in Africa has been too slow and has not witnessed any genuine collaboration between the concerned countries. This has strengthened my conviction of the necessity to incite the African paediatric nephrologists to work together, through a common book, shedding light on the specific data our African continent has in the field of paediatric nephrology.

As a matter of fact, the idea of coming up with a book on paediatric nephrology in Africa has sprouted for five years now, particularly at the council of the International Paediatric Nephrology Association (IPNA) where I noticed not only the faint attendance and slight participation of the African continent, but also the quasi-absence of the French-speaking counter part of which I have been the first representative.

It is worthwhile to mention that there have been neither IPNA training courses before nor grants for the paediatrics working in this area. After having integrated the IPNA functioning, I, therefore, run some IPNA courses in Morocco, first in Casablanca in 2008 and then in Marrakesh in 2010. Since there has not been any directory, it took me three full years to collect the colleagues’ contact details of each country. It was actually a task as difficult as exhilarating because the objective was to give birth and succeed a relatively ambitious project.

As a representative of Africa in IPNA, I quickly realized how precious and enriching the contributions of both African paediatric nephrologists and paediatrics interested in the paediatric nephrology would be in the writing of a common edition of this scientific document as this will enable us to collect African data according to significant specificities.

This basic tool written in collaboration with several African paediatric nephrologists with particular wide field-experience is enriched by international data in the field of PN. The book able to provide information, often crucial to young African practitioners and respond, hopefully, in a concrete manner to their daily concerns.

Of course, we have not excluded the expertise of our western colleagues who are already familiar with the African regions through some syntheses around certain diseases in paediatric nephrology, waiting, thus, for the collaboration of other colleagues coming from other continents who have a good knowledge about Africa.

In the end, it is the authors of African countries who have helped give birth to this book that includes 30 chapters. The target readers are the African paediatricians. The content was meant to be both practical and adapted to local characteristics and limited resources.
To reach the widest possible readership, thanks to the support of the International Paediatric Nephrology Association, this book, published in two languages, French and English, will be distributed for free. I hope that this collaboration will last - for a continuous and mutual enrichment of our competencies - and will be realized in the form of other projects that will allow us to address and deal more efficiently with the kidney damage in order to reduce its impact on our children’s health.

I conclude by extending my sincere thanks to all my colleagues, particularly in Africa, thanks to whom I learned a lot about the practice of medicine as well as the medical education in Africa.

Have a good reading!

Amal Bourquia
Casablanca - Morocco
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PART I

EXPLORATIONS

CHAPTER 1

EXPLORATION OF THE RENAL FUNCTION

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HIGHLIGHTS
✓ In pediatric nephrology, as in many other specialties a good clinical examination can provide much information.
✓ The interrogatory seeking personal history, dating back to the antenatal ultrasound and family history.
✓ The biochemical and cytological analysis of urine is the key exploration in detecting uro nephrologic childhood illnesses.
✓ The dipstick, a very simple examination that can be carried out at the cabinet, provides very important information for both the child who routinely consults the doctor and the sick child.
✓ Microalbuminuria allowing the early screen of kidney diseases is not affordable in most African countries.
✓ Ultrasound remains the key examination in pediatric uro nephrology whereby results determine other investigations.

I- INTRODUCTION
Many diseases affect the kidney and may engage life or functional prognosis in children. While in developed countries, the pediatric nephrology witnesses much progress today, Africa, sub-Saharan Africa in particular, is still incipient in an environment marked by a lack of resources. The clinical approach plays its full role, supplemented by some available paraclinical examinations to help reach an efficient diagnosis and an adequate management. In this article, we will first present the suspected child or the one with the kidney disease.

II- ANATOMICOPHYSIOLOGICAL REMINDERS
The kidney is bean-shaped a double organ symmetrically placed at each side of the spinal column in the lumbar fossa. The functional unit is the nephron, consisting of a glomerulus, which is followed by a tube divided into several segments: the proximal convoluted tube, the manifold distal convoluted tube and manifold tube.
The kidney plays two main roles:
- Role of treatment: development of urine and elimination of toxic waste in accordance with fluid electrolyte and acid-base balance of the body.
- Endocrine Role:
  . Regulation of blood pressure by the renin-angiotensin-aldosterone system
  . Phosphate metabolism by the activation of vitamin D,
  . Secretion of erythropoietin needed in hematopoiesis.
These functions are subject to disruption by different pathologies. A thorough exploration allows, therefore, to effectively diagnose the problem.

III- INDICATIONS OF A RENAL EXPLORATION
The situations that draw attention to the possibility of kidney disease are summarized in Table 1.
Table 1: Major indications of a renal exploration

<table>
<thead>
<tr>
<th>Signs and symptoms</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Family history</strong></td>
<td>urinary infection, renal failure, lithiasis, Hematuria.</td>
</tr>
<tr>
<td><strong>Prenatal history</strong></td>
<td>oligohydramnios, large placenta.</td>
</tr>
<tr>
<td><strong>History of childbirth</strong></td>
<td>Asphyxia, umbilical catheterization, hypotrophy.</td>
</tr>
<tr>
<td><strong>Antecedents</strong></td>
<td>aminoglycosides prescription, cisplatin, NSAIDs, diabetes ...</td>
</tr>
<tr>
<td><strong>Functional Signs</strong></td>
<td>Deafness, polyuria, polydipsia, incontinence.</td>
</tr>
<tr>
<td><strong>Physical Signs</strong></td>
<td>urine anomalies, proteinuria, glycosuria, hematuria, pyuria, growth retardation, dysmorphia, rickets, paleness, sacred agenesis, edematous syndrome. Hypertension.</td>
</tr>
<tr>
<td><strong>Biological Signs</strong></td>
<td>Acidosis, anemia, hypokalemia, hyperkalemia, proteinuria, hematuria, increased of creatinine and urea.</td>
</tr>
<tr>
<td><strong>Supervision of known kidney disease</strong></td>
<td></td>
</tr>
</tbody>
</table>

IV- CLINICAL EXAMINATION

The exploration is oriented with clinical examination including an interview and a physical examination.

A- Interview

The main points of the interview of a suspect child with kidney disease include:

1- Antenatal history

- The amniotic fluid volume: oligohydramnios in fetuses with low diuresis due to a urinary tract obstruction or severe renal failure hydramnios in polyuric states, for example, the Bartter syndrome.
- Maternal history: diabetes (associated with sacral agenesis, a multicystic dysplastic kidney or other renal abnormalities), medications used during pregnancy, abortions or earlier stillbirths.
- The intrauterine development: the delay in intrauterine growth may reflect an anomaly.
- The paraclinical abnormalities during pregnancy including ultrasound abnormalities (for example hydronephrosis).

2- Childbirth

- The type of childbirth
- The Apgar score: notion of fetal distress or hypoxia,
- Birth weight: low birth weight is associated with a reduced number of nephrons a birthweight may be related to a genetic disease such as Beckwith syndrome - Wiedeman,
- The number of umbilical vessels: a single umbilical artery is associated with a renal anomaly (for example: renal aplasia or hypoplasia, bladder exstrophy) in 30% of cases.
- The weight of the placenta: when higher than 25% of body weight in most cases, it often reflects the congenital nephrotic syndrome.
3- Neonatal period
• Respiratory symptoms may be associated with oligohydramnios and abnormal lung development.
• Neonatal umbilical catheterization is associated with thrombosis of the artery or renal vein.
• The deadline for the first urination.

4- Other important points of the interview
- Family antecedents:
  . The notion of consanguinity: for recessive genetic kidney disease.
  . The notion of renal disease known by deafness, hypertension or diabetes in the family.
- Abnormalities of micturition: quality of urinary stream (urination ‘drop by drop’ is a symptom of posterior urethral valves), the notion of dysuria, pollakiuria, or hematic disorders of urine.
- The history of angina or pyoderma.

B- Physical examination
In pediatric nephrology, particular attention must be paid to the items summarized in Table 2.

C- Urinalysis
Table 2: the Key elements to be sought while carrying out the physical examination

| - Growth: weight, height, cranial perimeter, pubertal stage. |
| - Blood pressure, peripheral pulse, temperature, respiratory rate. |
| - General signs such as pallor and edema. |
| - State of the urinary system: large kidneys, pain of lumbar fossa, distended bladder. |
| - Examination of other systems: |
  • Facial dysmorphia. |
  • Number of renal arteries if the child is seen at birth. |
  • Ocular abnormalities: aniridia, coloboma, uveitis. |
  • The auricular deformities. |
  • Presence of abdominal muscles. |
  • Cryptorchidism and other genital abnormalities. |
  - Bony vertebral anomalies including sacral agenesis, signs of rickets. |
  - Examination of the urine dipstick, which must complete each clinical examination. |

It is crucial in the search for a uro-nephrological pathology in children. The observation of color, examination of reagent strip and microscopic examination are used to make diagnostic hypotheses.

1- The color
The color is to be observed after the issuance of urine. The straw yellow color of urine may be subjected to variations of concentration according to the importance of water inputs and, therefore, the amount of eliminated urine. Low intakes of water or extra-renal water losses result in slightly abundant and dark urine. Conversely, a lot of water intakes will result in an abundant diuresis and very clear urine. Red urine may then be noted which would lead us to consider hematuria...In case of renal failure, the inability of the kidney to concentrate urine explains their unusually light color.
2- The urine dipstick

Of high interest in the African context, the urine dipstick is a simple complement to the clinical examination of the doctor who can, on the spot, provide valuable information for a better management of the affected child. This is also an excellent monitoring means at the disposal of the parents of a child with certain affections such as nephrotic syndrome and uropathy responsible for recurrent urinary infections.

a- Search for proteinuria

This is the simplest way to highlight glomerular disease because there are a few glomerular affections without associated proteinuria. Some tubulopathies are also accompanied by proteinuria. The systematic search of proteinuria is an excellent measure of public health and should be included in the health record booklets for the detection and early management of nephropathic glomerular. This systematic search of proteinuria in school age children in Japan has revealed that the prevalence of urinary abnormalities is 0.52% among children in elementary school and 0.75% among high school students.

If the search for proteinuria is very positive late in the day and negative in the morning, an orthostatic proteinuria should be evoked. The search for proteinuria should be systematic whatever the location of edema is. The result is almost immediate. Furthermore, there are false positive results when the urine is strongly basic (pH = 9) and in the presence of quaternary ammonium salts. It is therefore necessary to avoid them for the toilet.

b- Search for leukocytes and urinary nitrite

The urinary dipstick is very useful while screening for the urinary infection. The urine should be collected with rigor in a sterile manner as in the urine culture. The leucocyturia has a high sensitivity (67% to 94%), the specificity is lower. Thus in a lot of cases, the urinary dipstick allows to avoid cytobacteriological repeated examinations. If the results of strips nitrites and leukocytes are positive, the examination must be completed by a urine culture to find out the germ and antibiogram.

c- Search for hematuria

Hematuria can be diagnosed at the strip. Beware of its high sensitivity. In some cases, a physiological microscopic hematuria can lead to positive results. Hemoglobinuria and myoglobinuria also give positive results this is why they should always be checked by cytological examination of the urine. There are false positive results in case of urinary infection on account of a microbial peroxidase. We must agitate prior to practicing the test to prevent the RBCs sediment in the bottom.

d- Search for glucosuria

The dipstick is an effective way to monitor glycosuria in patients with diabetes mellitus. When blood glucose is normal, the presence of glycosuria indicates proximal tubular injury. This normoglycemic glycosuria may be strictly isolated or be part of a more complex proximal tubulopathy.

e- Urinary PH

The chemical principle is a system with double indicator. The red color in Methyl and the blue one in bromothymol are used to generate a color change from orange to green and blue on a scale of 5 to 9 with a precision of one unit. This test is interesting in the case of blood acidosis.

f- Urinary density

The test allows the determination of density between 1000 and 1030. We need to know the
limitations of this test. A strongly alkaline urine can cause a decrease in results and highly acidic urine causes an elevation of the result. The presence of glucose and protein in urine increases the urinary density. There is no «normal urinary density» since it depends on the amount of water intake and hydration status.

In case of dehydration, the urinary density is high: 1025 to 1030. If the child is dehydrated but the urinary density is low, it reflects a disorder of the urinary concentrating ability and a very probable kidney disease injury justifying complementary explorations. For this reason, it is good clinical practice to study the urinary density in a dehydrated child.

Upon completion of the clinical examination, a diagnostic orientation is generally recommended, that further exploration will help confirm

V- BIOLOGICAL EXPLORATIONS

A- Blood tests
(See reference values in annexes).

B- Urinary examinations

1- Urine collection
Its quality depends on the reliability of the findings.
- For the dipstick: urine freshly issued urine in a clean container preferably the first morning urine.
- For collecting 24H (24H proteinuria or creatinine clearance for example) it should be noted the start time of collection (7 am in the morning) and to empty the bladder. Discard the first urine.

Then collect all urine issued by the child in a covered container overnight at the same time (7H).
At this time, we oblige the child to urinate, and add the last urine to the previous one before their prompt delivery to the laboratory.
- For Urine culture, sampling can be done in mid-stream, via urine bladder (Urinocol®) by suprapubic puncture or vesical catheterization.

2- Exploration of the glomerular function

Glomerular filtration permits the passage of water and small molecules but prevents passage of blood cells and plasma proteins through the renal filter. It results in the formation of primitive urine whose is approximating the plasma. This primitive urine will undergo secondary tubular retouch to form the ultimate urine.

3- Glomerular Filtration Rate (GFR)

It is the best indicator of glomerular function. This allows an estimation of functional renal mass and can reflect the severity of the kidney disease. It can be determined by the creatinine clearance, calculated by the formula:

\[ \text{CrCl (ml / min / 1.73m2)} = \frac{\text{UV}}{\text{P}} \times 1.73 \times \text{SC}. \]

\( U = \text{urinary creatinine (mg / dl)}, \quad V = \text{urine volume per minute (ml / min)}, \quad \text{collection 60} \times \text{P = plasmatic creatinine (mg / dl)}, \quad \text{SC (m2) = body surface area (\sqrt{\text{weight (kg)} \times \text{Height (cm)}} / 3600)} \).

GFR can be estimated from plasmatic creatinine and the size of the child by the formula HAYCOCK-SCHWARTZ:

\[ \text{GFR(in ml / min / 1.73m2)} = \text{height (cm)} \times k / \text{plasmatic creatinine (mg / dl)}. \]
The value of k depends on age and sex as shown in Table 1 and the normal values according to age groups are indicated in Table 2.

Table 1: Values of k for the estimation of glomerular filtration rate

<table>
<thead>
<tr>
<th>Values of k</th>
<th>Plasmatic Creatinine</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mg/dl</td>
<td>µmol/l</td>
</tr>
<tr>
<td>Low birth weight</td>
<td>0.27</td>
<td>24</td>
</tr>
<tr>
<td>On time newborns</td>
<td>0.37</td>
<td>33</td>
</tr>
<tr>
<td>0-12 month infants</td>
<td>0.45</td>
<td>40</td>
</tr>
<tr>
<td>2-12 year boys and girls</td>
<td>0.55</td>
<td>49</td>
</tr>
<tr>
<td>13-21 year girls</td>
<td>0.55</td>
<td>49</td>
</tr>
<tr>
<td>13-21 year boys</td>
<td>0.70</td>
<td>60</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Age</th>
<th>GFR average (ml/mn / 1.73m²)</th>
<th>Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>birth</td>
<td>20.3</td>
<td>-</td>
</tr>
<tr>
<td>7 days</td>
<td>38</td>
<td>26-60</td>
</tr>
<tr>
<td>1 days</td>
<td>48</td>
<td>28-68</td>
</tr>
<tr>
<td>2 month</td>
<td>58</td>
<td>30-86</td>
</tr>
<tr>
<td>6 month</td>
<td>77</td>
<td>41-103</td>
</tr>
<tr>
<td>9 month</td>
<td>103</td>
<td>49-157</td>
</tr>
<tr>
<td>12 month</td>
<td>115</td>
<td>65-160</td>
</tr>
<tr>
<td>2 years</td>
<td>127</td>
<td>89-165</td>
</tr>
<tr>
<td>4 years</td>
<td>127</td>
<td>89-165</td>
</tr>
<tr>
<td>8 years</td>
<td>127</td>
<td>89-165</td>
</tr>
<tr>
<td>12 years</td>
<td>127</td>
<td>89-165</td>
</tr>
<tr>
<td>Adult</td>
<td>131</td>
<td>88-174</td>
</tr>
</tbody>
</table>


There are other estimations of the glomerular filtration rate, which will not be covered here methods since they are not useful in the African context.

4- Exploration of the tubular function

The primitive urine undergoes a retouch (through reabsorption and secretion) to form the final urine. The proximal convoluted tubule ensures the complete reabsorption of sodium, glucose,
African Pediatric Nephrology Guidebook

Amino acids, and phosphate when the plasma concentration is below the renal threshold. The distal tube concentrates, dilutes urine depending on the concentration of the internal milieu, and acidifies urine.

The following are the examinations exploring the tubular function:

a- Some parameters of the dipstick

- **Glucose**
  Normally, plasma glucose is below the renal threshold. If for normal glucose, the dipstick shows glycosuria. This means a lack of proximal tubular reabsorption of glucose (in Fanconi disease).

- **pH**
  If before a state of metabolic acidosis, urinary pH is > 5.5, then it is a lack of urine acidification within the scope of acidosis of renal origin: urinary leak of bicarbonates in case of proximal tubulopathy, trouble of removing H+ ions in case of distal renal tubular acidosis.

- **The urinary density**
  It varies from 1000 (very dilute urine) to 1030 (very concentrated urine) for most of the models. In practice, it helps in the diagnosis of abnormalities of water reabsorption in the tubules.

b- Tubular reabsorption of phosphate

In order to achieve it, it is necessary to measure both the phosphate and the creatinine on concomitant samples of blood and urine. The calculation of the excretory fraction of phosphate (EFF) lets one know if there is a urinary leak.

\[
EFF = \frac{\text{Urinary Phosphate}}{\text{Plasma Phosphate}} \div \frac{\text{Urinary Creatinine}}{\text{Serum Creatinine}}
\]

The normal value is 85-90%. Below 85% indicates a urinary leakage.

c- The excretory fraction of bicarbonate (FEHCO3)

This is the filtered bicarbonate fraction that is excreted by the kidney (eliminated in urine). It has a diagnostic and therapeutic value in metabolic acidosis. It is calculated by the formula:

\[
FEHCO3 = \frac{\text{UHCO3}}{\text{PHCO3}} \times \frac{\text{PCr}}{\text{URC}} \times 100.
\]

UHCO3 = urinary bicarbonate; PHCO3 = plasma bicarbonate; PCr = plasma creatinine; UCR = urinary creatinine. UHCO3 is measured directly or calculated from the equation: \(pH = Pk + \log (HCO3^- / 0.03 PCO2)\) where \(Pk = 6.33 \times \sqrt{\text{UNa UK}}\).

Normally FEHCO3 is less than 5%, as is also the case in renal tubular acidosis type 1 (or distal type). FEHCO3 a ≥ 15% is found in renal tubular acidosis type 2 (or proximal type); in renal tubular acidosis type 4, the FEHCO3 is also less than 10%.

4- Urine acidification test

Ammonium chloride (0.1 g / kg) is administered orally. If, in case of acidosis, the urinary pH 2 hours after ingestion is ≥ 5.5 then it is very probably a urine acidification defect (defection of excretion in urine of H ions, as is the case in distal renal tubular acidosis, or type 1).

5- Test of fluid restriction and Minirin test® (DDAVP)

These tests allow assessment of water reabsorption at the level of the collecting tubule and thus make the diagnosis of diabetes insipidus.

It begins with proper hydration of the child 24 hours before the test. Measure the weight of the child, emptied bladder. Take blood sample for the hematocrit and osmolality. Make fluid restriction
during 7H, measuring body weight and urine specific gravity every hour. Stop the test when the body weight loss approaches 5%. Then recollect the blood sample for the hematocrit, urea and osmolality.

Normally, the urine osmolality increases substantially; the urine density increases beyond 1010 and the urinary volume substantially decreases, while the blood osmolality increases only slightly. In case of diabetes insipidus, urinary density remains below 1005; the urine osmolality remains below 150 mOsm / L; there is no reduction in urine volume; blood osmolality is more than 290 mOsm / L, and the urea and hematocrit are increased.

To differentiate between central and peripheral diabetes insipidus, Minirin® is administered at the end of the fluid restriction test, at a 10 ug dose (child less than one year) or 20 ug (child of more than one year). In case of diabetes insipidus of central cause (default secretion of antidiuretic hormone), there is reduction in urinary volume and an increase of urinary density beyond 1010. In case of nephrogenic diabetes insipidus (insensitivity of the renal tubule the antidiuretic hormone) neither the volume or urine nor the the urinary density specific gravity undergo modifications.

**VI- RADIOLOGICAL INVESTIGATIONS**

They require a close collaboration between the clinician and the radiologist. From the quality of the information provided by the clinician to the radiologist depends the quality of the interpretation of results by the latter.

**A- X-ray of abdomen without preparation**

```
Bilateral renal calculi
(primary hyperoxaluria)
```

It is very useful for the diagnosis of pathologies such as gallstones, abdominal masses, intra-abdominal calcifications, including nephrocalcinosis, sacral agenesis, and spina bifida occulta.

**B- Ultrasound**

It is a very useful examination in nephrology and has the advantages of being without irradiation and not painful. Its major inconvenience is being operator-dependent. It measures the size of the kidney.

Many malformation syndromes or genetic abnormalities include kidney damage which is detectable on ultrasound. The indications for ultrasound examination include:
- History of renal structural abnormalities in parents or a sibling.
- A single umbilical artery (risk of vesicoureteral reflux).
- An abnormality of the external ear or hearing loss.
- A chromosomal aberration.
- Screening for renal polycystic or other cystic kidney disease.

It is an excellent way of diagnosis of hydronephrosis, renal masses, and stones that are not radio-opaque.

It also allows the study of the bladder, its wall and residual urine (valves of the posterior urethra or other bladder obstructions, VUR of high grade).

It can also help, alongside the cytobacteriological urine examination, in the diagnosis of acute pyelonephritis (large hyperechoic kidney with loss of the cortico-medullary differentiation).

**C- Intravenous urography**

Less and less used in developed countries, this examination has still its place in the technical level of most African countries. It provides important information on renal anatomy in particular in cases of obstructions of the urinary tracts (abnormalities of the ureteropelvic junction “UPJ” or vesico-ureteric junction, nephrolithiasis, etc.).
D- Voiding cystography
This is the reference for the diagnosis of posterior urethral valves and vesicoureteral reflux. It must be done after ensuring that the child is not (or no longer) suffering from UTI. It entails the risk of iatrogenic infection and for this reason it is important to observe the maximum aseptic precautions and use prophylactic antibiotics. For example, we could administer cotrimoxazole at a dose of 30 mg / kg / day once daily for 3 days starting the day before the examination.

Initial images allow highlighting ureteroceles and bladder diverticula, which disappear ("are compressed ") when the bladder is in full. The oblique or lateral views, without a catheter in place, are necessary to underline the posterior urethral valves.

E- Renal scan
It provides excellent information about the anatomy of the kidney and the urinary tract. It is indicated in the assessment of abdominal masses, pyonephrosis, nephrocalcinosis, or urolithiasis, and renal trauma. Its major drawback is its very high radiation dose.

VII- ISOTOPIC INVESTIGATIONS
They can assess the total renal function or that of each kidney and specify some urologic malformations. They include dynamic scintigraphy (MAG3) and static (DMSA), which both allow the measurement of relative function of each kidney. These investigations are mostly inaccessible in African countries.

VIII- HISTOLOGICAL STUDIES
These are not available in most countries of Sub-Saharan Africa; even when there is the analysis of the biopsy piece it is frequently incomplete because it is not possible to arrange for immunofluorescence, for example.

IX- CONCLUSION
As an organ of elimination of waste and the balance of the internal environment, the kidney is a noble body whose pathologies can be addressed through appropriate clinical approach to which it is important to stress, in an African context, that the paraclinical investigations are for
the most part difficult to access. Based on appropriate analysis of the available investigations, carefully selected, there is a better chance to make an appropriate diagnosis. Regarding imaging, the emphasis must be put on the importance of collaboration with the radiologist to which all relevant clinical information should be provided for better image interpretation.

Références

CHAPTER 2

RENAL BIOPSY

Ashraf Bakr, Ayman Hammad, Ahmed M El-Refaey
Mansoura - Egypt
HIGHLIGHTS

✓ Renal biopsy is an essential diagnostic tool for clinicians.
✓ The main clinical indications are nephrotic syndrome and rapidly progressive renal failure.
✓ It permits the classification of kidney disease, dictate a therapeutic approach suitable for histopathological lesions and to assess the prognosis of the disease.
✓ This is a quick and simple, which must be done by a pediatrician nephrologist and requires clinical monitoring in a hospital infrastructure.
✓ The material collected must be sufficient for optimal pathological examination based on three complementary analyzes: optical microscopy, immunofluorescence and electron microscopy.

I- INTRODUCTION

Renal biopsy is the best standard for renal tissue analysis. It allows histologic diagnoses of renal diseases and determines the extent of disease severity and damage to kidneys. Also renal biopsy is an essential investigation for establishing the morphologic diagnosis and prognosis of renal disease in children and adults. Before the routine use of renal biopsy, pathologists relied on autopsy material for investigation of disease pathophysiology. However, its development and advanced procedures since the late 1950s has been fundamental for the diagnosis of clinical syndromes and the discovery of new pathologic variants.

The first percutaneous kidney biopsies were performed over 50 years ago using a liver biopsy needle and intravenous pyelograms for screening. Renal biopsy can be performed by an open surgical procedure but the percutaneous method is the preferred manner of obtaining the renal biopsy sample in most children. Percutaneous renal biopsy of palpable tumors was first performed in 1934 by Ball and its use for the diagnosis of renal diseases was firstly introduced by Iversen and Brun in 1951 (1). The use of real-time ultrasound and automated biopsy needles during the last two decades made the procedure simple and improved its success and safety (2).

II- INDICATIONS OF RENAL BIOPSY

Renal biopsy may be indicated in two broad categories:

A- Diffuse disease renal disease

The use of renal biopsy in diffuse renal disease is indicated to:

• Determine the morphologic type of the renal disease.
• Predict prognosis and disease prognosis.
• Select the appropriate therapy protocol.
• Monitor the response to therapy.

The management of the renal disease has been modifies according to the result of renal biopsy in about 42% of cases (3).

Table 1: Indications of renal biopsy

<table>
<thead>
<tr>
<th>Hematuria</th>
<th>Rapidly progressive glomerulonephritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent non postural Proteinuria</td>
<td>Chronic Renal Insufficiency.</td>
</tr>
<tr>
<td>Nephrotic syndrome.</td>
<td>Systemic Diseases.</td>
</tr>
<tr>
<td>Acute nephritis.</td>
<td>Follow-Up the progression of disease</td>
</tr>
<tr>
<td>Acute renal failure.</td>
<td>Renal transplantation.</td>
</tr>
</tbody>
</table>
1- Hematuria
It is indicated if there is isolated glomerular hematuria (no proteinuria, normal function of the kidney, no hypercalciuria or familial or urologic disease and presence of Red blood cell casts or dysmorphic red blood cells)(4,6). One-quarter to nearly one-half of the patients with isolated hematuria have normal biopsies (7).

2- Nephrotic syndrome
Children with typical presentation of NS will undergo a therapeutic trial of corticosteroids without a need to perform renal biopsy as most of them are minimal change nephrotic syndrome with good response to corticosteroids. Therefore, Renal biopsy is indicated in atypical nephrotic syndrome (age <1 year or >8 years, persistent hypertension, gross hematuria, low C3, decreased renal function or corticosteroid therapy resistance)

3- Acute nephritis
Renal Biopsy is indicated in atypical course and resolution of acute post-streptococcal glomerulonephritis.

4- Acute Renal Failure:
Renal Biopsy is considered when parenchymal disease is suspected. It is also indicated if acute renal failure is associated with nephritis, NS, or evidence of vasculitis or systemic diseases. When the cause remains uncertain after complete evaluation, renal biopsy may be necessary for diagnosis (8).

5- Chronic renal insufficiency
In cases with CRI the diagnosis of primary disease is important to assess the severity of the disease, determination of risk of recurrence in eventual kidney transplant, and suitability of cadaveric vs. living-related donor transplantation (9).

6- Systemic diseases
Renal biopsy may be performed to assess the severity of renal involvement in systemic disease (systemic lupus erythematosus, hemolytic-uremic syndrome, Henoch-Schönlein purpura or diabetes mellitus).

7- Transplantation
Transplant biopsy is helpful in the following situations clinically suspected rejection, renal impairment, decreased urine output, detecting the development of de novo or recurrent disease, and Drug toxicity may be diagnosed by morphologic findings.

B- Focal masses (open method)
The indications for renal biopsy of a focal renal mass(es) may include:
• Suspected metastatic spread to the kidney.
• Suspected primary renal neoplasm with evidence of metastatic disease outside the kidney (where biopsy of the renal tumor is safer than biopsy of the metastatic disease)
• Inflammation (Sarcoidosis, Amyloidosis)
• Renal mass without clear imaging characteristics.
III- CONS-INDICATIONS OF RENAL BIOPSY

There are absolute cons-indications to renal biopsy when the situations have high risks. The relative cons-indications are those circumstances that affect the safety of the procedure, or increase its difficulty leading to increase in the risk of complications. The benefits and risks of the procedure in should be considered in each patient and then the pediatric nephrologists’ decide if the procedure is indicated or not. The alternative procedure in patients with contraindication to percutaneous procedure is open surgical renal biopsy.

Table 2: Cons-indications of renal biopsy

<table>
<thead>
<tr>
<th>Absolute</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Solitary native kidney.</td>
</tr>
<tr>
<td>• Ectopic, or horseshoe kidney.</td>
</tr>
<tr>
<td>• Abnormal renal vascular supply.</td>
</tr>
<tr>
<td>• Uncontrolled bleeding diathesis</td>
</tr>
<tr>
<td>• Severe hypertension</td>
</tr>
<tr>
<td>• Failure to get consent.</td>
</tr>
<tr>
<td>• Acute pyelonephritis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Relative</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Severe azotemia.</td>
</tr>
</tbody>
</table>

With use ultrasound guidance and automated biopsy instruments, solitary kidney may be biopsied safely in selected patient (10).

IV- RENAL BIOPSY PROCEDURE

A- Preparing the patient

The patient may be brought to the hospital on the day of the biopsy. The pre-biopsy patient evaluation include history taking, physical examination, laboratory evaluation, and ultrasonographic evaluation. The history should include information about bleeding diathesis, allergies to agents used during the renal biopsy, use of drugs that affect bleeding profile (aspirin, anti-platelets or other anticoagulation therapy), and a history of severe hypertension. The physical examination important points are blood pressure evaluation and assessment of anatomic abnormalities. For safety, laboratory values are obtained, including hemoglobin, platelet count, prothrombin time, partial thromboplastin time, and bleeding time. In addition, serum creatinine, electrolytes, and urine dipstick analysis may be used as baseline parameters in case of complications (11). Before performing the biopsy ultrasonographic evaluation of the kidneys should be done, to rule out the anatomic abnormalities that might constitute absolute or relative contraindication for a percutaneous renal biopsy (2).

B- Biopsy procedure

The biopsy should be done at the procedure room with continuous cardiorespiratory monitoring. Small children will receive general anesthesia. In larger children the procedure can be safely performed with mild sedation. The patient is placed in a prone position with a foam roll or sand bag under the upper part of the abdomen to stabilize and push the kidney towards the operator.
The kidneys are localized by ultrasound from the back. The lower pole of the left kidney or that of the easiest to reach is then chosen for biopsy. The exact position of the kidney during inspiration is determined, and mark the site of the needle entry on the skin then the skin is cleaned with antiseptic solution (povidone-iodine). If the patient is not under general anesthesia, infiltrate the skin, subcutaneous tissue, and muscle with a local anesthetic. After a small incision is made, the needle, spring-loaded biopsy gun (gun biopsy) is slowly introduced with ultrasound guidance until the kidney is reached. Biopsy guns have been widely replaced manually operated needles because they are easier to use and have lower complications. The needle is quickly introduced to the capsule of the kidney and then the biopsy gun is fired. Continuous cardiorespiratory monitoring should be started before the procedure and continued until the recovery phase. In the absence of any complications, patients are returned to their rooms for post-biopsy care.

C- Post-renal biopsy care

After doing renal biopsy, the kidney will be examined by ultrasound to search for pericapsular hematoma. Once the ultrasound is completed, the skin is cleaned with antiseptic solution and a pressure dressing is applied. If there are no complications the child lie on his back and transported to the ward with continuous cardiorespiratory monitoring. The post-biopsy procedure observation should focus on monitoring the vital signs for any evidence of hypovolemia and anesthesia-related complications. (Table-1). There is controversy regarding length of post-biopsy hospital stay with evidence that a shorter observation period (8 hours) with same day discharge from the hospital is sufficient in non complicated cases and is more economical (12,13).

Table 2: Post-biopsy follow up sheet

| Monitor vital signs | Every 15 minutes for 1 hour  
|                    | Every 30 minutes for 2 hours  
|                    | Every 1 hour for 4 hours  
| After 4 hours of biopsy | Obtain hemoglobin/hematocrit  
| Inform physician if  | Changes outside normal parameters value.  
|                      | Back pain, abdominal pain.  
|                      | Bleeding at the biopsy site.  
|                      | Anuria for 6 hours.  
|                      | Macroscopic hematuria  

V- COMPLICATIONS OF RENAL BIOPSY

A- Minor

- Microscopic hematuria
- Transient Macroscopic hematuria.
- Small perinephric hematoma.
B- Major

- Prolonged macroscopic hematuria requiring intervention.
- Clinically significant Perirenal hematoma
- Arteriovenous fistula
- Need for a major surgical intervention
- Death

References

CHAPTER 3

AFRICAN EXPERIENCE EXAMPLE
RENAL BIOPSY IN CHILDREN IN DAKAR

Younoussa Kéïta, C Dial, M Moreira, B Diouf, M Sar, Dakar - Senegal
I- INTRODUCTION
The renal biopsy (RB), an essential tool for the diagnosis of primary and secondary renal diseases, is usually done under ultrasound and has become a routine exam in clinical nephrology in Dakar university hospital (1,2). The aim of our study was to clarify the different RB indications and describe the histopathological injuries.

II- PATIENTS AND METHODS
This was a retrospective descriptive study on a series of 31 ultrasound-guided renal biopsies performed using a Silverman needle between January 2010 and May 2011 in the departments of Nephrology and Pediatrics at the University Hospital Aristide Le Dantec, Dakar. This included all nephropathies having been biopsied during the study period. Renal biopsies reducing medullary fragment and those reducing a fragment containing less than 5 glomeruli were excluded. The reading was done systematically and immunofluorescence was performed in some cases. The clinical information was obtained through the request form biopsy and the patient’s file. Two kidney fragments were collected for each patient, fixed and sent immediately to the histopathology laboratory. The results were analyzed using the software SPSS.16 and the threshold p <0.05 was considered significant.

III- RESULTS
We have performed a renal biopsy in 33 patients. A fragment bringing 4 glomeruli and another medullary were excluded from the study, a success rate of 93.93%. We, therefore, included 31 patients in the study. The average age of these was 9.19 years (extremes: 2 to 15 years) and the sex ratio was 1.8. Renal biopsy indications are shown in table I. Three patients had gross hematuria complicating renal biopsy and have (it) disappeared in less than 24 hours. We have diagnosed during the nephrotic syndrome 14 cases of Minimal Glomerular Lesions (MGL) namely 58.30%, 7 cases of Hyalinosis and Focal Segmental (HFS) namely 29.2% (Figure 1), 3 cases of Diffuse Mesangial Sclerosis (DMS) namely 12.5%. In the rapidly progressive glomerulonephritis (RPGN), we have found a case of segmental glomerulonephritis with segmental cellular crescents (Figure 2) and 2 cases of glomerulonephritis with diffuse fibro-cellular crescents. During severe Plasmodium falciparum malaria with acute renal failure prolonged, we have noted a case of acute tubular necrosis (Figure 3) and one case of cortical necrosis effects (Figure 4). Lupus nephritis was class II according to the WHO. The renal biopsy of the patient with tubulointerstitial nephropathy syndrome was found mutilating interstitial fibrosis associated with nephronic reduction of 80%.

IV- COMMENTS
The practice of ultrasound-guided renal biopsy in children is an act of routine in Dakar University Hospital. Our success rate of 93.93% was comparable to the study done by Desrentes in patients aged between 1 and 82 years old at the main hospital in Dakar, which was 92%, and that of literature as in Backman, Hachicha and Lankester studies where it was respectively 93% and 97% (5,6,7). The median age of the patients was 9.19 years and the sex ratio of 1.8. In the Paripovic study, Serbia, published in 2012, the median age was 11.5 years (range 0.2 to 20 years) with a sex ratio of 0.78 [8]. In Ali study, published in 2011 in Pakistan, age ranged from 3 to 15 years with a sex ratio of 1.6 (9). Complications in our series were mainly of immediate post-biopsy hematuria type in 3 patients, a frequency of 0.09%. In Tondel study, Norway, macroscopic hematuria was
developed after biopsy in 1.9% of patients, 0.9% of patients required blood transfusion and 0.2% of them have been subjected to surgery / catheterization (10). These results show that the practice of renal biopsy is a low-risk procedure for all ages, although it is not frequently indicated in children as it is in adults (1).

Throughout our study, RB indications were dominated by a steroid-resistant nephrotic syndrome and multiple relapses in 74% of biopsies. In Paripovic and Ali series, nephrotic syndrome was the main indication of the RB in children with respective percentages of 32.9% and 50% (8,9). Other indications were variable from one geographic area to another. The authors describe, for example, infectious nephropathy, Berger’s disease, rheumatoid purpura, kidney damage during lupus etc.. (8,11). In our study, other RB indications were rapidly progressive glomerulonephritis in 3 cases, prolonged acute renal failure during Malaria in 2 cases, glomerular proteinuria in lupus female patient in 1 case and chronic tubulointerstitial nephropathy in 1 case. Histopathological injuries during the NS were dominated by the GML in 58.30% of cases, the HFS was found in 29.20% (Figure 2). These two injuries are more described in the literature (Table II.). Membranous glomerulonephritis injuries (GEM) have been described in the NS associated with malaria plasmodium in Senegal in 1975 by Morel-Maroger Aristide Le Dantec (12) hospital. The lipoidalnephrosis of GML, known for its corticoid-sensitivity, has a good long-term prognosis. Other histological types during the NS are changing and have a highly variable prognosis, they often need to resort to treatments heavy for significant side effects and the results are often random (13,14,15).

The histopathological study of other biopsy parts outside the NS showed injuries of glomerulonephritis in 1 case of cellular crescents and fibrocellular crescents in 2 cases, one case of lupus glomerulonephritits, WHO class II, and one case of mutilating interstitial fibrosis associated with nephron reduction of 80% in a syndrome of chronic tubulointerstitial nephropathy. The biopsies in two cases of prolonged acute renal failure (ARF) during falciparum malaria showed tubular necrosis injuries in one case and cortical necrosis in the other case. AdonysKoffy et al. have raised the general problem related to the lack of ARF data during malaria in children (16). Their results showed that infections were partly responsible in tropical areas in the pathogenesis of renal disease in children (12,15,16).
V- CONCLUSION

The RB, which has become an act of routine in children in Dakar, adds value to the understanding and treatment of kidney disease in children. The most common histological injury during the NS was the GML. Various renal injuries were shown in our study, especially during malaria. The continued practice of renal biopsy will establish a child kidney register child in Senegal.

### Table 1: Frequency (%) of primitive glomerular nephritis with nephrotic syndrome

<table>
<thead>
<tr>
<th>Histological Injuries</th>
<th>Our serie</th>
<th>Moyen (13)</th>
<th>Maisonneuve (14)</th>
<th>Bourquia (15)</th>
<th>Printza (11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LGM/ MCD</td>
<td>58,30</td>
<td>42,8</td>
<td>65,5</td>
<td>16</td>
<td>10</td>
</tr>
<tr>
<td>HFS/ FSGS</td>
<td>29,20</td>
<td>28</td>
<td>6,8</td>
<td>25</td>
<td>15</td>
</tr>
</tbody>
</table>

**Figure 1:** Focal and segmental glomerulosclerosis → X400

**Figure 2:** NG with Cellular crescents in the urinary chamber → proliferation endocapillary ●, green light TM X 400

**Figure 3:** Acute tubular necrosis: desquamation of tubular epithelial cells ↓, cellular debris in the tubular light → TM green light X 150

**Figure 4:** Cortical necrosis: apoplexy glomerular → 1, interstitial fibrosis → 2, tubular necrosis → 3 X 150 (HE)
References

PART II

GLOMERULOPATHIES

CHAPTER 4

ACUTE POST STREPTOCOCCAL GLOMERULONEPHRITIS

Damte Shimelis, Addis Ababa - Ethiopia
HIGHLIGHTS

✓ Acute Post streptococcal Glomerulonephritis (APSGN) is the most common glomerular disease in children.

✓ It occurs sporadically, but can also occur in epidemics in rural communities and in urban conditions overcrowded. It usually complicates pharyngitis in winter and early spring, and impetigo in summer and autumn.

✓ A delayed nonsuppurative complication of pharyngeal infection or impetigo with certain nephritogenic strains of group A β hemolytic streptococci.

✓ Treatment is symptomatic based on diet and lifestyle especially sodium and water restriction measures.

✓ Evolution of APSGN is often favourable (90%).

I- INTRODUCTION
Post-streptococcal acute glomerulonephritis (APSGN) is a delayed nonsuppurative complication of pharyngeal infection, impetigo or by certain nephritogenic strains of beta-hemolytic streptococcus group A. APSGN following a pharyngitis is the most frequently associated serotype M-12, and that following a impetigo M serotype-49. This disease is closely linked to a low socio-economic level as well as overcrowding. Improving living conditions significantly reduces the incidence rate.

II- PATHOGENESIS
The pathogenetic mechanisms leading to renal damage are not fully understood, however, circulating immune complexes are associated with glomerular damage. Theories on the pathogenesis of post streptococcal glomerulonephritis could be summarized as follows: a direct toxic effect of streptococcal products on the glomeruli, antibody elicited by the nephritogenic streptococci may cross-react with one or more renal antigens leading to antibody-mediated glomerular injury or circulating immune complexes composed of streptococcal antigen and antibodies deposited in the glomeruli.

The evidences for immunologic injury are: a) There is a latent period between infection and the development of nephritis b) hypocomplementemia is almost always present during the acute phase of the disease c) immunoglobulins, complement, and antigens that react with streptococcal antisera can be detected in involved glomeruli d) several investigators have demonstrated the presence of streptococcal antigens in the glomeruli of these patients.

III- PATHOPHYSIOLOGY
Symptomatology in acute post streptococcal glomerulonephritis is due to the result of reduction in glomerular filtration rate. The surface of glomerular filtration is markedly reduced because of the inflammatory process and renal blood flow is reduced. This results in elevation of creatinine and blood urea nitrogen. The child becomes acidotic and because of enhanced absorption of fluid and solute in the distal tubule and collecting tubule oliguria or anuria results clinically. Because of fluid retention and expansion of intravascular volume, the child develops hypertension and oedema. The child could be isonatremic or could develop dilutional hyponatremia. Serum potassium and phosphate levels are elevated serum calcium level could be normal or reduced.
IV- EPIDEMIOLOGY

It is the commonest glomerular disease in children. It occurs sporadically but might also occur in epidemics in some rural communities and overcrowded urban living conditions. It usually follows pharyngitis in winter and early spring, and impetigo in summer and fall. A study in a tertiary referral hospital in Addis Ababa has shown that admissions due to APSGN in children were highest in the months of December and January (graph 1). A Nigerian study showed two peaks in the occurrence of APSGN May-July and October to January (graph 2).

Graph 1: Streptococcal infections among Ethiopian children

Number of monthly admissions of ARF patients and APSGN patients in the Ethio-Swedish Children's Hospital, Addis Ababa during 1990 and GAS carrier rate among apparently healthy school children.

Graph 2: Yearly distribution of APSGN in Nigerian Children
Incidence might be difficult to determine because of a high rate of asymptomatic or mild cases but overall attack rate is 10-15%. Only < 5% of cases is < 2 years of age probably because group A streptococcal pharyngitis is uncommon in this age and children in this age are not able to mount immunologic response against group A streptococcal infection. The youngest child affected in literature is 8 months old. It is most common in children between 5 to 15 years of age.

V- CLINICAL FEATURES
The triggering event is an initial infection with streptococcal pharyngitis or skin infection. The usual skin infections in underprivileged populations of Africa are infected scabies and jiggers. Latent period is 7-14 days following pharyngeal infection and up to 6 weeks following impetigo. Subclinical cases are common. Previously healthy child classically presents with gross hematuria, oliguria, oedema, acute renal dysfunction and symptoms of hypertension. Occasionally, the child presents with ascites, pleural effusions or congestive heart failure. Severe cases may develop encephalopathy and seizure.

VI- LABORATORY DIAGNOSIS
Urinalysis usually shows hematuria and leukocyturia. Sometimes associated red blood cell casts are seen. Urine dipstick usually shows low grade proteinuria (+1 or +2 sometimes nephrotic range proteinuria). Blood urea nitrogen and creatinine are elevated but could also be normal in mild cases. ASO titer elevated in APSGN following throat infection but it rarely rises after streptococcal skin infection. The best single antibody titer to measure is anti DNase B antigen the other alternative is Streptozyme test. If there is an active lesion, culture throat swab or from pyoderma. C3 complement is low.

**Table 1: Symptoms suggestive of acute post-streptococcal glomerulonephritis**

- Oedema or simple weight gain
- Digestive symptoms (abdominal pain, vomiting)
- A hematuria (blood in the urine stained red)
- A oliguria (lack of urine)
- Hypertension
- A convulsion, an amaurosis secondary to high blood pressure, are possible
- Proteinuria and hematuria can confirm the diagnosis
- Measurement of serum complement C3 fraction is decreased
- Nephrotic syndrome is sometimes associated
- Streptococcus is rarely found in the throat swab.

VII- HISTOLOGY
Renal biopsy should be reserved for those cases with atypical presentation, have a protracted course and when the child fails to improve in three to four weeks. Biopsy shows focal or diffuse proliferation of mesangial and endothelial cells, infiltration of glomeruli by polymorphonuclear leukocytes and sub epithelial immune complexes (humps).
VIII- TREATMENT STRATEGY

No specific treatment, but the management is that of acute renal failure or treatment of complications. Though a 10-days course of systemic penicillin is recommended to prevent the spread of the nephritogenic organisms, there is no evidence that antibiotics change the course of the illness. In our experience most children with AGN present after the clearance of either the throat infection or

Table 2: Indications for renal biopsy

- Anuria
- Kidney failure for more than 2 weeks (high blood urea and creatinine, decreased creatinine clearance)
- Nephrotic syndrome beyond the 2nd week
- A persistent hypertension after the 2nd week
- Proteinuria > 1 g/24 h after 1 month
- Lower-than-normal levels of the complement proteins C3 after 4 months of evolution
- A persistent hematuria after 18 months of evolution
- A relapse of nephritis or gross hematuria

The above immunoflorescent microscopic picture shows granular bumpy deposits of complement 3 and IgG.
pyoderma or they might have trivial symptoms at the onset of infection and throat swabs are not yielding. In such cases antibiotics will not help. Some patients present with pulmonary congestion, fever and cough and chest x-ray might be interpreted as pneumonia, in such situations we treat them for pneumonia. Resistance to penicillin is unusual and a seven to ten days course is given but for penicillin allergic patients, erythromycin could be used. Activity does not need to be restricted, except in the acute phase of the illness. Fluid and salt restriction is indicated in situations where there is an evidence of fluid retention manifested by oedema, hepatomegaly, ascitis, congestive heart failure and pulmonary oedema. In our experience, severe clinical manifestations are the reasons for seeking medical attention and children with AGN present with full-blown picture of nephritic syndrome but ascitis and low serum albumin are not usual findings. The 24 hours urine output has to be measured for planning future fluid management.

The twenty-four hour fluid requirement shall be limited to insensible loss plus any output. The estimated insensible loss is 400ml/m2. This fluid shall be replaced as electrolyte free fluid since insensible losses do not contain significant electrolytes. Unless the child is unable to take orally, oral intakes shall be encouraged other than giving IV fluids. Hypertension and other signs of volume overload shall be treated with furosemide to promote diuresis.

In our experience loop diuretics alone are enough for the control of hypertension but we sometimes add nifedipine if diuresis has not taken place within 24 hours and if the patient is still oliguric. In our experience most of the patients’ signs of congestion and hypertension improve or resolve within one week but there are few cases in which hypertension remains for up to 2-3 weeks. By the time of discharge from hospital, all anti-congestive or anti-hypertensive medications shall be discontinued. Hypertensive encephalopathy shall be treated with sodium nitroprusside. Hyperkalemia, hyperphosphatemia and acidemia might occur in severe cases. Monitor urea and potassium level. Restrict potassium and phosphate intake and alkalinize with sodium bicarbonate. Hyperkalemia may temporarily be treated with rectal or oral exchange resins, administration of insulin with glucose and counteracting the effect of hyperkalemia with the administration of calcium gluconate. These temporary measures might fail and dialysis might be required. We have seen patients who required peritoneal dialysis due to failure of the other supportive measures. The outcome to peritoneal dialysis is excellent. Watch for recovery within 7 days, keep high index of suspicion for diseases other than acute post streptococcal GN.

IX- PREVENTION

Post streptococcal sore throat or skin infection has to be treated but it is not yet clear whether antibiotic treatment prevents APSGN. Immunity against streptococcal infection is type specific and long lasting. Recurrence is rare and it ranges between 0.7 to 7%. A ten days course of oral or intramuscular penicillin or erythromycin in penicillin allergic patients is the choice of treatment to prevent the spread of streptococcal infection especially in resource-limited situations. Cephalosporins are also alternatives.

X- PROGNOSIS

About 95% of children recover without sequel but prognosis depends on the severity of glomerular injury. Studies have shown that if more than 50% of the glomeruli are involved with crescent formation the prognosis is poor. Persistence of hypertension and nephrotic range proteinuria are also indicators of poor renal outcome. By 8 weeks C3 must return to normal, proteinuria might
resolve but it may remain positive for about six months, (microhematuria may continue up to 1-2 years). Less than 5% of patients suffer chronic renal impairment.

References
3) Holm S. La pathogénie de la glomérulonéphrite aiguë post-streptococcique dans de nouvelles lumières APMIS 1988 96: 189-193
CHAPitre 5

NEPHROTIC SYNDROME
GENERAL AND SPECIFIC AFRICAN ASPECTS

Rajendra Bhimma, Durban - South Africa
The nephrotic syndrome (NS) is characterised by a triad of massive proteinuria (> 40mg/m2 per hour or 50mg/kg per day), hypoalbuminaemia (≤2.5mg/dL), and hyperlipidaemia (serum cholesterol >200mg/dL or 6.5mmol/L) (1,2). Other supporting characteristics include the presence of oedema and a raised β2 globulin on serum electrophoresis, although these are not essential for the diagnosis. In physicians managing young children in whom 24 hour urine collections are difficult, the Children’s Nephrotic Syndrome Study Group Consensus Conference recommended the use of the protein: creatinine ratio on a spot early morning sample of urine with a urine protein: creatinine (Up/Ucr) ratio ≥2.0 2.

NS may be classified according to aetiology (primary or secondary), age of onset (congenital, infantile, acquired or late onset NS), or histopathology (minimal change disease, mesangial hypercellularity, focal segmental glomerulosclerosis (FSGS), membranous, membranoproliferative). However the most useful classification for management purposes is to define the disease according to its response to steroids (steroid sensitive or resistant with steroid sensitive disease being further classified into frequent relapses and steroid dependent NS) as patients who are steroid sensitive have an excellent prognosis with preservation of kidney function whilst those that are steroid resistant are more prone to complications with a high risk of having deterioration of kidney function and progression to end-stage kidney disease needing renal replacement therapy. More recently single gene mutations affecting podocyte differentiation and function have been described in steroid resistant disease, predicting unresponsiveness to immunosuppressive therapy (3).

The characteristics of the NS presenting in childhood varies considerably in developing countries compared to developed countries, influenced by environmental factors, infections and ethnic origin, which determine the histological expression of the disease (4). Whilst in developed countries steroid sensitive minimal change disease predominates, the NS amongst black children in Africa does not conform to the model established in other continents (5). Black children have a paucity of minimal change disease and an increasing frequency of focal segmental glomerulosclerosis (FSGS), a high incidence of steroid resistant disease, a less satisfactory outcome and an identifiable causative agent in many (5).

The epidemiology of infectious agents varies considerable as one traverses from the most northern regions of Africa to the south (6). Often there is a strong correlation between the infectious agent and histopathological expression of the disease, and thus the pathology of NS has a strong regional bias (5). Schistosoma haematobium and mansoni, together with Salmonella typhi, have been are the major cause of NS in Egypt, whilst a post-infectious type of proliferative nephropathy is seen in Tunisia (northern Africa) (7). Onchocerca has been a common causative agent in the Cameroons, whilst Plasmodium malariae is the most frequent aetiological agent in the malarial-infested regions of Kenya, Nigeria, Uganda and parts of Ghana (8). In regions where there was a high incidence of hepatitis B, such as in South Africa, prior to the introduction of the hepatitis B vaccine there was a strong correlation with hepatitis B carriage and membranous nephropathy (9). Following the introduction of the Hepatitis B vaccine as part of the routine Expanded Programme for Immunisation in Childhood (EPI), there has been a sharp decline in the incidence of Hepatitis B virus associated nephropathy, with the disease now being almost totally eradicated (10).

The human immunodeficiency virus (HIV) epidemic has been ravaging through Africa for over three decades and Sub-Saharan Africa bears the greatest burden of disease (11). Renal disease has become an increasingly prevalent entity in HIV-infected patients nonetheless, a general lack of surveillance and reporting of renal disease in HIV-infected children exists in most developing regions of the world where HIV is highly prevalent (12). It has been suggested that a possible
contributing factor to the low prevalence of reported HIV related renal diseases in Africa is the poor socioeconomic conditions leading to early death before the onset of nephropathy and end stage kidney disease (13). In one of the largest series of children with HIV-1 related kidney disease reported from Africa, commonest histological finding was FSGS present in 62.7% children (14).

In various regions of the world contemporary literature has documented a rising incidence of FSGS–induced NS which is less likely to be responsive to glucocorticoids, and has a higher risk of progression to end-stage kidney disease (15, 16). In South Africa and other regions of Africa, FSGS is the most common cause of chronic kidney diseases progressing to end-stage kidney disease which has a poor outcome due to failure of early detection, late referral and limited resources leading to failure to provide renal replacement therapy which comes at a high cost (17).

Acquired NS is a disease characterised by recurrent relapses necessitating the use of immunosuppression with its attendant complications. Children with steroid resistant NS have an increased risk of developing end-stage kidney disease with a need for renal replacement therapy. Perhaps the greatest challenge is the risk of recurrence of the disease post-transplant, which is 30-50% for the first graft and higher for subsequent one (18). The nature of the condition and the proportion of familial forms of NS have led to much work on the genetics of NS, with a resultant expansion in the knowledge of genes involved.

Congenital and infantile NS, which occur in children less than one year of age can be either secondary (mostly due to infections in developing countries) or primary. In developed countries over 85 percent of cases that occur during the first three months of life have a genetic basis and a poor outcome (19). Reports of congenital NS from Africa are lacking but unpublished data from Durban, South Africa shows that about 40% of children have congenital NS secondary to cytomegalovirus with one case due of HIV associated nephropathy with collapsing FSGS.

This chapter reports on congenital and acquired NS, with an emphasis on idiopathic NS with respect to its pathogenesis, management, complications and outcomes.

References

CHAPTER 6

IDIOPATHIC NEPHROTIC SYNDROME

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HIGHLIGHTS

✓ The nephrotic syndrome is defined by the combination of an abundant proteinuria superior than 50 mg / kg / day and a lower hypoalbuminemia 30g / l.
✓ The edema is the main symptom often preceded by an infection or an allergic reaction.
✓ The nephrotic syndrome is idiopathic in 90%, at least between the ages of 2 and 10 years.
✓ The initial data for immunologic basis of nephrotic syndrome showed dysfunction of T cells.
✓ The majority of patients (> 90%) with idiopathic nephrotic syndrome are responsive to corticosteroids and have minimal glomerular lesions with histology.
✓ The idiopathic nephrotic syndrome is a disease, which relapses in the majority of cases. In case of relapse the use of the corticosteroid therapy is the rule. The prognosis depends on the cortisol sensibility.

I- INTRODUCTION

Contrary to the adults, to whom it represents only about 25% of cases (14), the most frequent form of nephrotic syndrome (NS) steroid sensitive, at the children, is idiopathic (13). Idiopathic nephrotic syndrome (INS) has an annual incidence of 3 new cases per 100,000 people aged under 18. The boys are affected twice as often as the girls. In these children, histopathological results show minimal glomerular lesions by light microscopy, diffuse mesangial proliferation or GSSF. In electron microscopy, the glomeruli show the fusion of epithelial feet. The evolution of the disease is variable: about a third of them, after a first episode and corticosteroid treatment, returned in remission and only 10 to 20% relapse several months after stopping treatment (Table 1). After three or four episodes of relapse, remission is maintained by corticosteroids. About 40 to 50% of the remaining patients have frequent relapses or shortly after discontinuation of treatment or after a reduction in the dose of corticosteroids is called SN corticosteroid. Although patients with SN dependent on corticosteroids -in as they remain sensitive to steroids - these children and those with frequent relapses, have an excellent prognosis, with minimal risk of progression to chronic kidney disease terminal (1).

II- IMMUNE PATHOGENESIS

Although the precise mechanism of injury of podocytes and -two proteinuria main factors in the pathogenesis of INS remains imperceptible, recent studies suggest a change of immunizing reactions affecting the control of the function of T cells (1). The hypothesis is that the NS is an immune disease that the kidney is the sole target.

A- clinical and therapeutic evidences for an immune disease

The first data for an immunological basis of NS showed a dysfunction of T cells. These cells release cytokines that act on the glomeruli to induce an increase in permeability to plasma proteins. Conventional data for a dysfunction of T lymphocyte are (2):
- The absence of immune deposits in glomeruli in the NIS
- The presence of remission, following infection with measles that suppresses T-cell function
- The particular association with thymic tumors
- The response to immunosuppressive agents that inhibit T cells, such as corticosteroids and inhibitors of calcineurin.
The disorder of the permeability of the filtration barrier that is in connection with a circulating factor related to immune dysfunction lymphocytes. This soluble circulating factor would be the intermediary between the immune system and glomerular wall and has never been identified (3).

B- Mechanism of proteinuria
NS is due to anatomic or functional abnormalities of the glomerular basement membrane, which is normally impermeable to proteins from a certain molecular weight (60 000 daltons) and those negatively charged like albumin. The proteinuria NS is due to the increase in the filtration of macromolecules such as albumin through the glomerular filtration barrier. It consists of endothelial capillary cells fenestrated, glomerular basement membrane and podocyte foot, which are highly specialized epithelial cells. The podocytes connect to form a membrane slot, which is a dynamic structure of molecular ultrafiltration control (6). Filtration of macromolecules through the glomerular filtration barrier is limited by two mechanisms: the selectivity and the load size selectivity. The loss of this selectivity leads the passage of urine protein. If proteinuria is important, it can lead to hypo-serum protein (7).

C- Other symptoms
• The NS is accompanied by sodium retention with a very low natriuresis, lower than 5 mmol / day. The sodium retention classically explained by the decrease in oncotic pressure, resulting in hypovolemia and sodium leak and water in the extravascular area with expansion of the interstitial space.
• The hypovolemia is responsible for stimulation of the renin-angiotensin system with hyperaldosteronism responsible of sodium reabsorption in the distal tubule. This is surely not the only explanation for the retention of sodium, insofar as the blood volume can be normal as well as the plasma aldosterone levels. The exact pathogenesis of sodium retention is not currently fully understood. The hypovolemia also stimulates the secretion of antidiuretic hormone, which stimulates water reabsorption in the collecting duct.
• The edematous syndrome is related to a combination of reduced oncotic pressure and fluid retention, water and sodium diffusing in the interstitial area.
• Plasma disturbances are secondary to urinary albumin leak. The albuminuria causes hypoalbuminemia when the hepatic synthesis is no longer sufficient to compensate for urinary leakage. It seems to be the decrease in secondary oncotic pressure hypoalbuminemia that is the regulatory factor of the hepatic synthesis of albumin and other proteins synthesized by hepatocytes. Serum protein is a markedly reduced and usually increased plasma lipid. Protidemia is often less than 50 g / L and serum albumin falls below 30 g / L. In severe NS, albumin may drop below 10 g / L. Electrophoresis of proteins is not only shows a hypoalbuminemia, but also an increase in alpha-2 globulins and, to a lesser extent, beta-globulins, while the rate of gamma globulin is variable depending on the cause of the NS.
• Hyperlipemia is the consequence of an increase in the synthesis of cholesterol, triglycerides and lipoproteins, and a decrease in the catabolism of lipoproteins secondary to decreased activity of lipoprotein lipase, decreased LDL receptors and an increase of urinary leakage HDL. When the hypoalbuminemia is deep, triglycerides and VLDL are increased.
• The serum sodium is often normal. It can be reduced due to hemodilution secondary to abnormal fluid retention secondary to hypovolemia and inappropriate secretion of antidiuretic hormone.
• Serum potassium levels may be increased in patients with renal failure with oliguria.
• Serum calcium is still low due to the hypo-serum protein. The ionized calcium levels may also be low in case of SN due to a prolonged urinary leakage 25-OH vitamin D. The plasma creatinine levels is usually normal, but may be slightly increased due to a decrease in glomerular filtration.
• Hemoglobin and hematocrit are increased in patients with hypovolemia.
• A microcytic anemia is sometimes observed in SN prolonged, probably due to urinary leakage transferrin.
• The platelet count is often increased and may reach 5 \times 10^5 to 10^6 / mm3.

III- STEROID SENSITIVE NS

A- Clinical Presentation
The disease, which can manifest itself in the first year of life, usually occurs between 2 and 7 years.

1- Oedema
Main symptom, sudden onset, edema is often preceded by an upper respiratory infection or an allergic reaction such as insect bite. Edema becomes clinically detectable at a water retention exceeding 3-5% of body weight. The initial event is generally in the form of a periorbital edema, often misdiagnosed as an allergic event.

Edema is sloping once the child upright periorbital edema decreases while that of the lower extremities increases when in prone position, edema is located in the area of the back and sacrum. Scrotum, penis or lips are the other areas that may become edematous. The edema was mild pressure on the shin area takes the bucket.

Some patients may develop hydrops with periorbital edema marked, farms and swollen eyelids, a marked peripheral edema, abdominal distension due to ascites, edema of the scrotum or vulva and pleural and pericardial effusions. The rapid formation of ascites is often associated with abdominal pain and discomfort. The abdominal pain may also be due to hypovolemia, peritonitis, vascular thrombosis or, more rarely, pancreatitis.

In severe cases, a secondary cardiovascular shock to a sharp fall in serum albumin levels may appear, causing abdominal pain and peripheral circulatory failure symptoms with cold extremities and hypotension (16,17).

2- Other clinical signs
• Appearance of an umbilical or inguinal hernia
• A dyspnea respiratory failure due to pleural effusion or severe ascites. Sometimes respiratory symptoms may be due to pulmonary infection or pulmonary embolism complicating hypercoagulable state associated with SNI
• Non-specific complaints such as malaise, fatigue, headaches, and irritability
• A rare gross hematuria observed in children with glomerulonephritis and who develop SN microscopic hematuria can be noted in 20% of cases of SNI
• Blood pressure is usually normal in most children. Hypertension is common in children with glomerulosclerosis, glomerulonephritis (15) and chronic kidney disease advanced (stage III-V).

B- Biological diagnosis
On initial examination of a child with NS, the physical examination is oriented towards the
accuracy of history, data indicating a possible infection, prior treatment and exclusion of a possible etiology (18). Although edema is generally in an initial sign, the presence of nephrotic proteinuria type and a hypoalbuminemia confirms the diagnosis of NS (Table 2).

1- Urine tests
a- Protein excretion in urine
The quantitative evaluation of the protein excretion is based on the collection of 24-hour urine. The definition of nephrotic proteinuria type corresponds to more than 50 mg / kg / day, but in the early days, the average value may be higher because the urinary protein concentration also depends on the concentration of plasma albumin.

- The urine dipstick
The urine dipstick analysis allows measuring the protein concentration rather than the protein excretion rate and cannot be used to accurately define a nephrotic range proteinuria. The nephrotic type of proteinuria on urine dipstick analysis is defined as 3+ or more protein (300-2000 mg / dl) in the urine, the first morning urine and for 3 consecutive days (1). This is often used as a screening test, pending information from quantitative studies of protein excretion.

b- Urine microscopy
Hematuria may occur in 20% of children with LGM NS, but it is more common in the presence of GSFS and glomerulonephritis (15).

c- Blood Tests
- Serum proteins
The hypo-albuminuria is a defining criterion of NS with usually severe hypoalbuminaemia (<25 g / l). In severe cases of NS, the serum albumin levels are less than 10 g / l (19). The serum globulins are relatively preserved with normal or slightly decreased levels, rates globulins alpha-1 and alpha-2 beta is increased. Gamma globulins vary depending on the etiology of SN, but they are usually lowered into the INS (LGM disease in particular).

- Lipids
Total serum lipids (including cholesterol and triglycerides) are high, with an increase in serum cholesterol levels inversely correlated to the concentration of serum albumin.

- Plasma urea and creatinine
In about 30 to 40% of children with INS, urea and creatinine serum levels may be elevated (blood urea being much higher than the creatinine), which is due, at least in part, to hypovolemia (15, 20). Nephrotic children hyperfiltration with a glomerular filtration rate (GFR) was generally above normal.

- The electrolyte disturbances
  • Hypernatremia and decreased excretion of free water may be present.
  • Hypocalcemia and hypomagnesemia are frequent and sometimes symptomatic patients on diuretics, necessitating replacement therapy.
- Other blood tests

- The blood count may show an increase in hemoglobin and hematocrit due to lower volumes with platelet counts between 500,000 and 1 million per microliter are common. The hemoconcentration and thrombocytosis can contribute to hypercoagulability and thrombotic complications (21).

- In children with SNI, serum complement is usually normal. A lowered C3 is usually found in the membranoproliferative glomerulonephritis, while there are low C3 and C4 in lupus nephritis.

C- Screening for secondary causes of NS

In developing countries, such as Africa, secondary forms of NS are common, so it is important to exclude, based on clinical and laboratory findings. Although the clinical presentation of the SN is stereotypical, some signs during the clinical examination, such as lymphadenopathy, rashes, arthritis, hepatosplenomegaly, chronic lung disease signs and nutritional status with severe weight loss, may suggest a secondary etiology.

The routine screening is common etiologic agents routinely. Studies include viral hepatitis, cytomegalovirus, HIV, Epstein-Barr virus, parvovirus, and herpes simplex type 1 and 2 and other endemic virus according to the region. Screening of bacterial infections is frequently out of streptococcal infections (throat swab, ASLO.), tuberculosis (tuberculin test, chest x QuantiFERON). Screening for autoimmune diseases (systemic lupus erythematous) should include tests for antinuclear antibodies.

D- Pathology

1- Indications for renal biopsy

Majority of patients (> 90%) affected by steroid sensitive have Minimal change disease (MCD) histology (15), hence the term disease to MCD becomes synonymous with cortical sensibility. In most centers, children with a cortical sensibility have no renal biopsy, the latter being reserved only for steroid-resistant children. Renal biopsy is recommended only when another cause, as MCD NSs suspected, such as:

- The age of onset of NS < 1 year or > 16 years
- A low serum complement (C3 complement lowered)
- The presence of gross hematuria
- Persistent severe hypertension
- Injury to the kidney function not attributable to hypovolemia
- Suspicion of a secondary cause of NS.

Renal biopsy can be performed for a reason other than resistance to steroids, such as treatment with calcineurin inhibitors for more than two years (1).

2- Histology

a- Minimal change disease (MGD)

If realized, the biopsy shows optically normal glomeruli without deposits.

Disease observed under an optical microscope, is present at more than 80% of patients with INS (10). In most cases, there is no deposit glomerular immunoglobulin or complement immunofluorescence is negative and the only significant results are only visible by electron microscopy, which shows the retraction of the feet of podocytes.
b- **Focal segmental glomerulosclerosis (FSG)**

In most cases of steroid resistant NS and in 5 to 10% of steroid sensitive NS, histopathological findings show (FSG) (11). In recent years, for reasons still unknown (12) the impact of increased HSF. In optical microscopy, there are hyaline deposits and focal sclerosis lesions (in some glomeruli) and segmental (only a portion of the glomerulus is affected) predominating at the beginning on the glomeruli of the deep cortex. By immunofluorescence, we note the presence of some deposits of IgM and C3 in segmental lesions. FS is most often associated with human immunodeficiency virus, infection with parvovirus or lupus, and quickly progresses to end-stage renal disease (ESRD) in 2 to 3 years not taking no load.

**IV- DIFFERENTIAL DIAGNOSIS**

The rule out other causes of edema that occurred during childhood is required. NS is distinguished from other causes of edema by the presence of hypoalbuminemia and the nephrotic range proteinuria (mass > 50 mg / kg per day or ≥ 40 mg / m² / h). Other causes of edema include: heart failure, protein-energy malnutrition, chronic liver disease, and protein-losing enteropathy in an increase in capillary permeability due to an allergic reaction or a hereditary angioedema. In this case, the edema is generally local.

**V- MANAGEMENT FOR INS**

**A- General**

A presumptive diagnosis can be made based on clinical and laboratory findings, once the NS of secondary forms have been excluded. In over 90% of cases, children with NS to meet the MCD steroids within four weeks (22). Based on this observation, corticosteroids empirically can be started with a high probability of response to steroids in INS, without the need of a kidney biopsy if the following criteria are met:

- Age greater than 1 year and less than 10 years
- Absence of hypertension and hematuria
- Normal serum complement
- Normal renal function.

Patients with cortisol sensibility and fulfilling these criteria typically show a positive trend, and renal biopsy, an invasive procedure not without complications can be avoided in over 80% of them. However, it is essential that the initial episode be managed appropriately, both in steroid dosage and duration of administration, because it is the start of therapy that determines the long-term outcome (23).

**B- Medication**

It aims to:

- Treat acute complications of NS
- Get a complete remission of NS
- Prevent Relapse
- Preventing and treating long-term complications associated with side effects of drugs to ensure the best possible comfort for patients who develop frequent relapses.
The therapeutic means, firstly symptomatic: diuretics, albumin infusion, and other treatments based on the risks and complications (antihypertensive, lipid-lowering, anticoagulant, antibiotic), on the other specific treatments: corticosteroids and immunosuppressors.

1- Treatment of the initial episode
As regards INS, prednisone or prednisolone has proven benefits in the treatment of proteinuria (24). To reduce gastrointestinal side effects, prednisone or prednisolone should be administered after meals, being the use of antacids required only during an outbreak of gastrointestinal symptoms. The treatment comprises administering 2 mg / kg per day (maximum 60 mg) in single or divided doses, for 6 weeks, then 1.5 mg / kg (max 40 mg), generally as a single dose in the morning and every other day, for the next six weeks, and digressive in the 8-12 weeks. The benefits of prolonged corticosteroid therapy should be weighed against the side effects, and if they are pronounced, steroids can be stopped.

The protocol of the French Society of Pediatric Nephrology recommends the back of prednisone at a dose of 60mg / m2 / day in 2 divided doses for 4 weeks. If cortisol sensibility prednisone was increased to 60 mg / m2 on 2 1day in a single dose in the morning for two months and then decreased 15 mg / m2 every 2 weeks to a stop.

2- Treatment of relapse
Most relapses occur following generally minor infections, such as upper respiratory tract, resulting in low-grade proteinuria (1+ 2+ to analyzing the dipstick). Symptomatic treatment of these infections typically leads to a remission of the disease. More pronounced proteinuria (3+ to 4+ on the analysis of strips) requires treatment with steroids. Prednisone or prednisolone is administered at a rate of 2mg / kg / day (maximum 60 mg) until the protein of the urine is negative or no trace for three consecutive days (defining remission).

In developing countries, where many patients can not afford the urine strips or have low levels of literacy, this treatment is administered for 2 weeks, patients being reviewed thereafter. If there is remission, steroid dose is reduced to 1.5 mg / kg per day and then administered every other day for four weeks, then reduced or stopped. There is no evidence that prolonged treatment relapse affect the long-term results.

If, despite two weeks of daily treatment with steroids there is no remission, treatment is continued for two weeks. Patients not achieving remission after 4 weeks of treatment are considered to have a late resistance to steroids. Frequent relapses -less than four relapses / an- require treatment according to the standard protocol described below (22).

3- Treatment of frequent relapses and steroid dependent NS
Patients with frequent relapses or steroid-resistant NS require treatment of longer duration. One method is to maintain in the long term, the patient under treatment with corticosteroids at a dose of 0.3-0.7 mg / kg for 9-18 months. Steroid administration prevents relapses due to minor infections (25). The other strategy is to use non-steroidal agents such as levamisole, cyclophosphamide, mycophenolate mofetil (MMF), inhibitors of calcineurin (cyclosporine and tacrolimus), and rituximab. These agents are indicated above:
- When steroid dose needed to maintain remission of> 0.7mg / kg
- In children developing steroid toxicity.
a- Levamisole
The drug, which can effectively reduce the frequency of relapses and steroid dependence is given at 2 to 2.5 mg / kg for alternative days for 12-24 months. The steroid dose is reduced every 2-4 weeks of 0.25-0.5 mg / kg, every other day, and may optionally be stopped. Although the drug is generally well tolerated, side effects, such as neutropenia, hepatotoxicity, seizures, skin rash may occur. During treatment, the leukocyte count should be monitored every 2-3 months.

b- Cyclophosphamide
It is administered at 2-2.5 mg / kg / day for 8-12 weeks, the cumulative dose should not exceed 168 mg / kg. Given its potential toxicity, repetitive administrations are not desirable. Corticosteroids at a dose of 1-1.5 mg / kg every other day, continued during therapy and stopped after 4-6 weeks. Leukocyte count should be monitored every two weeks and the drug should be stopped if they fall below 3000-4000 / mm (24). Children should be encouraged to increase fluid intake to help with disposal. Side effects include leukopenia, alopecia, nausea, vomiting and hemorrhagic cystitis. The long-term toxicity in the form of gonadotoxicity and malignancy may occur. Chlorambucil, another alkylating agent, is no longer used because of its low safety margin and its high toxicity.

c- Mycophenolate mofetil (MMF)
Increasingly used as an alternative to cyclophosphamide, especially in patients with risk of long-term gonadal toxicity. The main obstacle to its use in developing countries remains its high cost. The treatment consists of 600-1000 mg / m² / day or 20-25 mg / kg / day for two doses for 12-36 months. Prednisone is maintained at a dose of 1 to 1.5 mg / kg administered every other day during treatment, and then reduced to 4-6 weeks. Leukopenia is a common side effect, white blood cell count should be monitored every 1-2 months, provided that the treatment should be stopped if it falls below 4000 / mm. Abdominal pain and diarrhea, which usually disappear after 1 to 2 weeks, are the other side effects observed.

d- Cyclosporine and Tacrolimus
Usually reserved for children not meeting the above agents, cyclosporine A is administered at a rate of 4-5 mg / kg / day for 12-24 months and adjusted to maintain a residual level of 12 hours between 80-120 mg / ml. The dose of tacrolimus is from 0.1-0.2 mg / kg / day, adjusted to a residual level between 7-15 mg / ml. The prednisone is continued at a dose of 1mg / kg, days alternately and reduced to 6-9 months, once remission is achieved.

These two agents with potential acute and chronic nephrotoxicity, renal function should be closely monitored until achieving stability, then continued every 3 months. Cyclosporine can cause side effects aesthetic (hirsutism, enlarged gums), hypertension and hypercholesterolemia. Tacrolimus is also associated with an increased risk of hyperglycemia (especially when there is concomitant administration of steroids), elevated liver enzymes, diarrhea, tremors, headaches and seizures. Considering its long-term nephrotoxicity, renal biopsy is recommended every 3 years, during the treatment.

e- Retuximab
Considering its cost, rituximab is not frequently used and may not be available in some developing countries. Besides the fact that its use is reserved for patients with steroid dependence and not responding to other treatments or in patients with secondary toxicity to other drugs, it should be given in specialized areas. A considerable proportion of patients relapse after treatment with rituximab, most relapses occurring simultaneously with the resumption of the count B-cell
lymphocytes (26). In many cases (27) maintenance therapy with mycophenolate mofetil has proven effective in the prevention of relapse. Side effects include infusion-related reactions (hypotension, fever and chills), serious infections and progressive multifocal leukoencephalopathy (28).

4- Cortico-dependent NS: rational choice of agents against frequent relapses

The two main criteria for deciding between alternative agents for steroids used in the presence of recurrent and corticépendant SN is the absence of significant side effects and long-term effectiveness.

Limited resources, the cost and availability of these agents are important considerations in developing countries. The therapeutic arsenal available agents unfortunately not meet these criteria and the absence of large randomized controlled trials does not offer choices based on evidence related to a particular agent. Considering its lower toxicity compared to other agents, many centers use mycophenolate mofetil as an alternative of choice to steroids. In countries where it is available, levamisole is also increasingly used. However, some experts suggested the use of cyclophosphamide in patients frequently suffering from recurrent non stéroïdo NS-dependent. However, the long-term remission rate is much lower doses and do not induce a significant potential toxicity (24).

Despite its efficacy in maintaining remission, cyclosporine involves prolonged treatment increases the risk of nephrotoxicity. Also, its use is it mainly limited to patients who are unable to be maintained in remission after administration of mycophenolate mofetil or cyclophosphamide, without significant dose of steroids.

C- Other measures

1- General measures

Therapeutic education

The change in lifestyle is essential in management. Psychological support for the child and family may need. The goal of therapeutic education is to enable the child and his entourage to understand the disease and its treatment, to engage with health professionals (the information booklet can be used as support). The main points to be discussed are: monitoring by the family of proteinuria by dipstick testing, information about treatments, adherence to treatment and vaccinations.

2- Diet

A salt-free diet needed during relapse and when the child receives a high dose corticosteroid therapy with intake of salt (NaCl) of less than 35 mg / kg or 1 mmol / kg of sodium. In the other hand, the plan may be expanded when the corticosteroid dose is less than half a milligram per kilogram of weight every other day (Table 3). This restriction will be stopped as soon complete remission. In patients with hydrops, liquids shall be limited, but close monitoring should be instituted to excessive intravascular volume depletion. The protein restriction is implemented only in patients with severe CKD. However, the growth of these patients should not be overlooked.

This treatment is associated with a diet low in sugars (elimination of rapid absorption sugars) and fats by reducing the butter and cheese. Daily supplementation with calcium and vitamin D is recommended.

3- Activity

Most of the children with SN can be supported on an on an ambulatory base and a normal activity is recommended. Hospitalization can be indicated in case:
• On hydrops, especially if it is resistant to outpatient therapy and / or accompanied by respiratory distress, massive ascites, perineal or scrotal edema
• In severe hypertension
• On anuria or oliguria> 24 hours
• In severe acute renal failure
• infections such as sepsis, pulmonary infections, peritonitis, etc.

Table 1: Definitions

- **Remission:** urine protein <4 mg / m² / h or draw / trace for 3 consecutive samples in the early morning.
- **Relapse:** urine protein> 40 mg / m² / h or 3+ or 4+ for 3 consecutive samples early in the morning, having previously been sick in remission.
- **Frequent relapses:** two relapses 6 months to the initial response to four or more relapses within 12 months.
- **Corticosteroid:** two consecutive relapses during corticosteroid therapy or within 14 days after discontinuation.
- **Corticosteroid resistant:** no remission despite daily treatment with prednisolone dosed at 2 mg / kg daily for 4 weeks.


4- **Diuretics**

They should be used with caution in patients with edema very important because by aggravating hypovolemia, they can expose to thromboembolic complications. Diuretics used are furosemide (1 to 2 mg / kg), amiloride (0.5 to 0.7 mg / kg.), Aldactone (5 mg / kg). The use of amiloride or aldactone is against-indicated in patients with impaired renal function. Their administration has to monitor serum potassium. It is advisable to hospitalize the child and to correct any hypovolemia by albumin infusion before using diuretics.

The indications for albumin infusions are rare, and consist essentially symptomatic tachycardia with hypovolemia and hypotension. Infusion at a dose of 1g / kg should be slow in controlling blood pressure.

5- **Prevention and treatment of thrombosis**

The general measures include mobilization avoiding bed rest the correction of hypovolemia the proscription of arterial punctures or deep veins central line.

There is no consensus on anticoagulant therapy, some only major SN with hydrops warrant anticoagulant prophylaxis while moderate forms warrant treatment with aspirin anti-aggregation. For other authors, the presence of one of these anomalies is a risk of thrombotic complications factor justifying anticoagulation: albumin <20 g / l fibrinogen> 6 g / l antithrombin III <70% D-dimer> 1000 ng / ml.

It is recommended initially starting treatment with VKA in combination with a low molecular weight heparin treatment (LMWH) until obtaining the desired INR. The INR rate should be maintained between 2 and 3 until a higher albumin 20 g / l. Increased INR monitoring is required at the start of treatment.
6- infections

a- Bacterial Infection
The pneumococcal vaccine is systematic. In case of relapse contemporary NS infection, it is recommended to treat it in advance and wait a few days before resuming treatment with both a corticosteroid doses. The cure of the infection is sometimes enough to cause remission.

b- Viral Infection
- Chickenpox: rate control of varicella antibodies and if the rate is not protective, vaccination is made when the steroid is administered in a batch mode, every other day, a child in remission. If case of contagion in unprotected child, acyclovir per os 30 mg/kg for 5 days.
- Herpes: When pushed by corticosteroids or immunosuppressive treatment with oral acyclovir.

7- Vaccination
Routine immunization of children -from vivants- virus strains is safe in patients with SN in remission. It is against against indicated for steroid therapy and at least during the month following it. Caution should be exercised in children with recurrent SN that may require up on steroids shortly after vaccination.

The pneumococcal vaccine recommended at the first presentation, must be re every 3-5 years if the patient continues to have relapses.

Annual influenza vaccination is recommended to maintain immunocompromised patients with a serious illness and relapse following an infection.

The vaccine against chickenpox is safe in children with NS in remission and one month after treatment with stéroïdes post-exposure prophylaxis with varicella zoster immune globulin is recommended for non-immune patients. Patients with an infection should be treated with acyclovir and closely monitored.

VI- TO FOLLOW AND LONG-TERM RESULTS OF CORTICOL SENSIBILITY
The frequency depends on the changing profile of the INS. This monitoring includes: monitoring of proteinuria by urine strips in the family, two or three times a week, at least once a week thereafter for the duration of the treatment clinical monitoring (weight, height, blood pressure) biological monitoring, only in case of persistent proteinuria.

The ambulatory monitoring of the child and its response to treatment are very important in the overall management of the SN. Home monitoring of protein in the urine edema is an important component of care. Parents and / or caregivers should be trained to monitor the first protein in the urine in the morning at home with a dipstick. Weight should be monitored and a log must be kept at home, to save the patient’s weight, protein in the urine and the dose of steroids if the child receives.

For edema, weight gain or urine tests + 2 or more protein for more than 2 days, families and patients should contact the health facility. Rapid detection of proteinuria relapse using urine tests at home, may allow early initiation of treatment corticosteroids before edema and other complications arise. Urinalysis at home is also useful for monitoring the response (or non-response) to treatment with corticosteroids.
In the long term, data on outcomes in children with a cortical sensibility, as adults, are limited. Almost all patients retain normal renal function in adulthood. The number of relapses during childhood is the only predictor of relapse occurring later in their lives. In the report prepared by a single center, a single patient, a total of 102 patients developed end-stage kidney disease (8). In these patients, the long-term effects are usually linked to adverse drug effects.

References


CHAPTRÈ 7

COMPLICATIONS OF NEPHROTIC SYNDROME

*Rajendra Bhimma, Durban - South Africa*
HIGHLIGHTS
✓ In the idiopathic nephrotic syndrome (NS) complications may be due to the disease or the treatment.
✓ Complications of NS may be those of primary disease in secondary NS.
✓ The NS increases the risk of developing bacterial infections.

I- INTRODUCTION
Complications of idiopathic nephrotic syndrome NS may arise as a result of the disease itself or secondary to treatment. In children with secondary forms of NS, these may include complications of the primary disease causing the NS. There are five major complications directly related to the nephrotic state in children with idiopathic NS:
• Infection
• Thromboembolism
• Renal impairment
• Anasarca
• Hypovolemia

II- INFECTION
1- Factors predisposing to an increased risk of infection in children with NS include:
• Reduced serum concentration of immunoglobulin (1).
• Impaired ability to make specific antibodies (2).
• Decreased levels of alternative complement pathway factor B and D (3-5).
• Immunosuppressive treatment.

2- The most frequently encountered infections include:
• Upper respiratory tract infections.
• Urinary tract infections
• Peritonitis.
• Pneumonia.
• Acute gastroenteritis.
• Empyema.

Children with NS are at increased risk of developing bacterial infections, especially with encapsulated bacteria, due in part to loss of opsonizing factors (3,5). Ascites and pleural effusions provide a natural culture medium for bacterial growth thus predisposing to pneumonia, empyema, and peritonitis (6). Other serious infections include septicaemia, meningitis and cellulitis (7,8).

Common gram positive organism include Streptococcus pneumonia, Streptococcus haemolyticus and alpha-haemolytic Streptococcus (9,10). In developing countries gram negative organism such as Escherichia coli and Klebsiella pneumonia are also common (6).

The mortality rate in children with infections primarily due to NS has significantly decreased following the use of antibodies and glucocorticoids (11,12). To prevent serious complications and
death from pneumococcal infections, all children with NS should receive pneumococcal vaccine if not previously immunised.

Viral infections, particularly varicella, can cause significant morbidity and mortality in patients with NS (13,15). Vaccination is effective in preventing varicella infections and for children already infectious, treatment with high dose acyclovir is indicated.

III- THROMBOEMBOLISM
Factors that increase the risk of thromboembolism in children with NS include:
• Hemoconcentration
• Immobility (common in patients with anasarca).
• Infection
• Hypercoagulable state (due to thrombocytosis decrease levels of antithrombin III, free proteins, and plasminogen from increased urinary loss) increased platelet activation, hyperfibrinogenemia high molecular weight fibrinogen moieties in the circulation (16,17).

The incidence of thrombotic complications is between 2 and 3 percent (16). Both arterial and venous thrombosis has been reported with common sites being the pulmonary artery, renal vein, deep leg veins, inferior vena cava, and femoral iliac artery (16,17,18). Other sites include the cerebral and meningeal arteries, mesenteric and hepatic veins (16,18,20,21).

Thromboembolic complications may be associated with significant mobility including pulmonary embolism and renal vein thrombosis (22,24). Pulmonary embolic episodes are silent (25). Many pulmonary embolisms in children with NS should be suspected if they present with pulmonary or cardiovascular symptoms and can be confirmed by angiography or radioisotope scanning (26).

Prophylaxis anticoagulation is not recommended unless the patient has a high risk for thrombosis or a previous thromboembolic event. Factors that increase the risk for thrombosis include:
• Serum albumin concentration less than 2g/dL (20g/L).
• Fibrinogen greater than 6g/ L.
• Antithrombin III level less than 70 percent normal.

IV- ACUTE KIDNEY INJURY
Children with NS can have reduced glomerular filtration rate because of one or more of the following mechanisms:
• Hypervolaemia.
• Glomerular injury due to the underlying glomerular pathology.

Progression to chronic kidney (I-IV) leading to end-stage kidney disease (stage V) occurs in some patients, especially in children with SRNS.

V- ANASARCA
This is associated with the following complications:
• Scrotal or vulvar oedema resulting in inability to walk.
• Large pleural effusions and/or ascites leading to impaired diaphragmatic moment resulting in respiratory distress.

VI- HYPOVOLEMIA
This is most common in children with minimal change disease resulting in a decrease glomerular filtration rate. Clinical signs included tachycardia, signs of peripheral vasoconstriction (cold, clammy peripheries with reduced volume pulses), and oliguria. Laboratory findings include raised plasma renin, aldosterone, and norepinephrine levels (7). Typically hypovolemia occurs during the first presentation or a severe relapse. Overzealous use of diuretic, sepsis and gastroenteritis can lead to hypotension and, if severe, shock.

VII- GROWTH
Children with NS can develop growth retardation due to:
a) Malnutrition
b) As a complication of long-term steroid treatment

References


CHAPTER 8

STEROID-RESISTANT NEPHROTIC SYNDROME

Amal Bourquia, Casablanca - Morocco
HIGHLIGHTS

✓ There are several types of steroid-resistant nephrotic syndrome it represents 10% of cases of INS.

✓ This is a heterogeneous entity and recent studies have concluded that under the same term are classes of patients with completely different diseases.

✓ Renal biopsy shows minimal glomerular lesions, usually associated with focal segmental glomerulosclerosis.

✓ Renal failure occurs in over 50% of cases.

✓ A genetic cause should be looked for and there is no cure.

✓ A recurrence occurs in 30% of cases after transplantation.

I- INTRODUCTION AND DEFINITION

Steroid-resistant nephrotic syndrome (SRNS) is one of the most difficult and challenging diseases to treat in children because as of to date there are no sufficient and randomized controlled trials to guide treatment. Patients show a variable response to immunosuppression, adverse effects of prolonged therapy and an increased risk of progression to end-stage kidney disease.

Children are classified as having SRNS if they fail to achieve complete remission after 4 weeks of steroid treatment (2mg/kg/day or 60mg/m² per day). In the Francophone world, SRNS is seen after infusion of three doses of methylprednisolone, at a dose of 1000 mg / 1.73 m² (1) at daily intervals. These infusions are carried out in a hospital over a period of 4 to 6 hours with adequate control of blood pressure and heart rate. Oral corticosteroids are continued at the same dose between the infusions. The steroid resistance is defined by persistent proteinuria eight days after infusions. SRNS is classified as follows: initial resistance, with no remission in the first episode of NS and late resistance with initial response to steroids, but with the appearance of steroid resistance during a relapse (2).

A genetic study should be conducted in search of mutations in certain genes, especially the gene podocin, in particular if there is consanguinity among the parents. In these cases, only symptomatic treatment is referred antiproteinuric indicated, as immunosuppressant have no beneficial effects. These patients fall ill in early childhood, constantly progressing to renal failure and NS does not relapse after kidney transplantation. These features have been found in a number of patients within a family, suggesting autosomal recessive inheritance. Studies using microsatellite markers allowed locating a gene on the long arm of chromosome.

The absence of recurrence after transplantation suggested in this form of NS a primary abnormality of a protein of glomerular basement membrane (GBM) or podocyte cells. In affected families, prenatal diagnosis is possible (3,4).

Other familial forms of steroid-resistant NS are transmitted as autosomal dominant and several genes were located on chromosomes 19 and 11. Mutations in the gene encoding actinin 4, and located on chromosome 19, have recently been reported. This protein interacts with actin, a protein of cytoskeletal protein (5). On the other hand, about 30% of patients with steroid-resistant idiopathic nephrotic syndrome and who progressed to end stage renal disease (ESRD) have a recurrence of proteinuria after renal transplantation.
In these patients, it is likely that a circulating factor intervenes by increasing the permeability of the GBM. The disappearance of proteinuria after treatment with plasma exchange or immunosorbent is also an argument for the role of such a factor in the pathogenesis of nephrotic syndrome (6).

II- HISTOLOGICAL DATA
Approximately 10 to 20% of children with INS have no response to corticosteroids. These children with SRNS (initial or late) should have a renal biopsy before starting specific treatment. Renal biopsy is indicated to confirm that this is an INS:
- Minimal glomerular lesions with often-negative immunofluorescence, and deletion of pedicels of podocytes to electron microscopy.
- A hyper-cellular diffuse mesangial type.
- Lesions of HSF.
The majority develop segmental glomerulosclerosis and focal lesions. The presence of chronic tubulo-interstitial lesions on histopathology is associated with a poor prognosis. Histological diagnosis of other forms of SN, such as a proliferative and membranous glomerulonephritis (membranous nephropathy), is important to decide treatment (2,5).

III- PROGNOSIS
The long-term prognosis of idiopathic nephrotic syndrome is dominated by the risk of progression to end-stage renal disease (ESRD). Approximately 50% of patients with SRNS progress to ESRD. In these patients, treatment is aimed at reducing proteinuria to reduce the complications associated with NS and impaired renal function. Unfortunately, to date there is no effective therapeutic strategy. Children with genetic mutations are typically refractory to immunosuppressive therapy and progress to ESRD in a variable time (7). The analysis of therapeutic results must take into account the fact that the same term of steroid-resistant nephrosis includes patients with different conditions regarding the pathogenic mechanisms.

IV- MANAGEMENT OF SRNS
The prognosis of the disease is closely related to the level and persistence of proteinuria (3,7). The main aim is to achieve complete remission of proteinuria, thereby reducing the complications associated with NS, and preserving kidney function. Even partial remission confers a markedly better prognosis with kidney survival rates over 90% after 5 -10 years (6) Genetic forms of SRNS are usually refractory to all forms of immunosuppressive treatment.
There is no consensus on the therapeutic approach the proposed treatment usually involves a combination of a calcineurin inhibitor (cyclosporine or tacrolimus {off-label prescription} and prednisone.

A- Immunosuppressive therapy
There is no consensus on the treatment of SRNS. Adequate randomized controlled trials have not yet been reported to provide sufficient evidence to guide treatment of SNRS (7,8). To date, the only open multicenter, randomized trial, sponsored by the National Institute of Health, conducted in the United States, compared cyclosporine to mycophenolate mofetil combined with dexamethasone oral pulses (9). In both groups, proteinuria decreased with about 40% complete
or partial remission after one year. Six months later, 24% of 138 patients were still in remission. The study recommended that patients with impaired glomerular filtration rate use mycophenolate mofetil and oral dexamethasone, since the cyclosporine group had a greater decrease in the glomerular filtration rate. Since stopping treatment causes frequent relapses, to maintain remission the combination of mycophenolate mofetil and dexamethasone should also be recommended for children may become dependent on immunosuppression (10).

1- Cyclophosphamide
Administered orally, alone or in combination with oral glucocorticoids, is of limited efficiency in the induction of remission (11). Intravenous cyclophosphamide administered with reduced doses of glucocorticoids, administered at a monthly dose for six months induced remissions in 40% to 50% of patients with SRNS (11,12). The combination of cyclophosphamide and methylprednisolone administered intravenously was reported to induce a 65% remission rate (13), after a six-year follow-up, whereas in other studies, response rates were of the order of 40% (11). In some studies, for cost reduction, dexamethasone was used in place of methylprednisolone.

2- Tacrolimus
Similar to cyclosporine, it has a relatively selective inhibitory action in the CD4 T-helper and it is also a potent suppressor of pro-inflammatory cytokines (8). It has been shown that tacrolimus could reduce proteinuria in patients resistant to cyclosporine, although both agents are calcineurin inhibitors (8.9). Although remission rates between the two agents are similar up to two years, tacrolimus is associated with a lower relapse rate and fewer side effects (9).

3- Rituximab
In several series, it has been reported that rituximab used in combination with glucocorticoids and / or inhibitors of calcineurin, improved the remission rate for patients with SRNS (10,11), while another study showed that this was of no value (12). Serious side effects, such as hypertension, fever, severe infections and progressive multifocal leukoencephalopathy, are commonly observed during treatment with rituximab (11,12).

4- Follow-up
Until a response to treatment is achieved, patients should be monitored every month, then every 2-3 months. For most of them, there was treatment response in the space of 3 to 6 months, and those not responding to a type of therapy may still respond to a different type. There is no consensus as to the optimal duration of treatment. In the case of calcineurin inhibitors, treatment is continued for 2 to 3 years and if the biopsy shows signs of nephrotoxicity, less toxic agents such as mycophenolate mofetil or rituximab can be administered (12,13).

B- Adjuvant treatment
1- Angiotensin converting enzyme (ACE) receptor antagonists and angiotensin 2 (ARA2)
In NS, they are used to decrease proteinuria in case of failure of specific treatments (corticosteroids, immunosuppressants). They are not prescribed as first line therapy.

The reduction of proteinuria in the forms resistant to curative treatment is a key objective of symptomatic treatment of nephrotic syndrome. The use of drugs that interfere with the renin-angiotensin system appears necessary in this case. The medical specialist can offer the prescription of ACE inhibitors and / or ARA2 for this indication.
Antiproteinuric effects even in the absence of hypertension, was observed upon administration of inhibitors of angiotensin-converting enzyme (ACE), used alone or in combination with angiotensin receptor antagonists (ARA2). These are the preferred agents for the treatment of patients with SRNS with hypertension. In patients with side effects such as chronic cough, ACE inhibitors are often replaced by ARA2. It was also demonstrated that the two drugs had reno-protective effects through inhibitory actions on fibrosis, and they thus slow down the progression of kidney disease (13).

2- Lipid-lowering agents

Although there are no controlled studies showing good tolerance there are beneficial effects of lipid-lowering therapy with statins in children with persistent NS. Liver function tests and determination of muscle enzymes (CPK) should be performed at the start of treatment and during follow-up.

C- Kidney Disease Improving Global Outcomes Guidelines (KDIGO)

In order to improve the overall results of kidney disease, the KDIGO has in 2012 developed guidelines for the care of children affected by SRNS (13).

- The calcineurin inhibitors, combined with low-dose corticosteroid therapy should be administered for at least six months. In the absence of response, treatment is stopped. If there is a complete or partial response, treatment is continued for at least 12 months.

- All children should benefit from treatment with ACE inhibitors or if it is not tolerated, treatment with ARBs.

- In patients not responding to the above treatment, mycophenolate mofetil and corticosteroids bolus high-dose-or a combination of the two-is recommended. Alkylating agents are not recommended in children with NSS (10,11). There are insufficient data for the use of rituximab.

- In developing countries, where cost is a major concern, the administration of high-dose methylprednisolone or intravenous cyclophosphamide in combination with cyclophosphamide after 2-4 months, is used as a first line therapy in many centers (12,13,14).

References


CHAPTER 9

GENETIC NEPHROTIC SYNDROME

Amal Bourquia, Casablanca - Morocco
Rajendra Bhimma, South Africa - Durban
HIGHLIGHTS
✓ The congenital nephrotic syndrome is rare (3-6%).
✓ 60% of nephrotic syndromes diagnosed before the age of one year, have a genetic cause.
✓ Most are resistant to immunosuppressive therapy, do not reoffend after transplantation.

I- INTRODUCTION
Congenital nephrotic syndrome (CNS) is a rare form of nephrotic syndrome (NS) that presents at birth or within the first three months of life. It is due in most cases to genetic defects in the components of the glomerular basement membrane or may also present as part of a more generalized syndrome (1). NS presenting after three months up to one year of age is called infantile NS. The precise diagnosis of the glomerular lesion is based on clinical, laboratory and histological criteria (1) (Table 1).

II- GENETICS
The responsibility of the genes is often demonstrated in animal models. Genetic mutations are present in 10-20% of patients with Steroid-Resistant Nephrotic Syndrome (SRNS) and in a greater proportion of patients with familial SN (13% for autosomal recessive and 30% in the autosomal dominant SN (4, 5, 6).

The age of onset of the disease is an important indicator of anomaly located at a particular gene linked to a Steroid-Resistant Nephrotic Syndrome. These genes include the NPHS1, NPHS2, CD2AP, TRCP6 and ACTN4 (7,8,9). The genes expressed in the glomerular basement membrane include LAMB2 while others are expressed in mitochondria (COQ2) or encode transcription factors required for normal development (WT1 Lmx1b) (Table 3). Considering the present state of our knowledge, genetic screening of sporadic steroid-resistant NS should be limited to the entire coding sequence of NPHS2 and exons 8 and 9 of WT1. The mutation analysis of the INF2, profitable only in the autosomal dominant cases can probably be limited to exons 2 through 5 (9,10)

Place and indications for genetic testing
The children with genetic forms of corticoresistant NS (SRNS) is less likely to respond to immunosuppression, it is important to identify in advance, to avoid any excessive exposure to unnecessary immunosuppressive therapy (3, 5,11, 12, 13) and direct genetic counseling. Factors that increase the probability of a genetic form of SNCR include:
• Family history of Steroid-Resistant Nephrotic Syndrome (3.5)
• The appearance of NS in the first year of life (5)
• A parental consanguinity (14)
• The Steroid-Resistant Nephrotic Syndrome

For children in who is suspected a genetic etiology of the NS, considering the number of different abnormalities of the gene (5, 14, 15), a stepwise screening approach is recommended:
• Presentation Age:
  - In congenital SN screening NPHS1 mutations must first be performed before the mutations NPHS2. While among older children, we must first identify mutations NPHS2.
• The presence of extra-renal abnormalities:
  - In children with eye abnormalities, detect first the LAMB2
  - Among those with ambiguous genitalia, start with a screening WT1
• histological injury:
  - Among children with diffuse mesangial sclerosis on histopathology, or WT1 LAMB2 detect mutations.

Since over 85% of children with SNI are sensitive to steroids, that only about one-third of children with SNRS undergo genetic mutations and only 5% of children with SNI suffer genetic mutations, genetic testing to routine for all children with SNI are not currently recommended

III- THE GENETIC FORMS OF CNS

A- Non-syndromic hereditary forms of the NS

1- Forms autosomal recessive

Homozygous or heterozygous mutations compared to the genes encoding podocyte proteins, are the following ones:

• NPHS1 code nephrin. Although mutations in this gene are most often associated with the Finnish type congenital SN, about 10% of children with SNCR that arise before the age of five have mutations in the NPHS1 gene (6,15,16).
• The NPHS2-NPHS2 mutations encodes podocin, an integral membrane protein localized exclusively in glomerular podocytes. Heterozygous and homozygous mutations of this gene are made more frequently found in children with familial SNCR and less often when it comes to sporadic SNCR. To date, no mutation was found among children with steroid-sensitive NS (7,9). There are strong regional variations: 10 to 30% of cases of sporadic SNCR in Middle Eastern and European children with this mutation (8, 10, 14), while among African Americans (15) the frequency of mutations is low. These children have an early onset of the disease, rapid progression to end-stage kidney disease and in some cases associated heart defects (16).
• The NPHS3 mutations are generally associated with a congenital SN and a diffuse mesangial sclerosis (17,18).
• The CD2AP mutations, protein involved in the regulation of the actin cytoskeleton and the endocytic

2- Autosomal dominant form

Three genes are involved in the dominant forms of SNCR with GSSF, and manifesting in adolescents and young adults. This is ACTN4, TRPC6 and INF 2 (19, 20, 21, 22).
• The WT1 mutations in the Wilms’ tumor suppressor gene have been reported in Europe among men (at 5% in men and 9% in women) with sporadic NSS, but no mutation was found in SN sensitive to steroids (18). Patients with idiopathic SNCR objects of this mutation are at increased risk of contracting Wilm's tumor (19).
• The APOL1 gene - variants of this gene in African-American patients are associated with GSSF and HIV nephropathy. This gene is located immediately adjacent to the MYH9 on chromosome 22 (20, 21).
B- Syndromic hereditary forms of the NS

Extra-renal manifestations contribute to identifying the appropriate gene for testing syndromic forms of NSS.

- The LAMB2 mutations are associated with a syndrome characterized by ocular manifestations and diffuse mesangial sclerosis (22, 23, 24).

- Other genetic forms of CNS, mention mutations in the tumor suppressor gene of Wilms (WT1), laminin-β2 genes (LAMB2) gene and phospholipase epsilon (PLCE1).

Suppressor gene of Wilms tumor (WT1) encodes a transcription factor WT1 which plays a crucial role in embryonic kidney development and genitals. The WT1 mutations can cause an isolated CNS or more types of development syndromes (Denys-Drash, Frasier and WAGR syndrome). Patients usually have moderate proteinuria and histopathological results show the diffuse mesangial sclerosis of the glomeruli (24,25, 26).

- The Lmx1b mutations are the cause of the Nail-patella syndrome (bone onycho- splasie). Less than half of patients Nail-Patella’s syndrome develop clinical renal disease characterized by microscopic hematuria and mild proteinuria, usually presenting in adolescence or adulthood (27,28).

- The SMARCAL 1 mutations, associated with Schimke syndrome, characterized by a T-cell deficiency, an original dysplasia, cerebrovascular disease and stunted growth. Patients develop a SNCR with GSSF progressing to ESRD (27,28).

The Middle East and Europe (3), in 50 to 60% of patients with NSS, no underlying genetic abnormality has been identified. In other regions, the prevalence is unknown, it is possible that mutations of unidentified genes are the cause (29,30).
C- Family Forms sensitive steroid NS
There are hereditary forms, often autosomal recessive, diagnostic average age is 4 years.

IV- NONGENETIC FORMS
While genetic forms of CNS are more common in developed countries, in way of the developing countries, non-genetic form of the CNS, usually due to infections are the most common.
- Congenital syphilis causes nephrotic or nephritic syndrome in newborns. Patients present with hematuria and proteinuria but severe SN is rare. Histopathology showed a mixed model with membranous nephropathy and mesangial proliferation. Antimicrobial treatment (penicillin is the drug of choice) led to complete resolution of all kidney injury (31,32).
- Congenital toxoplasmosis presents with proteinuria at birth or during the first three months and leads to the CNS. Ocular and neurological abnormalities associated are common (33,34). Histopathology showed mesangial proliferation with or without FSGS. The treatment of toxoplasmosis in combination with steroids generally leads to remission of proteinuria.
- Congenital cytomegalovirus infections may occur with CNS. Additional renal manifestations such as hepatitis, neurological abnormalities and respiratory illness are common. It is important to note that cytomegalovirus is common during the first months of life, and detection of the virus in patients with CNS does not exclude an underlying genetic abnormality, especially when there are no response to antiviral treatment. Treatment with gancyclovir son and / or valganciclovir causes the remission of the disease (35).
- The CNS has also been reported in association with other congenital infections such as human immunodeficiency virus, the virus of hepatitis B and rubella.
- Non-infectious causes of CNS have been reported in association with maternal systemic lupus erythematosus and neonatal allo-immunization.

V- DIAGNOSIS OF CNS
The most severe forms of CNS presents with anarsaca, severe proteinuria (>20 g/L), and severe hypoalbuminaemia (<10 g/L) in the newborn period. Depending on the aetiology (genetic forms of CNS being most severe), the degree of proteinuria is variable and hence clinical sign of NS may only present after a few weeks of life 2.
Also the true magnitude of proteinuria may only be apparent after partial correction of hypoalbuminaemia with albumin infusions. Microscopic haematuria and leucocyturia are often present. Blood pressure may be low due to the hypoproteinaemia or elevated if severe chronic kidney disease is already present. An increased placental weight (usually >25% of birth weight) suggests NPHS1 mutations but may be seen in other forms of CNS 4. Presence of extra-renal malformations may point to syndromic forms of CNS.
These include genital abnormalities (WT1), eye defects (LAMB2), and neurological disorders (Mowat Galloway). Cardiac ventricular hypertrophy without structural defects is common 2. At the time of diagnosis blood urea and serum creatinine are usually normal but kidney failure invariable develops, varying in time, depending on aetiology.
Unfortunately kidney biopsy may not reveal the diagnosis of CNS as lesions may be focal and biopsy findings may be misleading. Genetic forms of CNS may cause several histopathological
patterns of glomerular lesions, including mesangial expansion, minimal change disease, FSGS, and diffuse mesangial sclerosis. There may overlap of these different entities. Tubular dilatation and interstitial fibrosis and inflammation are also seen in other forms of proteinuric disease. The lack of nephrin and podocin on immunohistochemistry suggests a severe form of CNS that is unlikely to respond to anti-proteinuric therapy.

Prenatal diagnosis in families with a known risk for CNS should be based on genetic testing whenever possible. Elevated alpha fetoprotein in maternal serum and amniotic fluid in the absence of foetal anencephaly or other malformations is strongly suggestive of NPHS1 mutations. However, heterozygous cases of NPHS1 mutations may have temporary elevations in alphafoeto protein. A therefore repeated measurement of amniotic alphafoeto protein before the twentieth month of pregnancy is recommended in cases with high alphafoeto protein (36, 37).

VI- MANAGEMENT OF CNS

Table 2: CNS management of infants with heavy proteinuria

| Protein substitution parenterally (20% albumin infusions, 3-4 g/kg per day of albumin) |
| Nutrition |
| • Hypercaloric diet (130 kcal/kg per day) |
| • Protein Supplementation (Rapeseed/sunflower oil) |
| • A, D, E and water soluble vitamins |
| • Calcium and magnesium supplementation |
| Medication |
| • Anti-proteinuric drugs (angiotensin converting enzyme inhibitors, indomethacin) |
| • Thyroxin supplementation |
| • Anticoagulation (warfarin, aspirin, anti-thrombin III-infusion) |
| • Parenteral antibodies when bacterial infection suspected |


The main objective is to control oedema and uremia, prevent and treat complications such as infections and thrombosis, as well as provide adequate nutrition for optimal growth of the child. In many cases, the ultimate healing therapy is renal transplantation (Table 2) (2).

A- Control oedema

Control of the symptoms of edema is produced by parental albumin infusions using 20% albumin (5-20 mg / kg / day), given in 6 hours with furosemide intravenously (0.5 - 1 mg/kg given midway and at the end of the albumin infusion) is useful for controlling the threatening edema life protein malnutrition, reduced growth, and secondary complications such as thrombosis (2). Thiazide diuretics and aldosterone antagonists are used as adjuvant for the control of edema. The reduction in protein excretion includes administration of angiotensin inhibitors of enzymes and indomethacin. Patients with severe NPHS1 and NPHS2 mutations inhibiting nephrin and podocin expression (stop codons, missense mutation deletions) do not respond to this treatment.

As the disease progresses, the loss of the thyroxine bound to globulin and thyroxine leads to an
increase of thyroid stimulating hormone. This requires substitution of thyroxine, the adjusted dose according to the TSH levels.

The anticoagulation therapy with aspirin and dipyridamole aid is indicated as urinary protein loss due to imbalance of plasma clotting factor levels, which predisposes to hypercoagulability and thrombosis risk. Finnish patients with NPHS1 mutations have also been successfully treated with warfarin 3 to 4 weeks of age. Before surgery or vascular surgery, warfarin is stopped, and antithrombin III (50 IU / kg) is given to temporarily correct the deficit (2).

Urinary losses gamma globulin and complement predispose patients with CNS to bacterial infections. The usefulness of prophylactic antibodies was not shown because it may induce resistant bacterial strains (2). A high index of suspicion is necessary for infection because the symptoms are vague and often masked by signs of focal infection occurring simultaneously. Parenteral antibodies should be started quickly if sepsis is suspected providing cover a broad spectrum. Prophylactic use of immunoglobulin does not reduce the incidence of bacterial infusion, but was used as an adjuvant treatment with antibodies to control sepsis (2). Treatment response was favorable in most cases, if it is started early.

B- Nutrition

A high energy (130 kcal/kg per day) and high protein (3-4 g/kg per day) diet is indicated. Breast milk and milk formulas are first used with excess protein given as caseinbased protein products. Glucose polymers are given to increase energy intake, and a mixture of rapeseed and sunflower oil is given to balance lipid levels27.

Vitamin D supplementation is used starting with 400 iu/day) and adjusted to maintain 25-OH vitamin D levels between 30-100 ng/L. Alphacalcidol is indicated for secondary hyperparathyroidism to present renal osteodystrophy.

Multivitamin preparations are given according to recommended dietary allowances for healthy children of the same age. Supplemental magnesium (50 mg/day) and calcium (500–1000 mg/day) may be required to maintain normal serum levels. Fluid intake is adjusted to 100–130 mls/kg per day. Most patients may require supplemental feeding via a nasogastric tube or stomach peg to ensure adequate energy intake.

Unilateral nephrectomy to reduce protein losses has been done in some centres as a temporizing procedure to decrease the frequency of albumin infusions whilst ensuring adequate kidney function, so that kidney transplantation can be postponed to an older age38. In other centres bilateral nephrectomy and peritoneal dialysis are postponed early to avoid complications. Kidney transplantation is the only definitive treatment for children with severe CNS unresponsive to medical therapy. This is feasible when the child weighs more than 9 kg and the extra-peritoneal placement of the graft is possible 2.

An alternate option is to perform early, pre-emptive kidney transplantation with an intraperitoneal placement of the kidney graft and the native kidney removed at the time of the transplant being done 2.

The use of adult size kidneys in a small recipient is surgically demanding and increases the risk for thrombotic and ureteral complications compared with older recipients. Adequate hydration post-transplant (3000 mls/m2 per day) is necessary to maintain adequate aortic and renal artery perfusion and avoid low flow rates resulting in thrombotic complications and graft loss 39.
The use of immunosuppressant therapy must be optimised to prevent rejection but avoid over suppression with its complication of sepsis and malignancy.

Recurrence of NS in the graft is rare but has occurred in some NPHS1 children who developed anti-nephron antibodies after transplantation. Treatment of recurrence with cyclophosphamide and plasmapheresis is helpful 40. Patients’ survival at 5 years post-transplant is over 90% and graft survival over 80% in this group of patients. Chronic allograft nephropathy is a major problem with most patients needing second kidney transplantation in adulthood (41, 42).

### Table 3: Genetics of Nephrotic Syndrome

<table>
<thead>
<tr>
<th>Gene</th>
<th>Locus</th>
<th>Protein</th>
<th>Location</th>
<th>Inheritance</th>
<th>Phenotype specific histology, if any</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPHS1</td>
<td>19q13.1</td>
<td>Nephrin</td>
<td>Slit diaphragm</td>
<td>AR</td>
<td>Congenital nephrotic syndrome characteristics changes</td>
</tr>
<tr>
<td>NPHS2</td>
<td>1q25-31</td>
<td>Podocin</td>
<td>Slit diaphragm</td>
<td>AR</td>
<td>Congenital nephrotic syndrome or early onset SRNS focal segmental glomerulosclerosis (FSGS)</td>
</tr>
<tr>
<td>PLCE1/</td>
<td>10q23</td>
<td>Phospholipase C epsilon 1</td>
<td>Intracellular</td>
<td>AR</td>
<td>Early onset SRNS diffuse mesangial sclerosis (DMS) FSGS</td>
</tr>
<tr>
<td>NPHS3</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>WTI</td>
<td>11p13</td>
<td>Wilms’ tumor 1</td>
<td>Intracellular</td>
<td>DR</td>
<td>Early onset SRNS, Denys-Drash or Frasier syndrome DMS (Denys-Drash syndrome) FSGS (Frasier syndrome)</td>
</tr>
<tr>
<td>LAMB2</td>
<td>3p21</td>
<td>Laminin-β2</td>
<td>Glomerular basement membrane</td>
<td>AR</td>
<td>Pierson syndrome, early onset SRNS DMS (syndromic) FSGS (isolated)</td>
</tr>
<tr>
<td>CD2AP</td>
<td>6p12.3</td>
<td>CD2 associated Protein</td>
<td>Slit diaphragm</td>
<td>DR</td>
<td>Adult onset SRNS (heterozygous), early onset FSGS ( homozygous), FSGS</td>
</tr>
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<td>ACTN4</td>
<td>19q13</td>
<td>α-actinin-4</td>
<td>Intracellular</td>
<td>DR</td>
<td>Adult onset SRNS (incomplete penetrance slow progression) FSGS</td>
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<tr>
<td>TRPC6</td>
<td>11q21-22</td>
<td>Transient receptor Potential ion channel 6</td>
<td>Cell surface</td>
<td>DR</td>
<td>Adult onset SRNS FSGS</td>
</tr>
<tr>
<td>INF2</td>
<td>14q32</td>
<td>Inverted formin 2</td>
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<td>DR</td>
<td>Adult onset SRNS FSGS</td>
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<td>LMX1B</td>
<td>9q34.1</td>
<td>LIM-homeodomain transcription factor 1β</td>
<td>Intracellular</td>
<td>DR</td>
<td>Nail-patella syndrome, SRNS</td>
</tr>
<tr>
<td>APOL1</td>
<td>22p</td>
<td>Apolipoprotein L1</td>
<td>Intracellular</td>
<td>Complex</td>
<td>Adult onset SRNS (incomplete penetrance) FSGS</td>
</tr>
</tbody>
</table>

References


CHAPTER 10

ALPORT SYNDROME

Ayah Y. Elmaghrabi, Khartoum - Soudan
HIGHLIGHTS

✓ About 80% of people with Alport syndrome (AS) have a form of the disease linked to the X chromosome, caused by mutations in COL4A5.
✓ Hematuria is common in SA nephropathy, which is progressive, leading to proteinuria, hypertension and ultimately kidney failure (KF).
✓ The extra-renal anomalies are often associated such as neurosensory deafness and ocular lesions.
✓ In the AS, the severity and the progression rate towards the KF are related to genotype.

I- INTRODUCTION

Cecil Alport, a South African physician, first described the syndrome as a combination of progressive hereditary nephritis with sensorineural deafness in 1927. Later Alport Syndrome (AS) and Thin Basement Membrane Nephropathy (TBMN) were described as genetic disorders involving type IV collagen, which is the major collagenous component of the basement membranes. Those basement membranes are found in the kidney glomeruli, the skin epidermis, lungs, cochlea and the eye. The mutations in type IV collagen genes are associated with a continuum of disease severity. While heterozygous mutations typically cause isolated, nonprogressive hematuria, the mutations in both alleles of the autosomal type IV collagen genes or hemizygous mutations in the X-linked gene encoding the alpha 5 chain of type IV collagen, result in progressive renal disease that is often associated with sensorineural deafness (1,2,3).

II- GENETICS

The genes for type IV collagen are distributed in pairs on 3 chromosomes. The genes COL4A1 and COL4A2 on chromosome 13 encode for the β1 and β2 chains, COL4A3 and COL4A4 on chromosome 2 encode for the β3 and β4 chains, and COL4A5 and COL4A6 on the X chromosome encode for β5 and β6. The β1 and β2 chains are present in all basement membranes. The β3 and β4 chains are restricted to the basement membranes of the glomerulus, cochlea, and eye. The β5 chain is expressed in the glomerulus, cochlea, eye, and epidermis (1).

About 80% of those with AS have the X-linked form of the disease (XLAS), which is caused by mutations in COL4A5, the gene encoding the β5 chain of type IV collagen. Autosomal recessive Alport syndrome (ARAS) accounts for about 15% of affected individuals and arises from mutations in both alleles of COL4A3 or COL4A4, which are the genes encoding for β3 and β4 chain of type IV collagen. The remainder of those with AS, about 5% has autosomal dominant Alport syndrome (ADAS) due to heterozygous mutations in COL4A3 or COL4A4. However, the majority of those with heterozygous mutations of COL4A3 or COL4A4 have a form of familial hematuria that is usually nonprogressive: TBMN (1).

The autosomal recessive form cases has been known since several years, on the contrary, the autosomal dominant form has only recently been identified in some families. The autosomal dominant form is caused by mutations in COL4A3 and COL4A4 in the chromosome region 2q35-q37 (4). Children with AS usually have normal development and intelligence. However, a rare contiguous gene-deletion syndrome involving chromosome Xq22.3 has been described this has been named Alport syndrome and mental retardation (ATS-MR) (5).
III- CLINICAL FEATURES

AS and TBMN are common causes of persistent haematuria in children. They can be indistinguishable in early childhood, particularly with the limited diagnostic resources available for pediatric nephrologists practicing in the developing countries of Africa.

A- Renal Manifestation

Though hematuria is common to both conditions, the nephropathy of AS is progressive, leading to proteinuria, hypertension and ultimately renal failure (6). Thus recognition of AS is more important because of its inevitable progression to end-stage renal failure and the ability of treatment to slow the rate of deterioration.7 This will be discussed under the genotype-phenotype correlations.

B- Extra-renal Manifestation

The renal manifestation in individuals with AS is frequently associated with extra-renal abnormalities, such as sensorineural deafness and ocular lesions (6).

1- Cochlea

Bilateral high-frequency sensorineural hearing loss usually begins by late childhood or early adolescence. In the early stages of the disease, hearing loss is detectable only by means of audiometry. As hearing loss progresses, it extends to the low frequencies, including those of human conversation, and patients require hearing aids.

2- Eye

Ocular abnormalities have been reported in 9%-82% of Alport syndrome patients. They are rare in childhood and increase in frequency and severity with age. The types of ocular defects described mostly involve the lens, the retina and more rarely the cornea. The most common changes are anterior lenticonus and perimacular retinal flecks (8). Anterior lenticonus is a conical or spherical protrusion of the anterior surface of the lens into the anterior chamber. Kaimbo et al reported an AS case in 1992 which has not been previously described in the Black African or Zairian ophthalmological literature. Their patient had an anterior lenticonus with microopacities of the lens his fundus had albipunctatus-like appearance with midperipheral retinal flecks and macular hole, in addition to other features of AS (9).

3- Other Associated Abnormalities

The Alport syndrome-diffuse leiomyomatosis association can be defined as a hereditary disease of type IV collagen combining features of AS and leiomyomatosis involving oesophagus (diffuse type), tracheobronchial tree, and genitals (only in women). This entity is transmitted as an X-linked dominant trait. Mutations of both the COL4A5 and COL4A6 genes, located head to head in Xq22 encoding the alpha 5 and alpha 6(IV) chains are responsible for the abnormalities (10).

IV- GENOTYPE-PHENOTYPE CORRELATIONS

As the severity and the rate of progression to renal failure in AS are related to the genotype they are discussed further here under the genotype-phenotype correlations.

Jais et al in their study of 195 families with AS, found that all male patients were hematuric, and the rate of progression to end-stage renal failure and deafness was mutation-dependent. While in Large deletions, nonsense mutations, or small mutations changing the reading frame conferred to affected male patients a 90% probability of developing end-stage renal failure before 30 year
of age, the same risk was of 50 and 70%, respectively, in patients with missense or splice site mutation (11). And in the large study done by Bekheirnia et al among males with XLAS, a genotype–phenotype correlation for both renal and extrarenal manifestations of the XLAS was observed. Their results indicate that deduced premature termination of the collagen β-5 (IV) chain associated with large and small deletions and truncating or splice mutations cause the most severe clinical phenotype. In contrast, missense mutations result in a less severe phenotype. Notably, mutations at the 5' end of the gene have the greatest effect and the worst prognosis. The rate of progression of both renal and extrarenal manifestations of XLAS was associated with the type and location of the underlying mutation (12). And COL4A3/COL4A4 mutations may range from monosymptomatic hematuria (BFH) to severe renal failure (AS), depending on the gene dosage (13).

Kharrat et al, in their study of a large Tunisian family conclude that autosomal dominant Alport’s syndrome, follows a rare mode of inheritance and exhibits a milder phenotype than usually observed in classic X-linked Alport's syndrome. They also recommended doing a larger study to confirm the frequency of this mode of inheritance (4). And finally Hertz et al also found that truncating mutations, comprising nonsense mutations, frame-shifts, and larger structural rearrangements cause a juvenile form of the disease with a mean age at ESRD of 21.6 years, compared to 33.1 years in patients with a non-truncating mutation (14). Thus genetic analysis seems to be a better prognostic indicator than either renal or skin biopsy (12).

V- DIAGNOSTIC CONSIDERATION

Molecular approaches may eventually supersede histological methods for diagnosis of AS and TBMN but currently renal biopsy and skin biopsy are the tools most clinicians rely upon for diagnosing these conditions, 1 especially in the African continent.

The presence of 3 of the following 4 proposed diagnostic criteria is usually used to establish the diagnosis of Alport syndrome (15):

1. Family history of hematuria, progressing mostly in males to end-stage renal disease (ESRD)
2. Thickening and splitting of the glomerular basement membrane detected by electron microscopy
3. Progressive, high frequency, sensorineural deafness
4. Anterior lenticonus and perimacular flecks

Electron microscopy is essential to diagnosis of TBMN and Alport syndrome on renal biopsy, although electron microscopy alone is of limited value in distinguishing between TBMN, the heterozygous carrier state of X-linked Alport syndrome, autosomal recessive Alport syndrome, and even early stages of X-linked Alport syndrome. Using a combination of electron microscopy and immunohistology for β-3 (IV) and β-5 (IV) enables pathologists to definitively diagnose these disorders on renal biopsy in most cases (16).

White et al in reviewing 130 biopsies found that, the grades of GBM attenuation did not correlate with either age at biopsy or sex. In 11 biopsies with atypical lamina densa changes in thickened GBM segments, there were no differences in clinicopathological correlations compared with classical biopsies. Their data indicates that diffuse GBM attenuation can be an ultrastructural variant of the Alport nephropathy, but do not support the contention that it is the initial lesion (17).

We have to keep in mind that the electron microscopy is not available for most of the clinicians practicing in Africa. In addition to that late presentation with already small and shrunken kidneys is common, thus renal biopsy would not be obtained. Although the molecular approaches will
eventually become the gold standards, it is unfeasible in most of the developing countries of Africa, due to the unavailability, the cost or both.

VI- TREATMENT

A- Angiotensin-converting enzyme (ACE)

It’s inhibitors and/or angiotensin 2 type 1 receptor antagonists reduce urinary protein excretion and preserve glomerular filtration in pediatric patient with AS (18). And the recent “Expert Guidelines for the Management of Alport Syndrome and Thin Basement Membrane Nephropathy” by Savige et al recommends that Males with X-linked AS and Individuals with ARAS should be managed lifelong by a nephrologist and have their risk factors for progressive renal failure optimized, including careful management of hypertension, proteinuria, and dyslipidemia. Treatment with ACE inhibitors, even before the onset of proteinuria, especially in individuals with genetic mutations or a family history consistent with early-onset renal failure, may delay the onset of end-stage disease and improve life expectancy. Affected individuals should avoid ototoxic medication and industrial noise exposure to minimize further hearing loss (7).

B- Renal Replacement Therapy

Successful kidney transplantation from a living donor is the most effective renal replacement therapy for children with end-stage renal disease due to AS. However two aspects of Alport syndrome set the disease apart from other causes of terminal renal failure. First, an understanding of the genetics of AS is needed to make appropriate decisions regarding potential related kidney donors to Alport patients requiring renal transplantation. Second, renal transplantation for AS may be complicated by post-transplant anti-GBM nephritis, a problem that is nearly unique to this disease (19). Post-transplant anti-GBM nephritis occurs in about 3% of transplanted patients.

There are many challenges facing nephrologists caring for children with end stage renal disease in Africa. El-Husseini et al, in their study among 292 children and adolescents (20 years old or younger) who received live-donor renal allotransplants in one center, hereditary nephritis (Alport’s syndrome) compromised 20% of the study population, and they concluded their study stating that “Despite long-term success results of pediatric renal transplantation in a developing country, there is a risk of significant morbidity” (20,21).
THIN BASEMENT MEMBRANE NEPHROPATHY

TBMN was initially named Benign familial hematuria (BFH) was characterized by its autosomal dominant inheritance, thinning of the glomerular basement membrane (GBM) and normal renal function (22), TBMN is the most common cause of persistent glomerular bleeding in children and adults, and occurs in at least 1% of the population (23).

I- GENETICS

About 40% families with TBMN have hematuria that segregates with the COL4A3/COL4A4 locus, and many COL4A3 and COL4A4 mutations have now been described. These genes are also affected in autosomal-recessive Alport syndrome, and at least some cases of TBMN represent the carrier state for this condition. Families with TBMN in whom hematuria does not segregate with the COL4A3/COL4A4 locus can be explained by de novo mutations, incomplete penetrance of hematuria, coincidental hematuria in family members without COL4A3 or COL4A4 mutations, and by a novel gene locus for TBMN (23).

II- CLINICAL FEATURES

While AS is progressive nephropathy associated with extra-renal manifestations, TBMN is clinically defined by the absence of the extra-renal findings and the development of proteinuria or hypertension is unusual (6). But it cannot be clinically differentiated from the initial stages of AS (22).

TBMN clinical course is usually benign. However, some adults with TBMN have proteinuria >500 mg/day or renal impairment (23). Thus in a subset of patients, a benign familial hematuria disorder, may not be so benign. Proteinuria and hypertension in patients with TBMN appear to be risk factors for the development of progressive renal insufficiency (24). Also it is shown that heterozygous COL4A3 missense mutations, when symptomatic, can be associated with a broad range of phenotypes, from familial benign hematuria (TBMN) to the complete features of AS (25).

III- PATHOLOGY

The abnormal gene product produces a defect in collagen that interferes with the normal meshwork architecture of the GBM. Thus, the genetic defects in Alport’s syndrome and TBMN are similar, resulting in abnormal GBM formation however, the clinical sequelae are different, since patients with Alport’s syndrome have progressive renal insufficiency, whereas patients with TBMN are thought to have a more benign course (24).

IV- DIAGNOSTIC CONSIDERATION

Alport syndrome and TBMN may be clinically and ultrastructurally indistinguishable, and some clinicians mistakenly use the term TBMN in females and boys with X-linked Alport disease. The distinction between Alport syndrome and TBMN is, however, critical because of the different risks of renal failure and other complications for the individual and their family members, but the genetic testing for COL4A3 and COL4A4 mutations is not usually required for the diagnosis of TBMN. Screening for COL4A5 mutations to exclude X-linked Alport syndrome is often more
important. Individuals suspected of having TBMN should undergo renal biopsy if they have atypical features (proteinuria in adults >1.0 g/d or renal impairment [estimated GFR < 90 ml/min per 1.73 m2]), or if X-linked Alport syndrome or a coincidental glomerular or tubulointerstitial abnormality cannot be excluded (7).

V- TREATMENT
In the absence of significant proteinuria and renal dysfunction, patients can be reassured and safely followed up by periodic measurements of blood pressure, urinary protein excretion, and renal function (24). Individuals with poor prognostic indicators (hypertension, proteinuria, renal impairment) should be managed by a nephrologist, and treatment should include an ACE inhibitor to delay the onset of renal failure. Other individuals with TBMN may be reviewed every 1–2 years for hypertension, proteinuria, and renal impairment by their primary care provider (7).

VI- CONCLUSION
Alport syndrome is a hereditary, progressive, hematuric nephropathy characterized by glomerular basement membrane abnormalities with frequent hearing defects and ocular anomalies. The disease is associated with mutations in genes encoding the $\beta_3$, $\beta_4$, or $\beta_5$ chains of type IV collagen.

The published studies about AS in Africa are limited. The frequency of the disease is based on extrapolated data in most of the African countries and the molecular aspect of the disease is largely unknown. The burden of the disease might be more than expected. It was mentioned previously by El-Husseini et al, AS compromised 20% of the transplanted patients population (21) and this much higher than expected considering the prevalence of AS. In Sudan hereditary nephropathy compromised 6.8% of the 205 children diagnosed with chronic renal failure, and in another clinico-pathological study Alport’s syndrome accounted for 1.8%, among 321 children diagnosed with nephritis/nephrosis (26,27).

The study from Tunisia by Kharrat et al (4) focused on the genetic/molecular aspects of the disease and added valuable insight into the pattern of AS in an African population.

Finally the many different animal models for AS have provided invaluable tools to study the mechanisms leading to progressive deterioration of the glomerular basement membrane and ultimately to renal failure, and promising targets for functional studies, which is an important resource for gene therapy studies, thus makes AS a reliable candidate for future gene therapy in humans (28,29).

In conclusion both clinical and basic science studies of AS are limited in Africa, leaving a whole wealth of knowledge about the genetics and the underlying etiology of the disease undiscovered. Conducting studies in different parts of the globe

Thus international research collaboration needs to be established in Africa with the developed world to evaluate the natural history and molecular genetic basis of Alport syndrome. This will both enhance our understanding of this condition and contribute to an international database, ultimately generating larger scale international studies for effective therapies.
References

PART III

GENERAL KIDNEY DISEASES

CHAPTER 11

LUPUS NEPHRITIS

Ashraf Bakr, Ayman Hammad, Ahmed M El-Refaey
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HIGHLIGHTS

✓ 60-90% of children with SLE develop renal impairment during their illness.

✓ Lupus nephritis (LN) may be expressed by isolated microscopic haematuria associated with proteinuria, nephrotic syndrome and progressive renal failure.

✓ Renal biopsy should be performed in all patients with proteinuria ≥ 0.5 g/d to specify the severity of the damage and guide the initial treatment.

✓ Six different classes of LN were identified. The histological damage can change from one class to another over time in the same patient.

✓ The pathogenesis is complex and genetic and environmental factors play an etiological role.

✓ The renal prognosis in five years, from the time of diagnosis, is extremely variable.

I- PATHOLOGY OF LUPUS NEPHRITIS

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by loss of immune tolerance to a variety of self-antigens with subsequent production of autoantibodies (1). The pathogenesis of the disease is complex. Genetic and environmental factors play an etiologic role (2). About 60 – 80% of children with SLE have renal affection during their disease course (3). Renal affection ranges from asymptomatic urinary findings up to renal failure. Renal affection is more common in children than adults with SLE( 4). Renal disease occurs within two years from disease onset in 90% of paediatric patients (5). In lupus nephritis (LN), the severity of renal involvement is dependent on activated T cells and macrophages, which secrete a variety of inflammatory mediators into the kidney including cytokines and growth factors (6,7).

II- HISTOPATHOLOGY OF LN

LN was histopathologically classified for the first time by the World Health Organization (WHO). The WHO classification was based mainly on the histological changes found by light microscopy examination (8). Six different classes of LN were identified in this classification system (Table 1). The “proliferative” forms of the disease included classes III and IV. Proliferative glomerulonephritis is defined by the presence of proliferating endocapillary cells within the glomerular capillary loops. Patients with WHO class III LN, or focal proliferative glomerulonephritis, have less than 50% of the volume of a single glomerulus or less than 50% of their total number of glomeruli with endocapillary proliferation. Patients with severe class III may have extracapillary proliferation (crescents) or focal necrosis (karyorrhexis) (9).

WHO class IV, diffuse proliferative, LN patients demonstrate more extensive histopathology than class III. Class IV is defined when more than 50% of glomeruli have proliferative lesions. Class IV patients usually demonstrate extensive crescents and karyorrhexis. It should be remembered that both crescents and karyorrhexis are not required for staging a particular biopsy as class III or class IV, but they are considered as predictors of patients who develop progressive renal disease(10). Class I is characterized by normal glomeruli by light microscopy but mesangial immune deposits by immunofluorescence(8). Class II mesangial proliferative LN shows mesangial hypercellularity and immune deposits(11). Membranous LN (WHO class V) is defined by the presence of thickened capillary loops and mesangial expansion, but without significant crescent formation or endocapillary proliferation(12). Class V can be subdivided into three other forms. Patients with class Vb have membranous features in addition to mesangial proliferation, while class Vc and Vd
demonstrate focal or diffuse endocapillary proliferation (12). Class VI represents the advanced stage of LN where most glomeruli are sclerotic(8). WHO class I-II histology was found in 25 – 26.9% while class III-IV histology was reported in 65 – 72.6% of paediatric LN, supporting a high frequency of severe renal involvement in paediatric SLE (13, 14). Class V accounted for about 9% of patients (13).

Histological signs of activity and chronicity were proposed in 1976 (15). Later, activity and chronicity indices were introduced. Active lesions are potentially reversible with treatment and include cellular crescents, endocapillary proliferation, fibrinoid necrosis & karyorrhexis, hyaline thrombi & wire-loops with subendothelial immune deposits, glomerular leucocyte infiltration and interstitial mononuclear cell infiltration. Each lesion is graded 0–3 (with exception of necrosis and cellular crescents which are graded 0–6) to give a total activity index ranging from 0 to 24. On the other side irreversible lesions do not respond to treatment. They include glomerular sclerosis, fibrous crescents, tubular fibrosis and interstitial fibrosis. Each lesion is graded 0–3 to give a total chronicity index ranging from 0 to 12 (16).

Table 1: World Health Organization (WHO) classification of lupus nephritis

<table>
<thead>
<tr>
<th>WHO Class</th>
<th>Class I</th>
<th>Class II</th>
<th>Class III</th>
<th>Class IV</th>
<th>Class V</th>
<th>Class VI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name</td>
<td>Normal</td>
<td>Mesangial expansion</td>
<td>Focal proliferative</td>
<td>Diffuse proliferative</td>
<td>Membranous</td>
<td>Sclerosing</td>
</tr>
<tr>
<td>Light microscopy</td>
<td>Normal</td>
<td>Mesangial expansion</td>
<td>&lt;50%Glomeruli endocapillary proliferation</td>
<td>&gt;50%Glomeruli endocapillary proliferation</td>
<td>Thickened capillary loops</td>
<td>Interstitial fibrosis</td>
</tr>
<tr>
<td>Normal</td>
<td>IgG</td>
<td>+/-Karyorrhexis crescents</td>
<td>+/-Karyorrhexis crescents</td>
<td>Absent proliferation/crescents</td>
<td>IgG mesangial subepithelial</td>
<td>IgG/IgM mesangial</td>
</tr>
<tr>
<td>Immuno-fluorescent microscopy</td>
<td>Immune complex deposits</td>
<td>IgG/IgM Mesangial staining</td>
<td>IgG-IgM to full house</td>
<td>IgG-IgM to full house</td>
<td>IgG mesangial subepithelial</td>
<td>IgG/IgM mesangial</td>
</tr>
<tr>
<td>Electron microscopy</td>
<td>Immune complex deposits</td>
<td>Mesangial dense deposits</td>
<td>Mesangial subendothelial deposits</td>
<td>Mesangial subendothelial/ subepithelial</td>
<td>Mesangial subepithelial</td>
<td>variable</td>
</tr>
</tbody>
</table>

The international society of nephrology/renal pathology society (ISN/RPS) has recently revised the classification of LN with the objectives to standardize definitions and emphasize clinically relevant lesions Table 2 (17). In this last classification Class IV was sub classified according to the distribution of the lesions into: segmental (IV-s) - affecting less than 50% of the glomerular tuf- or global (IV-g) - affecting more than 50% of the glomerular tuft. In diffuse segmental lupus nephritis more than 50% of the glomeruli show segmental lesions of endocapillary proliferation. In diffuse global lupus nephritis more than 50% of the glomeruli show global and diffuse endocapillary proliferative lesions. In addition, active lesions are often seen such as necrotic lesions, karyorrheks, hematoxylic bodies, leucocytic infiltrates, wire-loops and hyaline thrombi. Tubulointerstitial mononuclear cell infiltration is common. Immunofluorescence and electron microscopy show diffuse mesangial and more or less extensive subendothelial immune deposits (18).
In pure class V there is thickening of the glomerular capillary walls with presence of global or segmental continuous subepithelial immune deposits separated by “spikes,” and little or no cellular proliferation with or without mesangial alternations. It may occur in combination with lesions of class III or IV (19). In the ISN/RPS classification the ‘normal’ class I category was replaced by ‘minimal mesangial lupus nephritis’ (18). Although the ISN/RPS classification does not require the use of classic activity and chronicity indices as it depends mainly on the proportion of glomeruli with active and chronic lesions however some clinicians still include these indices as they find this information useful especially when repeated renal biopsies are compared (20) by immunofluorescence, IgG deposits are dominate, mostly IgG1 and IgG3. IgA and IgM are also present, as well as complement components, C4, C1q and C3. Full house is a term used to indicate the positivity for all three Ig classes as well as C3, C4 and C1q, which is highly suggestive of LN. In class IV biopsies fibrin deposits may be found (18).

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Minimal mesangial lupus nephritis</td>
</tr>
<tr>
<td></td>
<td>Normal by light microscopy but mesangial deposits by immunofluorescence</td>
</tr>
<tr>
<td>Class II</td>
<td>Mesangial proliferative lupus nephritis</td>
</tr>
<tr>
<td></td>
<td>Mesangial hypercellularity and mesangial deposits by immunofluorescence</td>
</tr>
<tr>
<td>Class III</td>
<td>Focal lupus nephritis</td>
</tr>
<tr>
<td>Class III (A)</td>
<td>with active lesions</td>
</tr>
<tr>
<td>Class III (B)</td>
<td>with active and chronic, sclerosing lesions</td>
</tr>
<tr>
<td>Class III (C)</td>
<td>with chronic, sclerosing lesions</td>
</tr>
<tr>
<td>Class IV</td>
<td>Diffuse lupus nephritis</td>
</tr>
<tr>
<td>Class IV-S (A)</td>
<td>Diffuse segmental proliferative lupus nephritis with active lesions</td>
</tr>
<tr>
<td>Class IV-G (A)</td>
<td>Diffuse global proliferative lupus nephritis with active lesions</td>
</tr>
<tr>
<td>Class IV-S (A/C)</td>
<td>Lupus nephritis diffuse segmental proliferative and sclerosing</td>
</tr>
<tr>
<td>Class IV-S (C)</td>
<td>Lupus nephritis diffuse segmental sclerosing</td>
</tr>
<tr>
<td>Class IV-G (C)</td>
<td>Lupus nephritis diffuse segmental sclerosing</td>
</tr>
<tr>
<td>Class V</td>
<td>Membranous lupus nephritis</td>
</tr>
<tr>
<td></td>
<td>Global or segmental subepithelial immune deposits</td>
</tr>
<tr>
<td></td>
<td>Lupus nephritis in combination with class III or class IV with sclerosing lesions</td>
</tr>
<tr>
<td>Class VI</td>
<td>Advanced sclerosing lupus nephritis</td>
</tr>
<tr>
<td></td>
<td>&gt;90% sclerosed glomeruli without active lesions</td>
</tr>
</tbody>
</table>
III- CLINICO-PATHOLOGIC CORRELATION

Urine analysis can be normal or reveal microscopic haematuria and mild to moderate proteinuria in class II LN (11). The clinical presentation of class III LN depends on the extent of the pathologic changes. When small segmental lesions are found in less than 20% of the glomeruli, patients usually have mild renal affection with low-grade proteinuria without nephrotic syndrome and normal GFR (21). On the other side the clinical manifestations are more severe with active urine sediment, nephrotic syndrome, hypertension and even moderate renal insufficiency when more than 40% of the glomeruli are affected and the prognosis in this case is similar to that in class IV LN (22). The clinical symptoms in class IV are often severe usually in the form of hypertension, haematuria with RBCS casts, nephrotic syndrome, and moderate or severe renal impairment (8). Moderate proteinuria accompanied by haematuria in 50% of cases is reported in class V LN patients. Nephrotic syndrome usually occurs in these patients. One quarter of the patients have moderate renal failure and hypertension (13).

IV- PROGNOSIS

The five-year kidney survival from the time of diagnosis is highly variable among different studies, ranging from 44–93% (23, 24). Several studies have been performed in childhood SLE nephritis, to investigate the prognostic relevance of demographic, clinical, and histopathological features. Although the results of these studies regarding factors affecting renal outcome remain controversial, male sex, black race, age at onset before puberty, persistent hypertension, impaired renal function, nephrotic syndrome, anaemia, class IV nephritis and increased histological index scores have been identified as significant prognostic parameters (25, 26). Prognosis of class II LN is generally excellent except if transformation to a more severe form has occurred (11). The long term renal prognosis of patients with class III LN is generally considered to be better than class IV however, Najafi et al reported that only 52% of patients with class III LN versus 75% for patients with class IV had functioning kidney after follow up period of 10 years (27). The extent of the pathologic changes in class III LN was also found to have a prognostic impact. When small segmental lesions are found in less than 20% of the glomeruli, patients usually have favourable outcome with less than 5% risk of progression to end stage renal failure after 5 years (21). On the other side when more than 40% of glomeruli are affected the prognosis becomes similar to class IV LN (22). More than 70% of patients with class IV LN progress to end-stage renal disease within 5 years if significant immunosuppressive therapy was not received (28). The long-term renal survival of class V lesions is mainly determined by the extent of associated proliferative lesions. Patients with lupus membranous nephropathy and concurrent proliferative lesions had significantly reduced 10-year survival. Patients with WHO class V and focal proliferative lesions had 55% in comparison to those with associated diffuse proliferative lesions who were found to have only 20% 10-year survival, respectively (29). Activity and chronicity scores has gained wide acceptance as prognostic markers in LN. When compared to activity scores chronicity index was found to be more predictive for outcome of LN (30).

V- INDICATIONS OF RENAL BIOPSY

At the initial presentation of any lupus patient the presence of abnormal urinary findings renal impairment or clinical evidence of renal disease are indications for renal biopsy (31). Most of clinically asymptomatic renal patients have mild to moderate histological changes usually in the
form of mild mesangial deposits and proliferation but some may rarely have diffuse proliferative
glomerulonephritis (silent lupus nephritis). It was generally found that silent proliferative LN
has good prognosis and thus renal biopsy is not indicated routinely in clinically asymptomatic
patients (31). Transformations from one class to another are possible, either via aggravation or
regression of the histological lesions. Repeated renal biopsy may thus help to detect changes in
the histopathology of LN that may need modification in therapy. Unexplained persistent worsening
of the clinical symptoms (proteinuria, renal insufficiency) are indications of repeat renal biopsy.
Repeat renal biopsy is thus mainly indicated in: refractory nephrotic syndrome or persistent active
urine sediment despite adequate therapy, recurrent proteinuria and/or haematuria after remission
or an unexplained increase in serum creatinine (32). LN is frequently focal and thus large tissue
samples are required to give a more accurate assessment of the extent of glomerular involvement.
Biopsy should contain a minimum of 10 glomeruli to adequately rule out a focal lesion (33).

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CHAPitre 12

RENAL DAMAGE IN THE SICKLE CELL DISEASE

Djénèba Diallo, Bamako - Mali
HIGHLIGHTS
✓ Sickle cell anemia (sickle cell disease) is an autosomal recessive genetic disease.
✓ It is characterized by the presence of hemoglobin S (HbS) as a result of the substitution of a glutamic acid by a valine at position 6 of the β-globin chain of hemoglobin A chromosome 11.
✓ The sickle cell disease or sickle cell syndrome (MDS), includes homozygosity SS, double heterozygosity thalasso-SC and sickle cell β-thal, double heterozygosity SO Arab, Punjab SD, and SE.
✓ It is a child’s illness, life expectancy depends on the quality of the therapeutic management. It is manifested clinically by vaso-occlusive events, a chronic hemolytic anemia with episodes of acute exacerbation, and bacterial infections.
✓ The sickle cell disease is most often found at the age of three months by vaso-occlusive crises (CVO) or syndrome “hands feet” in infants with dactylitis (painful swelling of the fingers and feet), infections, frequent and severe (bacterial pneumonia, osteomyelitis, meningitis, septicemia), acute splenic sequestration.
✓ Diagnosis emergency MDS based on the test Emmel or sickling test and testing Itano and the final diagnosis is based on hemoglobin electrophoresis.
✓ Renal involvement in MDS patients is one of the frequent early and debilitating complications, the overall prevalence is estimated at 25% in children aged 2-18 years.
✓ It must be sought systematically in every sickle cell homozygous or heterozygous AS. These tubular dysfunction (hyposthenuria, polyuria, enuresis, hematuria), sickle cell nephropathy, renal failure, renal medullary carcinoma and high blood pressure.
✓ The pathophysiology of renal injury remains poorly understood.

I- INTRODUCTION
Sickle cell disease or sickle cell anemia is an autosomal recessive genetic disease characterized by the presence of hemoglobin S (HbS), resulting from the substitution of glutamic acid by valine at position 6 of the β-globin chain acid A hemoglobin of chromosome 11. This structural hemoglobinopathy is characterized by three main clinical manifestations, including: chronic hemolytic anemia, painful vaso-occlusive crises and extreme susceptibility to infection. It was discovered in 1910 by JB Herrick, Chicago (USA), in a Jamaican student, and was described for the first time in 1943 in Cameroon (Africa).

II- EPIDEMIOLOGY
This disease of children from a black race is known in sub-Saharan Africa, America (USA, Brazil), the Caribbean, Madagascar, in the Maghreb, throughout the Middle East, Saudi Arabia, in the Indian sub-continent and in the Mediterranean basin. Sickle cell disease or sickle cell syndrome (SCS) gathers homozygous SS, double heterozygosity SC and sickle cell β-thal, SO Arab double heterozygosity, Punjab SD and SE (1). It is 5 to 20% of the disease-carrying or heterozygous AS in West Africa, up to 40% in certain ethnic groups of central Africa (Congo, Zaire) and Nigeria (Begue), and 1-15% in Mediterranean regions. In Togo, the incidence of SCS was 16% with 3% homozygotes. In Mali, the prevalence is estimated at 12% with 3% in the homozygous form (2).
Life expectancy, which depends on the quality of the therapeutic management is 40/50 years for
SS patients and 65 years for SC in the United States. This is a known and well-documented disease in the scientific field and health care is better codified today, which contributes to improving the quality of life. The number of children with sickle cell disease reaching adulthood is steadily increasing (2). Renal damage in patients with major sickle cell syndromes (MDS) or sickle cell disease is a common, early and disabling complication, among others. This complication, in which the overall prevalence is estimated at 25% in children aged 2 to 18 years, appears at the age of ten years. Glomerulosclerosis and arterial thrombosis, two main renal complications in sickle cell patients, cause microalbuminuria before the onset of proteinuria and renal failure (3).

III- PATHOPHYSIOLOGY

Renal injuries’ pathophysiology remains poorly understood. The decrease in the oxygen pressure in the arterial capillaries (vasa recta) promotes the development of hemoglobin polymers, resulting in an increase in blood viscosity. In the renal medulla, especially in the papilla, the sickling is promoted by hypertonicity, hypoxia and acidic pH prevailing locally (4,5).

Thus, thrombosis of the vasa recta by sickled red blood cells can lead to papillary necrosis, most often asymptomatic, causing myocardial and papillary tissue necrosis with scar and segmental interstitial fibrosis, hematuria, the development of collateral vessels and disorders of urine concentration (hyperfiltration). Moreover, these necrotic buds can cause an obstruction of the urinary tract.

In sickle cell patients, the glomerular filtration rate and renal plasma flow are increased, causing, thus, glomerulosclerosis injuries. Glomerulosclerosis may be complicated by proteinuria, nephrotic syndrome, and even kidney failure. The hyperfiltration, reported from the age of 2 years, which increases during the first fifteen years of life, decreases at the end of the second decade. This hyperfiltration could be the result of nephron loss through the destruction of juxtamedullary nephrons, secondary to papillary necrosis and / or cytokine vasodilator secretion, following vascular endothelial injuries and leukocyte activation (4,5).

IV- DIAGNOSIS

A- The sickle cell disease

Sickle cell disease, which has a large variability of clinical expression, is marked by three major categories of clinical vaso-occlusive features: vaso-occlusive phenomena, chronic hemolytic anemia with acute worsening episodes, bacterial infections. The natural history of sickle cell disease can be divided into three periods:

- Early childhood (3 months-5 years)
- Late Childhood (5 years-18 years)
- Adulthood (6).

1- The Early Childhood

Sickle cell disease appears most often from the age of 3 months (but never before the age of 2 months, due to the presence of HbF) by:

- The vaso-occlusive crises (VOC) or painful sickle cell crises: "mainspieds" syndrome in infants with dactylitis (painful swelling of the fingers and feet)
- Infections, frequent and severe bacterial pneumonia, osteomyelitis, meningitis, septicemia
An acute splenic sequestration succeeding a trivial infection, abdominal pain, shock, loss of consciousness, a constant painful splenomegaly requiring splenectomy (6).

2- Late Childhood
MDS is characterized by:
- Repeated hyperalgic VOC located in the abdomen and metaphyses members that dominate the symptoms
- The cerebral vascular accidents -which are the most serious complication in this age group
- A lower risk of infection (pneumonia + +), but with a significant incidence of osteomyelitis
- A pubertal delay of 2 to 3 years, with a normal final size and weight often low.
Factors promoting vaso-occlusive crises are dehydration, the muscular effort, hyperthermia, infection, hypoxia, ventilation disorders, asthma, exposure to cold, air travel, stays at a high altitude, hypertension, diabetes, pregnancy (6).
- Sickle cell disease diagnosis is biological.
MDS emergency diagnosis, which aims at identifying HbS, is based on the Emmel test or sickling test, and Itano test:
- The Emmel test is to put on a lamella a drop of blood in the presence of a drop of metabisulphite sodium to 2%, the lamella is luted with paraffin, the examination is done after 30 minutes via microscope and shows an aspect in sickle erythrocytes,
- The test of Itano, solubility test for hemoglobin, is carried out on a hemolysate hemoglobin adjusted to 4%. In the presence of sodium thiosulphate, hemoglobin S precipitates. After centrifugation, a pink clot and a supernatant were observed in the presence of HbS in the absence of HbS, the supernatant is red (1).

3- The definitive diagnosis
It is based on the study of hemoglobin. The goal is to separate and quantify the different hemoglobins. The classic test is electrophoresis at alkaline pH with a normal control and one or more controls containing abnormal fractions (F, S, C,...). Hemoglobin S is separated from the hemoglobin A1 electrophoresis at alkaline pH. The identification of HbS can be done by hemoglobin electrophoresis through isoelectric focusing. High Performance Liquid Chromatography (HPLC) on cation exchange column provides a good quantification of hemoglobic fractions A2, F, A1 and S. Table I summarizes the main MDS biological characteristics (1).

Table 1: Main biological characteristics of sickle cell syndromes

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>SS</th>
<th>SC</th>
<th>Sβ°ththal</th>
<th>Sβ+ththal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hg (g/dL)</td>
<td>12-16</td>
<td>7-9</td>
<td>10-12</td>
<td>7-9</td>
<td>9-12</td>
</tr>
<tr>
<td>Hb Electrophoresis (%)</td>
<td>95,5-97</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>80-90</td>
</tr>
<tr>
<td>A1</td>
<td>97</td>
<td>0</td>
<td>0</td>
<td>5-15</td>
<td>4-6</td>
</tr>
<tr>
<td>S</td>
<td>2-20</td>
<td>&lt;5</td>
<td>1-25</td>
<td>55-90</td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>2-3,5</td>
<td>0</td>
<td>5-15</td>
<td>4-6</td>
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</tr>
</tbody>
</table>
B- Renal complications of sickle cell disease

Renal disease should be sought systematically in all sickle cell homozygous or heterozygous AS. Renal clinical manifestations, which are well known, can occur at any time of life. It is a tubular dysfunction, sickle cell nephropathy, renal failure, renal medullary carcinoma and hypertension (7).

1- Tubular dysfunction

a- Hypostenuria and polyuria

In homozygous sickle cell children, a distal tubular damage with decreased ability of maximum urine concentration (hypostenurie) is constant from the age of 10 years. This failure is attributed to the occlusion of the vasa recta by sickled red blood cells, causing circulatory slowdown that disrupts the normal operation of the system against the current, thus limiting the concentration function. In young children, it has been shown that this anomaly was reversible through transfusions, but it becomes irreversible after the age of 15. Clinically, this lack of concentration causes polyuria and polydipsia, that are usually asymptomatic. This can magnify an enuresis in children or promote dehydration during diarrhea episodes or severe vomiting, and therefore the appearance of VOC (7).

b- Failure to acidification

The distal tubular functions, such as urine acidification and potassium secretion are impaired in sickle cell patient, by ischemia of the nephron distal segment, without thereby causing metabolic acidosis under physiological conditions. However, where there is a kidney failure, even a moderate one, lack of acidification can then manifest as a table of incomplete distal tubular acidosis, not being accompanied by any hypokalemia, hypercalciuria or nephrocalcinosis (4). Potassium secretion failure doesn't have any clinical impact unless there is an associated renal insufficiency, or during a vaso-occlusive sickle cell crisis. De Fronzo team showed that this failure was not related to a renin angiotensin axis anomaly. Rather it seems to be a direct consequence of distal tubular damage (4,8).

In contrast to the distal tubular abnormalities, proximal tubular function seems preserved or even abnormally increased in the sickle case. It was indeed shown that the reabsorption of phosphorus and β2 microglobulin + as the secretion of creatinine and uric acid was increased in the sickle case (4).
2- Hematuria
Whatever their age, hematuria (HU) is frequently asymptomatic found both in patients with MDS and in heterozygous AS. This hematuria is due to microthrombotic infarction in the vasa recta and peritubular capillaries of the renal medulla, with blood extravasation in the collecting ducts (9). The microscopic HU, which can be chronic, punctuated by macroscopic HU episodes, is more common in men than in women, and may be bilateral, predominantly on the left side. This dominance is attributed to an anatomical difference, the left renal vein being longer than the right, which leads to an increase in the left venous pressure (9). In most cases, the bleeding disappears spontaneously but may persist for weeks or even months.

In case of gross hematuria, it is recommended to carry out a check-up including renal ultrasound with Doppler, IVU or even a CT urography. Hematuria should systematically seek a urinary tract infection, which can evoke acute pyelonephritis and / or papillary necrosis (PN). The occurrence of gross hematuria should also evoke a kidney lithiasis or urinary tract and, exceptionally, renal medullary carcinoma (7,9).

3- Papillary necrosis
Papillary necrosis may occur in homozygous or heterozygous patients. The painful gross hematuria, which is the most common presentation, can sometimes cause a nephritic colic array, PN creating a ureteral obstruction, infection or even sepsis and / or acute renal failure.

The association pyuria, hematuria, back pain evokes an acute pyelonephritis episode urinary sediment analysis and urine bacteriological examination straightens diagnosis.

On rare occasions, the PN may cause cortical infarction with or without the development of a perirenal hematoma. In case of renal infarction, one finds in ultrasound a heterogeneous part on the outer edge of the right kidney. On CT, there is a roughly triangular hypodensity Cortex base and top hilar. This does not enhance hypodensité is after injection of contrast. Renal outlines are clear and pyélocalicielles cavities are not dilated (10).

Patients with PN are most often diagnosed retrospectively during an imaging examination, through intravenous urography (UVI), ultrasound, CT or magnetic resonance imaging (MRI). In IVU, on the upper right caliciel group, addition images in bouquet are observed, simulating ductal precaliceal ectasia. The papilla footprint is no longer visible on the upper calyx.

The histological examination of autopsy nephrectomy parts reveals prenecrotic areas identified by leukocytes and polynuclears in the medulla and papilla. Vascular congestion with edema, and myocardial necrosis in the papillary region is associated with injuries of chronic interstitial nephritis type with fibrosis and tubular atrophy. Despite the importance of these injuries, a progressive interstitial nephritis leading to end-stage renal disease (ESRD) is rare because the injuries are more localized, with an infection rate lower than the one in PN cases induced by nephropathy with analgesics (7,10).

4- Renal medullary carcinoma
Renal medullary carcinoma is one of the complications observed in patients with sickle cell disease. Its incidence is 1.74 ‰ patient per year, and the mortality rate is 1.04 cases per year / patients. This cancer develops from the tubular epithelium near the papilla. It is described in children as young as 6 years. It is an aggressive carcinoma, particularly of a poor prognosis, rare, and whose diagnosis is almost exclusively associated with sickle cell trait, more rarely, to a MDS. The diagnosis is guided by renal ultrasound and confirmed by pathological studies, which
highlight an invasion of the cortex and peripheral tissues with, within the tumor, hemorrhagic necrotic areas. The macroscopic hematuria and back pain are the most common symptoms, in contrast to the weight loss and the presence of a palpable tumor mass (7,9).

5- **Glomerular impairment**

The glomerular impairment begins in childhood and results in microalbuminuria (MA) before the onset of final proteinuria (PU) and renal disease. This MA is an early and sensitive marker of renal damage in sickle cell patients. It appears in the first decade and is defined by the Albuminuria / creatinuria > 20mg / g of urination or = 30mg / g of 24H urine report. In many studies, proteinuria was investigated by semi-quantitative methods such as dipstick, assessing proteinuria from 0 to 4 crosses. The prevalence varies from 15% to 26% (7). In all these studies, proteinuria incidence increases with age and is associated with deterioration of renal function (RF) (9).

McBurney, in a study published in 2002 found an MA (defined by a MA report / creatinuria ratio> 30 mg / g) in 19% out of 142 children aged homozygous sickle cell disease aged from 2 to 20 years. The average age at diagnosis was 13 years. This study confirms the increase in prevalence with age (no case under 7 years, 24% from 7 to 14 years, 29% over 15 years). It shows a significant correlation between MA and low hemoglobin (Hb). The average Hb is of 76 g / l in children with MA, versus 82.2 g / l in the group of children without MA (9). This proteinuria can lead to nephrotic syndrome (> or 40mg/m2/h ≥ 50mg/kg/24H), with hypoalbuminemia and hypoproteinemia progressing to end-stage renal disease (ESRD), sickle cell nephropathy. However there are no pediatric studies reporting the prevalence of nephrotic syndrome (NS) in children (9).

At the histological level, the initial injuries of sickle cell nephropathy begin with glomerular hypertrophy (described for the first time in the sixties), with the gradual development of focal segmental glomerulosclerosis predominant in vascular pole. Other chronic glomerular lesions resembling those of membranoproliferative glomerulonephritis, or thrombotic microangiopathy, may gradually be superimposed on the lesions and focal segmental glomerulosclerosis (7).

In case of persistent proteinuria, nephrology consultation is recommended to discuss the indication for renal biopsy. It is indicated in case of high PU to eliminate non sickle cell associated nephropathy. Renal function tests may be performed to assess the impact of sickle cell disease on the renal function. In the absence of MA or PU, renal function tests in children could be carried out at the age of 15 years (9).

6- **Blood pressure regulation**

Surprisingly, the prevalence of high blood pressure (hypertension) in homozygous patients (2 to 6%) is below the one observed in the American black population (28%). We also note a resistance to the development of hypertension where there is a PU or RI. In patients who develop a PU, the blood pressure (BP) increases only moderately and only after the age of 40. Only patients with an advanced RI (creatinine clearance <30 ml / min) increase their BP values.

In patients with MDS other than SS, BP values are identical to those of the American black population, and increase with the development of a PU or RI (7).

This «relative» hypotension, being a cause or a consequence of renal abnormalities in sickle cell patients, is currently unclear. We mentioned lower resistance devices by releasing endogenous vasodilator substances (prostaglandins and nitric oxide) to correct tissue hypoxia. In addition, there is probably some degree of mandatory salt loss accentuated by the increase in renal blood flow, combined with the natriuretic effect of prostaglandins. Finally, in these patients, we find high
levels of renin and a decreased response to the vasoconstrictor effects of angiotensin (9).

7- Renal Failure

a- Acute Renal Failure

Acute renal failure (ARF) is the sudden interruption of kidney function, usually oligoanuric (less than 400 ml/24h diuresis), more rarely anuric (complete cessation of urine output), resulting in a nitrogen retention (a rapid rise in urea and creatinine). The blood urea report on blood creatinine is normal (35-50) in most ARF cases. The ARF can be functional- a drop in (flow) renal blood output, organic or parenchymal, due to ischemic factors, toxic or immuno-allergic and obstructive by obstacle in the urinary tract to the above bladder floor.

The diagnosis is made with the basic balance sheet, which includes, in the blood: NFS, urea, creatinine, electrolytes, uric acid, bicarbonates, calcium, and phosphorus in urine: the urinary sediment examination, urea, creatinine, sodium, proteinuria. In sickle cell disease, the ARF is often contemporary of multi-organ damage occurring during acute attacks (11).

In 1990, Sklar has attempted to clarify the incidence of ARF in 116 hospitalized patients with sickle cell disease in which 12 (10.3%) had at least a doubling of their serum creatinine. In most cases, the infection was the main reason for admission while volume depletion was the most common identifiable cause of RI. Two patients out of the three most affected, necessitated the resort to dialysis, and ten patients out of twelve survived (9).

b- Chronic Renal Failure

Chronic kidney disease (CKD) is defined as a progressive and irreversible deterioration of the renal function and results in the decrease in glomerular filtration rate. It can occur in children, even the very young ones (12). There are no pediatric studies reporting the prevalence of renal insufficiency (RI) in sickle cell children. These complications are most frequently described in adult sickle cell disease, their prevalence increased significantly with age. The median age at diagnosis of RI is 23 years with sickle cell SS and 50 years for CS in Powars prospective longitudinal series, containing 725 patients, children and adults (9).

In this study, the prevalence of chronic renal failure (CRF) in the homozygous sickle cell is 4.2% versus 2.4% in sickle cell CS, the median survival after diagnosis of RI is 4 years and the median age of death, despite the technical renal replacement is 27 years. In this study, case-control analysis of RI group identifies hypertension, PU, HU and NS as predictors of progression to renal failure (9).

In a more recent study with only adults (300 patients), Guash reported prevalence higher than 21%, and identical, regardless of the hemoglobin phenotype (homozygous SS versus other MDS). The RI degree is, however, advanced in homozygous patients. The albumin / creatinine report is inversely correlated with creatinine clearance in this study. Data from the United States National Registry show that the end-stage renal disease (ESRD), usually reached a little later, between 30 and 50 years- is, then, a major risk factor of mortality in sickle cell patient, in the absence of renal transplantation. In a recent Darbari cohort study, 23% of deaths are attributed to RI (9).

VI- TREATMENT

A- The management of sickle cell disease

This management, which must be done in specialized centers for screening, treatment and monitoring, and / or a hematology service and / or a general practitioner, consists of:
1- A newborn screening to the third day of life, after informing the family

2- Anti-infective preventive treatments
a- Antipneumococcal antibiotic penicillin V from the age of two months until the age of at least 5 years, at a dosage of 100 000 IU / kg / day up to 10 kg and 50 000 IU / kg / day 10 to 40 kg, taken twice,
- Elargi Programme vaccination on Immunization and Antipneumococcal vaccination,
- The antimalarial chemoprophylaxis

3- Curative anti-infective treatment
a- Antibiotic therapy appropriate to the germ responsible for the infection,
b- Systematic deworming by an anthelmintic, every 3 months, in children less than 5 years, every 6 months, more than the age of 5 years.

4- In the preventive analgesic treatments- Recognize the triggers
- Blood transfusion,
- Hydroxyurea,
- The repeated bleedings,
- Other molecules depend on individual cases: magnesium, vasodilators

5- In curative analgesic treatment
• Analgesics bearings I, II, III:
- Oral paracetamol (30 mg / kg or 1 g in adolescents over 12 years), if this grip is effective, it has to be renewed every 6 hours at a dose of 15 mg / kg or 500 mg in adolescents over 12 years
- In case of persistent pain after 30 to 45 minutes, ibuprofen (10mg/kg/dose) or other oral non-steroidal oral anti-inflammatory may be associated with paracetamol and if the first grip is effective, it has to be repeated every 6 to 8 hours, depending on the molecule and the dosage form used in pursuing paracetamol,
In case of persistent pain after 30 to 45 minutes, or in case of severe pain immediately, codeine orally (0.5 to 1 mg / kg / dose up to 30mg) may be associated with paracetamol and ibuprofen eventually, if this grip is effective, it has to be renewed every 6 hours.
• Associated measures: Drinks, more abundant than usual once a painful crisis occurs, a water bottle on the painful area may be useful. The application of cold is contraindicated.
• Parent education, emphasizing the VOC predisposing factors: exposure to cold, high altitude, continuous physical effort (hypoxia context), fever, dehydration
• Lifestyle and dietary rules, in particular the need for abundant hydration «the child must keep the urine as clear as possible»
• Breastfeeding
• A supplementation with folic acid (5 mg / day), zinc (10 mg elemental zinc) in pre-pubertal period, vitamin D, particularly during the pubertal period
• Iron supplementation is not recommended, since iron overload is linked to in transfusions
• Prevention of HIV / AIDS (risk of serious sepsis linked to pneumococcal if sickle cell anemia associated with HIV infection) (13,14).
B- Monitoring and treatment of renal disease in children with sickle cell disease
Apart from creatinine dosage with serum electrolytes and renal abdominal ultrasound during annual balance, there is no recommendation on the renal disease monitoring in children with sickle cell anemia.

1- Tubular abnormalities management
• Concentration failure, usually subclinical, does not require specific treatment, except:
  - A good alkaline hydration to compensate for any eventual incipient acidosis, which should be increased during VOC
  - A restriction in potassium and phosphorus intake in case of changes to the CKD, or thiazides or loop diuretics prescription able to increase potassium excretion
  - Allopurinol prescription in case of gouty access through hyperuricemia
• In enuresis, no treatment can be recommended, desmopressin, being ineffective and fluid restriction, being contraindicated because it may lead to dehydration, which can favour the occurrence of vaso-occlusive crisis (9,13).
• Hematuria treatment, associated with papillary necrosis, includes:
  - Rest in bed
  - Maintaining a high hydration with a high urine output
  - Transfusion in case of significant hematuria
  - A surgical opinion if hematuria is prolonged (9).

2- Glomerular abnormalities
In practice, from 5 years, systematic research is recommended, at least twice a year, from a PU to dipstick and from MA. This can be done either from a collection of 24-hour urine (difficult in sickle cell children often enuretic), or by using the MA / creatinine of 1 urination report (9). Therapeutically, few studies seem to show the effectiveness of CEI on the reduction of PU or MA in adults with sickle cell disease, but their interest in the longer term to slow the progression of sickle cell nephropathy has not been demonstrated. These data invite to expand the CEI indications in the prevention of sickle cell nephropathy, including the MA stage. They allow to hope, as has been shown in diabetic nephropathy, that the MA early treatment by CEI delays the deterioration of the renal function (9).

The CEI will be administered at the minimum dose (captopril 25mg/day, enalapril 5mg/ day), with serum creatinine monitoring 3 to 6 days after the start of treatment (onset of ARF). These doses may be increased to reach 50mg/day to 10mg/day for captopril and enalapril in the treatment of nephrotic syndrome (7).

The effectiveness of non-steroidal anti-inflammatory as well as the immunouppressive treatment’s (corticosteroids and cyclophosphamide) has not been demonstrated.

There are no studies demonstrating the effectiveness of regular transfusions in sickle cell nephropathy, but a protective effect is suggested by the Alvarez study. In this cohort of 120 children aged 4 to 20 years, 19 have a pathological MA and 23 receive regular transfusions for an average duration of 3.8 years. In transfused children, the average age, at the beginning of transfusion program, is significantly higher (12.2 years) in children with MA, than in children without MA (7.8 years) (9).
There are no reported prospective studies enabling to consolidate the hypothesis of hydroxyurea effectiveness in the prevention or treatment of sickle cell nephropathy however, a beneficial action is possible. Fitzhugh treated, with a CEI, 3 adolescents with P, then by CEI hydroxyurea association. In these three patients, PU, which was reduced by CEI treatment, was normalized after addition of hydroxyurea (15).

Finally, there are no data to assess the effect of hematopoietic stem cells transplantation on the progression of sickle cell nephropathy. However, RI has not been observed in the sickle cell transplanted patients suggesting that the transplant would prevent renal complications of sickle cell disease (7).

3- Renal Failure
a- Acute Renal Failure
Transfer in ICU as well as an exchange transfusion or transfusion is recommended. The management of the cause and aggravating factors is required. we may often resort to the substitution methods of renal function, such as peritoneal dialysis (PD), hemofiltration (HF), hemodiafiltration (HDF) and hemodialysis (HD). The management will be carried out in an appropriate service (nephrology or pediatric nephrology) (13).

b- Chronic Renal Failure
It is mainly a complication of adult sickle cell. However, if a CRF occurs in the child the management includes:
- Monitoring the good conduct and the specific treatment compliance of nephropathy and symptomatic protector treatment
- Treating ARF aggravating factors (hypertension, anemia, proteinuria, diabetes, hypercholesterolemia, hyperuricemia, hyperphosphatemia, ...)
- Preventing the risk of acute decompensation ( ensuring mainly the nephrotoxic agents)
- Identifying and managing CKD progressive complications of CKD
- Preparing the patient clinically and psychologically to an eventual substitution (13).

In homozygous sickle cell patients, recombinant erythropoietin is prescribed at high doses three times a week to correct the hematocrit and have a reduction in transfusion requirements (7).

Replacement therapy (PD or HD) should be started as soon as the first clinical signs of the IRCT appear. However, the total number of patients remains limited. Sickle cell disease is not a formal cons-indication to renal transplantation, although the experience of renal transplantation is limited in this population (13).

VII- CONCLUSION
The sickle cell child’s health requires careful monitoring to prevent the occurrence of complications, diagnosing them to treat them as soon as possible, as many of these are life-threatening or disabling of the affected organ. The bone marrow transplantation or even the gene therapy, may prevent the long-term illness complications, moving to a RI in particular, or at least reduce its progression. The innovations in immunosuppressive therapy should broaden the indications for transplantation in these patients.
References

CHAPTER 13

RENAL MANIFESTATIONS DURING HIV INFECTION

Ekulu Mfutu Pépé, Kinshasa - Congo Kinshasa
HIGHLIGHTS

✓ HIV infection considerably increases the probability of kidney disease, proteinuria being a reliable early marker of HIVAN, systematic monthly screening either to test strip or with proteinuria / creatinine (C / PU) ratio, is essential.

✓ In case of a black race patient, with a positive dipstick proteinuria or PU / C ratio ≥ 100mg/mmol, persisting for three consecutive months, without any obvious cause, immediately start antiretroviral therapy.

I- INTRODUCTION

The Acquired Immunodeficiency Syndrome (AIDS) remains to this day one of global health priorities. The pandemic affect all countries, but sub-Saharan Africa remains the region with the highest (1) morbidity and mortality rate. On one hand, opportunistic infections, on the other hand, various complications, including renal ones, realize this situation (2-5). The kidney is, indeed, a reservoir for the virus, even in the absence of circulating viral detected RNA (4,5).

II- HISTORY OF RENAL DISEASE RELATED TO HIV

The history of renal disease related to HIV dates back to the discovery of HIV. In 1984, in New York and Miami, clinicians have reported the first cases of adult patients infected with HIV who experienced significant proteinuria with rapid progression to end stage renal disease (6-8). This proteinuria was associated with glomerular histological injuries and tubulointerstitial features. This syndrome was named «HIV-associated nephropathy» (HIVAN), considered as a specific renal damage encountered in patients, mainly blacks, holders of HIV infection (9,10). Beside the HIVAN, other forms of kidney damage in relation to the presence of HIV in the human body, have also been described, including immune complex glomerulonephritis and haemolytic uremic syndrome (4). Later, in 1989, Strauss et al, as well as other authors have confirmed the presence of HIVAN in five children infected with HIV in Miami HIV was directly implicated (9-11). Towards the early years of the discovery of HIV infection, HIV-positive children died in less than a year after the diagnosis of HIVAN (12-18). Usually, HIV-positive children develop proteinuria approximately 2 to 5 years after the onset of infection. The average duration of proteinuria in end-stage renal disease ranges from 8 months to 3 years (12-15). The management of patients infected with HIV has evolved over time. The significance and prognosis of HIV infection have evolved considerably in a few years with the use of triple antiretroviral treatment. To be infected with HIV means in this context, to live with the virus for many long years (5). However, children infected with HIV, with kidney damage, have a poor prognosis.

III- EPIDEMIOLOGY

Throughout the world, many studies have been conducted describing a variety of manifestations including an erythrocyturia electrolyte disorders, isolated proteinuria, nephrotic proteinuria, acute and chronic renal failure (19-28). Various injuries, both glomerular and tubulointerstitial, have also been described histopathologically (21, 22, 26, 29). These renal manifestations in HIV infection have been adequately reported in the United States, as evidenced by the work of Strauss et al. (30), and several other American authors (31-34). Their studies based on clinical and histological criteria (proteinuria) and on large cohorts, reported a HIVAN prevalence ranging from 10 to 15%
of the population among these groups, 95% were African-American. In Miami, Chaparro et al., in a study published in 2008 reported a prevalence of proteinuria in children by 33%. (35).

In Latin America and Asia, these renal manifestations have been reported to a lesser extent. Some works may be cited: Gomes et al, of the Federal University of Pernambuco, Brazil, reported a prevalence of proteinuria in adult patients, by 5.6% (36). India Janakirama et al. confirmed the correlation between the evolution of TCD4 lymphocytes and kidney damage (37) Shah et al. reported beneficial effects of antiretrovirals in renal disease in children (38).

In Europe, the renal manifestations associated with HIV and especially the HIVAN are less reported, due to the fact that the weakest population is the black race (39). Van Der Reidjen et al. (40), leading a longitudinal study of 177 adult patients in the city of Amsterdam, encountered no cases of HIVAN. Baekken et al., University of Oslo, reported a prevalence of microalbuminuria by 8.6% in adult patients (41). Kabanda et al. (42), of the Catholic University of Leuven in Belgium, found a frequency of 86% in urinary protein excretion of low molecular weight, in 76 HIV positive adult patients. In Africa, until recently, data on HIV-related renal manifestations were rare, whereas it probably would be, taking into account the genetic susceptibility, the largest HIVAN concentration in the world (39). Over the past five years, more and more works are reported. In South Africa Gerntholtz et al, reported in a histopathological study, frequency of classical HIVAN by 27%, followed by immune complex nephropathy, with a frequency of 21% (43). In Nigeria, at the University Hospital in Port Harcourt, Anochie et al. have confirmed the presence of focal and segmental glomerulosclerosis, as basic histological lesions in 10 children with HIVAN (44). Also in Nigeria, at the University of Benin, Iduoriyekemwen NJ et al, found a prevalence of kidney disease of 16.2% and microalbuminuria by 11.1% in children infected with HIV receiving antiretroviral therapy (45). In Kinshasa, DR Congo, Ekulu PM et al. reported a prevalence of proteinuria by 23.8% in children infected with HIV, antiretroviral-naïve. In this work, the patients target of the study were seven times more likely to have proteinuria than uninfected children, and the main independent determinant of proteinuria was significant immunosuppression (46). In Ouagadougou, G. Coulibaly et al reported the prevalence of proteinuria by 14.8% in children infected with HIV receiving antiretroviral therapy (47). As this emerges from these few works, there is need for more epidemiological data on other renal manifestations in HIV infection (ARI, IRC, electrolyte disorders, renal toxicity of ARVs) just like the glomerular disease.

IV- RENAL MANIFESTATIONS IN HIV INFECTION

These manifestations are varied and relate to the kidney damage associated with the presence of the virus the foreground HIV-associated nephropathy, on the other hand, kidney damage related to drugs nephrotoxicity used to treat the disease. These manifestations can be classified into five categories (4):

. Acute renal failure
. Electrolyte disorders
. The glomerulopathies
. The nephrotoxicity of antivirals
. Chronic renal failure.
A- Acute Renal Failure (ARF)
Frequently found in patients with HIV infection (48), the distinction should be made between pre-renal, renal and post-renal causes.

1- Pre-renal causes (functional ARF)
They are formed by hypovolemia, following a hypoalbuminemia or extracellular dehydration, on the other hand, by low flow. The latter follows a decline in glomerular filtration rate after the use of converting enzyme inhibitor.

2- Renal causes (Organic ARF)
In this group, one can have a tubular damage of an infectious origin (Sepsis, shock) or iatrogenic (anti-protease, antineoplastic, aminoglycoside...) or an interstitial nephropathy of an allergic origin (cotrimoxazole), infectious (opportunistic infections) or neoplastic (Kaposi lymphoma).

3- Post-renal causes (Obstructive ARF)
Obstructive acute renal failure may occur following a hyperuricosuria secondary to antineoplastic chemotherapy, a sulfonamides crystal deposition (sulfadiazine) or of Indinavir crystals.

B- Electrolyte disorders
They can be associated or not to an ARF, these main disorders are:

• Hyponatremia due to depletion (digestive, urinary loss...) at a dilution (oligo-anuric renal failure) or an iatrogenic cause (foscarnet, cidofovir...)

• Metabolic acidosis due to digestive losses of bicarbonate (acute diarrhea), the tubular acidosis type IV, renal failure and lactic iatrogenic acidosis (AZT, saquinavir, isoniazid)

• A metabolic alkalosis due to digestive losses of H + ions (vomiting) and to volume contraction (dehydration)

• A dyskaliemia particularly, hyperkalaemia of overload (renal failure) and of transfer (metabolic acidosis), hypokalaemia of depletion (digestive losses) and of transfer (metabolic alkalosis) finally iatrogenic dyskaliemia: ritonavir, saquinavir, foscarnet.

• Other iatrogenic disorders: hypomagnesemia, hypercalcemia, dysphosphoremia, iatrogenic dysuricemias.

C- Glomerulopathies
The HIV infection is a major cause of glomerulopathies [4, 49]. Although the most common glomerulopathy remains the «HIV-associated nephropathy» (HIVAN), but beside it, other glomerular damage have been reported.

1- HIV-associated nephropathy (HIVN)
a- Definition
The term HIVAN refers to a severe and particular form of focal and segmental hyalinosis, occurring primarily in black patients, adults and children, regardless of the mode of infection and the stage of HIV infection, commonly type 1 (49). Clinically, HIVAN is manifested by proteinuria, often nephritic, and rapidly progressive renal failure, moving, in most cases to end stage renal disease. Despite the severity of proteinuria, typically, oedemas are absent. Hypertension is also absent or very moderate (39). Renal hyper-echogenicity is often observed.
b- Pathogenesis

The pathogenesis of this glomerulopathy is not precisely known. However, the specific pathogenic role of type 1 HIV is increasingly well documented. Field studies have shown the direct role of the virus in the occurrence of infection by HIVAN tubular and glomerular parietal epithelial cells (podocytes) (or cells of the Bowman’s capsule). Infection of podocytes leads to their proliferation, the origin of hyalinosis. The main histological injury is focal and segmental glomerulosclerosis. Different genes both virus (nef +++ tat transactivation) and the host (p27, p57) play an important role in the pathogenesis (49).

c- Clinical and renal echostructure (39)

Clinically, HIVAN is manifested by a sudden onset of a nephrotic syndrome with rapidly progressive renal failure, usually evolving to the final stage within a few months. Typically, despite the severity of the nephrotic syndrome, oedema is absent. Hypertension is also absent or very moderate. On ultrasound, the kidney size is maintained or increased even more frequently in the presence of advanced renal failure. Renal hyperechogenicity is often observed.

d- Diagnosis

Early and appropriate diagnosis of renal disease is essential to improve the prognosis in this disease (50). The HIV-associated nephropathy is suspected in persistent proteinuria and/or a sudden collapse of the glomerular filtration rate in an HIV positive patient. But the final diagnosis will be performed only after histopathological examination of the kidney (51,52). However, in our developing countries context, achieving this examination abuts against a real ethical problem, the benefit of such examination should be carefully assessed. This is why the persistent proteinuria (with dipstick or proteinuria/creatinine ratio) remains the most reliable orientation factor of renal damage (50). Microalbuminuria is cited as an early marker of glomerular damage in HIV (53). Its detection helps identify HIV-positive patients at high risk of kidney disease (41). The (C AU / creatinine) albumin / creatinine ratio detects glomerular damage and can be used to detect HIV-related nephropathy when the UP / C (total proteinuria secondary to glomerular or tubular) is not available, but it is not appropriate for the detection of secondary tubular damage related to ARV toxicities (tenofovir, for example). The thresholds for UA / C are: <30, 30-70 and >70.

e- Risk factors of HIV-associated nephropathy (HIVAN)

In the search for risk factors associated with proteinuria and renal failure in HIV infection, several studies confirm the predominance of the black race (20, 25, 54,55), the collapse of lymphocytes CD4 and the rise in viral load (56). Other factors are also mentioned, among others, age, sex, duration of infection, mode of transmission, co-infection to hepatitis C, high blood pressure, and the presence of serum beta-2 micro globulin.

f- Treatment

The therapeutic management remains poorly defined. However, various authors report beneficial effects the prednisone has on kidneys, used for a short time, inhibitors of angiotensin converting enzyme (ACE) and finally antiretroviral (49). Their work has shown that antiretroviral improve both the renal function and proteinuria in patients infected with HIV with renal damage. American IDSA recommendations, published in 2005, state that the treatment of HIVAN is based on an antiretroviral therapy, which must be commenced as soon as the diagnosis of renal damage is performed and whatever the stage of HIV (57) infection is. Thus, antiretroviral therapy remains
the best way indicated to prevent the onset of end stage renal disease in case of a suspected HIV-associated nephropathy.

Similarly, in the recommendations of the European Society for Clinical Research on AIDS (EACS), version 6, 2011, it is advisable to start treatment immediately if suspected HIV-associated nephropathy (HIVAN) or in case of a suspicion of complex immune disease. Renal disease is an indication of triple therapy, regardless of the evolutionary clinical or immunological stage (CD4) for HIV infection. To this end, as stated previously, persistent proteinuria is the factor of strong presumption of renal disease related to HIV in the context of developing countries its presence should indicate a set under triple therapy retroviral regardless of the infection stage.

2- Diffuse proliferative glomerulonephritis with immune deposits
The most frequent damage in the Caucasian race, they are most often responsible for a moderate proteinuria and nephrotic syndrome is rare. These glomerulopathies could be the result of immune dysregulation, originally a polyclonal activation of B cells.

3- Haemolytic Uremic Syndrome
This syndrome is frequently indicative of HIV infection at an advanced stage of immunosuppression. However, its incidence has significantly declined since the widespread use of new antiviral drugs (58). The role of the interaction between HIV and endothelial or megakaryocytic cells has been suggested to explain the frequency of this disease entity.

4- Other glomerular injuries
Membrano-proliferative glomerulonephritis, minimal glomerular injuries, extra-membranous glomerulonephritis, nephropathy with mesangial IgA deposits, rare frequency and in which the causal role of HIV is unlikely.

D- Renal toxicity of antiviral
The class of antiviral drugs has grown considerably since the advent of antiretroviral therapy. The increasing use of these drugs has highlighted a number of them who had a nephrotoxic potential toxicity (59).

1- Antiretrovirals
Among the antiretrovirals, there are mainly:

- Indinavir, which can induce crystalluria, related to imperfect solubility of the product in an alkaline environment (60)
- Ritonavir, which has been involved in some observations of acute renal failure (61-63). The pathophysiology of this disease is unknown
- Tenofovir: some observations proximal tubulopathy and elevated creatinine have been reported (64)
- The combination of antiretroviral therapy: two cases of severe acute pancreatitis associated with an IRA have been reported in patients receiving a combination of nucleoside analogues and protease (65).

2- Anti-CMV and Anti-HSV/VZV

- Aciclovir: the complication is a very rapid rise in creatinine, 2 to 3 days after the start of treatment. This complication has become rare since the introduction of systematic hydration before treatment
- Other: foscarnet, ganciclovir, cidofovir, vidarabine.
3- Anti-HBV

• Interferon. Various complications have been reported with interferon: induced glomerulonephritis, thrombotic micro-angiopathy, renal failure, proteinuria associated with hematuria
• The Adefovir is also to be mentioned.

E- End stage renal failure

In the absence of antiretroviral therapy, it is the inevitable outcome of renal disease associated with HIV. At this stage, alternative treatments, such as dialysis and kidney transplantation, yet with very limited accessibility in poor-resource countries, are needed.

HIV Infection is not officially a contrindication to substitution treatment. In the United States, the prevalence of HIV infection in dialysis centres was stabilized since 2001 at 1.5%. The black people are most affected (90%) and HIVAN is the most common (39) damage. In France, the rate was 0.63% in 2002 (66). Since the advent of tritherapies, the survival of HIV hemodialysis patients in France has increased significantly it is currently 89% at 2 years (39). Regarding renal transplantation, the main concern was for long time the fear of the infectious complications that may arise from the combination of immunosuppressive effects of HIV and anti-rejection treatment. The appeasement came when it was shown that anticalcineurins, mycophenolate mofetil and sirolimus (three agents commonly used in solid organ transplantation) were able to inhibit HIV replication in vitro (67, 68).

In Africa, data on the use of means of renal replacement therapy or renal transplantation in patients with HIV infection in general and children in particular, are rare. Therefore, it is essential, especially for countries with accessible technology for people, to make available data related to the monitoring of these children. This will be a motivation or impetus for other countries.

References

PART IV
TUBULOPATHIES

CHAPTER 14
POLYURIAS OR POLYURO POLYDIIPSIC SYNDROME

Mylène Grimaud, Cotonou - Benin
HIGHLIGHTS
✓ A polyuropolydipsic syndrome is defined by a higher urine output 50 ml/kg/day (polyuria), associated with increased fluid intake (polydipsia).
✓ It requires an exploration because if polyuria can be benign (potomania), it can be a serious condition.
✓ Polyuria can become dangerous by hypernatremia and dehydration.
✓ The diagnosis is based on clinical examination.
✓ It is necessary to eliminate a frequency, which corresponds to an increase in the frequency of urination with normal urinary volume.
✓ Clinical examination should look for signs of dehydration stress the neurological examination and the height and weight growth.
✓ It will measure the blood osmolarity (osmoP) and urinary (osmoU) to distinguish osmotic and hypotonic urination (potomania and diabetes insipidus).
✓ The diagnostic approach to see if polyuria is primary or secondary to polydipsia will be based on the creation of a water deprivation test.

I- DEFINITION
Polyuria is defined as diuresis higher than 50 ml/kg/day. This normally results in an increased oral fluid intake or polydipsia to compensate for urine loss, which creates polyuropolydipsic syndrome. Polyuria should be differentiated from pollakiuria, which is defined as an increased frequency of urination with normal daily urine volume.

The discovery of polyuria requires an exploration because it can be dangerous (hypernatremia and dehydration) where the thirst mechanism is disrupted or if access to water is limited or even impossible.

II- POSITIVE DIAGNOSIS
It is simple and based on the interview and clinical examination.

A- The interview seeks
• An antenatal hydramnios notion.
• Age of polyuria onset, its brutal or progressive nature.
• Surgery or cranial trauma history, psychological disorders.
• A special attraction to water (nocturnal thirst and weight loss are in favour of an organic cause).

B- The clinical examination seeks
• Signs in favour of dehydration: weight loss + +, febricula, irritability, constipation
• Disorders of weight and height growth: poor weight gain, weight curve break, growth delay.
• A polyuria, sometimes delayed when breastfeeding.
• The neurological examination should be emphasized for chronic dehydration signs.
C- Biology
Polyuria etiologic diagnosis is based on:
- Natremia.
- Plasma osmolality.
- Urinary osmolality.
- + / - Hydric restriction test and dDAVP test (desmopressin).

III- DIAGNOSTIC APPROACH
In case of a polyuria polydipsia syndrome, we must:
• Eliminate pollakiuria: 24h diuresis quantification
• Eliminate diabetes mellitus: dipstick looking for glycosuria
• Highlight urine concentration disorder: natremia, plasma osmolality (Osm pl) and urinary osmolality (U Osm)
• In case of hypotonic polyuria: hydric restriction test to determine if polyuria is primary or secondary to a polydipsia, eliminate primary polydipsia or potomania
• In case of diabetes insipidus: dDAVP or Minirin * test or to clarify its central or peripheral (nephrogenic) nature.

Table 1: Results of test

<table>
<thead>
<tr>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na+ (mmol/l)</td>
<td>&lt;143</td>
<td>&gt;143</td>
</tr>
<tr>
<td>Osm pl (mOsm/kg)</td>
<td>&lt;300</td>
<td>&gt;300</td>
</tr>
<tr>
<td>OsmU (mOsm /kg)</td>
<td>= PCM*</td>
<td>&lt;PCM</td>
</tr>
</tbody>
</table>

Primary Polydipsia
=Potomania

Urine Concentration Disorders of Central or Peripheral Urine

No Possible Conclusion:
Take Hydric restriction Test

*A MCP (Maximum Concentration Power) of urine according to age

A- Hydric Restriction Test
This is a test of AVP stimulation (vasopressin). It studies the capacity of urine concentration.
- It must be performed:
• In hospital, UNDER STRICT SURVEILLANCE of tolerance, in the complete absence of fluid intake during the examination.
• Strong suspicion of diabetes insipidus and / or abundant polyuria (> 3 nocturnal urinations), hydric restriction from 7am so it is a DAY test (if not at midnight).
• HOURLY clinical and laboratory monitoring:
• pulse, BP, weight, diuresis
• serum sodium, Osm pl and U Osm
• + / - AVP dosage at the beginning and end of the test (hard dosage)
Diagnostic approach to poly-urpolydipsique syndrome

Syndrome of polyuria-polydipsia(1) clinical context

Dipstick: glycosuria

- osmoU > 300 mOsm/l
  - osmotic polyuria (3)

- Glycosuria, hyperglycemia
  - YES: Diabetes mellitus
  - NO: mannitol overload

Diuresis urine osmolarity 24h

- Blood ionogramme

- osmoU < 300 mOsm/l
  - hypotonic polyuria

- Water Deprivation test (2)

- osmoU > 750 mOsm/l
  - Potomania primary polydipsia (4)

- osmoU < 300 mOsm/l
  - dDAVP test

- 15/ osmoU > 750 mOsm/l or between 300 and 750 mOsm/l
  - Central diabetes insipidus complete or partial (5)

- osmoU < 300 mOsm/l
  - Nephrogenic diabetes insipidus (6)

- Pollakiuria

Test stopping criteria:
- Signs of dehydration: weight loss ≥ or equal to 5% body weight
  - serum sodium > 150 mmol / l
- Stable U Osm stable in 2 consecutive hours (elevation <30 mOsm / kg)

B- dDAVP Test (desmopressin or Minirin*)

It enables to identify the central or peripheral origin of the disorder urine concentration disorders. At the end of the hydric restriction test, if the urine remained hypotonic, it consists of:
- Injecting subcutaneously, 2 micrograms of desmopressin
- Then measuring every 30 minutes for 2 hours, the above mentioned clinical and biological parameters
IV- ETIOLOGIES

A- Nephrogenic congenital diabetes insipidus (NCDI)

The NCDI is a rare hereditary disease that is transmitted in two modes:
- X chromosome linked (90% cases) by mutation of the gene encoding the V2 receptor of vasopressin (RV2 of AVP)
- Autosomal (10% cases) recessive or dominant through gene mutation encoding the channel to water aquaporin 2 (AQP2).

It is characterized by renal insensitivity to AVP.

1- Diagnosis

The diagnosis is usually simple and its early clinical manifestation has become a rule. In newborns and infants less than 3 months, there is a poor weight gain, anorexia, febricula, irritability, constipation, a special attraction for water and polyuria (well filled layers + + +). Sometimes a severe dehydration accident with neurological complications can reveal it.

Some later diagnoses are possible: forms of expression “minor”, neurological impact form of a chronic dehydration state, or urological with ureterohydronephrosis.

2- Treatment is symptomatic

a- Hydration:

adequate and regular water supply up to 300 ml / kg / day. This may require a continuous flow enteral nutrition in the early months of life. This ensures a satisfactory statural and weight gain growth.

Calculation of necessary fluid intake: V

\[ V = + \text{ extrarenal losses} + \frac{\text{QoSM}}{\text{Uosm}} \]

QoSM: osmotic load diet

Uosm: average urinary osmolality, estimated at 60 mOsm / kg in case of NCDI in its full form

\[ \text{QoSM} = \left(\frac{\text{Na} + \text{K}}{2}\right) + \left(\frac{\text{protidemia}}{4}\right) + \left(\frac{\text{Phosphorus}}{31}\right) \]

With Na, K in mmol / L, proteinsin and P in mg

b- Diet

• Limited in salt: Na 1mmol/kg/d
• Limited in proteins: 2 to 3 g / kg / d
• Mother’s milk is preferred in the first months of life as it is low in salt.

<table>
<thead>
<tr>
<th>Diuresis</th>
<th>Primary Polydipsia</th>
<th>DIC</th>
<th>DINC</th>
</tr>
</thead>
<tbody>
<tr>
<td>OsmoP (mOsm/l)</td>
<td>290 à 295</td>
<td>&gt; 295</td>
<td>&gt; 295</td>
</tr>
<tr>
<td>OsmoU (mOsm/l)</td>
<td>&gt; 750</td>
<td>&lt; 300</td>
<td>&lt; 300</td>
</tr>
<tr>
<td>OsmoU after Minirin®</td>
<td>Entre 300 et 750</td>
<td>&gt; 750</td>
<td>&lt; 300</td>
</tr>
</tbody>
</table>

Table 2: test of hydric restriction and DDAVP
c- Diuretics
• Hydrochlorothiazide (+ potassium): 2 to 4 mg / kg / day
  The extracellular volume contraction causes the proximal reabsorption of Na and water
• Amiloride: mg/m2/1 20, 73 / d - additive action
• Furosemide / amiloride association

d- Prostaglandin Synthesis Inhibitors
  The most widely used is the start of indomethacin at a dose of 0.5 mg / kg / day, gradually increased to 3mg/kg/j depending on diuresis and hydric needs. It induces preglomerular vasoconstriction, where a decrease of GFR and stimulation of the proximal reabsorption of Na, decreasing of distal tubular flow and reducing diuresis tubular flow.

  Note: Care should be taken in these patients to avoid occurrence of dehydration accidents. Each patient should carry with him/her a document explaining the disease, its management and precautions.

B- Other causes of hypotonic polyuria
  1- Central Diabetes Insipidus (CDI)
  • CDI is secondary to a deficiency in AVP either genetic (by AVP mutation o) or acquired (idiopathic, auto immune, secondary to a hypothalamic-pituitary, traumatic, postoperative, tumour, ischemic, infectious, granulomatous, pregnancy, injury).
  • The onset is often brutal. These children have a compelling thirst, persistent at night, generating anxiety when access to water is difficult.
  • Polyuria remains hypotonic during hydric restriction deprivation test despite the hypernatremia.
  • Minirin ® injection corrects the deficiency in AVP and reduces diuresis, with increased osmoU.
  • AVP deficiency may be complete or partial.
  • CDI can be isolated or associated with hypopituitarism.
  • CDI treatment is based on Minirin®administration.

  2- Potomania or primary polydipsia
  • It results from excessive fluid intake, causing a secondary polyuria.
  • The onset is usually gradual in children with psychological disorders altering the sensation of thirst.
  • Clinical examination is normal.
  • The hydric restriction test is well tolerated diuresis decreases with increasing urine concentration, without natremia disruption. It should be noted that in cases of chronic potomania, the response to the test restriction is partial as there is some resistance to AVP. It is often necessary to repeat the test or perform a Minirin®injection to differentiate CDI potomania.

V- DIFFERENTIAL DIAGNOSIS
A- Renal pathologies with urine concentration disorders
  • Renal hypoplasia
  • Severe uropathy
  • Tubular or tubulointerstitial injury: Bartter syndrome, nephronophthisis
B- Other causes

- Osmotic polyuria: diabetes mellitus, mannitol, salt
- Chronic electrolyte disorders: hypercalcemia, hypokalemia
- Sickle Cell
- Toxic: lithium, amphotericin B, cisplatin

VI- OUTLOOK

- Possibility to adapt treatment to each patient depending on the type of mutation introduced (it was reported more than AVPR2 200 mutations, and homozygous or compound heterozygous mutations of AQP2 in the autosomal recessive form)

- Development of molecular chaperones: non-peptide antagonist RV2 (SR 121463A, SR49059), but effectiveness depends on the nature of the mutations involved, MCF (agonist effect on NCDI receptors)

Possibilities in Africa: NCDI diagnosis and management remains simple and can be done anywhere in Africa.

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CHAPTE 15

NEPHROLITHIASIS AND NEPHROCALCINOSIS

Pierre Cochat, Lyon - France
HIGHLIGHTS
✓ The urolithiasis is relatively rare and should be considered in a variety of clinical presentations, usually involving pain and hematuria it may also be an incidental discovery.
✓ The initial management is based on the nephritic colic treatment.
✓ The nature of the lithiasis is specified based on available resources, ideally through crystalluria and gallstone analysis by infrared spectrophotometry, and sometimes by guided biochemical tests.
✓ The etiologies depend largely on the nutritional, geographical and cultural context we, thus, identify tubulopathies, hereditary metabolic diseases, infectious lithiasis, lithiasis associated with uropathies and drug-induced lithiasis.
✓ Surgical treatment has been replaced by non-invasive or minimally invasive methods, and each etiology has a specific medical treatment.
✓ The prevention of recurrence is based on the urine dilution by the hydration and the prognosis depends on the causal condition and the existence of nephrocalcinosis.

I- INTRODUCTION
Lithiasis formation is usually multifactorial and results from an imbalance between promoters (calcium, oxalate, uric acid) and inhibitors (phosphate, magnesium, citrate), which crystallize according to their solubility product and the urine Hp. Globally, we can oppose «lithiasis overnutrition» in adults in Western countries (urolithiasis prevalence in the United States rose from 3.8% to 5.2% between 1970 and 1990) and «malnutrition lithiasis» affecting many children in developing countries (1). Regarding pediatrics, developed countries are characterized by a predominance of calcium oxalate nephrolithiasis and struvite, while developing countries have reported a large number of ammonium urate calculi and recessive hereditary pathologies due to the consanguinity frequency in this context. In all cases, lithiasic pathology is a public health problem. However, there is no reliable epidemiological data in children as means of analysis are numerous. The prevalence is estimated at 1% in developed countries versus 5 to 15% in some developing countries. One common denominator: most pediatric series show a male predominance.

II- DIAGNOSIS
A- Clinical presentation
Nephritic colic semiology (Table 1) is all the more unusual since the child is young and the diagnosis is often brought before hematuria, urinary tract infection, the gallstones emission, recurrent abdominal pain, or incidental discovery of nephrocalcinosis or nephrolithiasis. Complications are always possible and can be inaugural, it is about therapeutic emergencies: infected urine retention and upstream obstructive urolithiasis, anuria (solitary kidney lithiase or bilateral lithiase), renal colic hyperalgic, enclosed urethral lithiase. History taking is essential. Clinical examination assesses growth, bone health, and signs of extrarenal volume diuresis. A brief dietary survey is often necessary, especially with regard to hydration habits.
Table 1: Clinical classical signs of the nephritic colic

**Pain +++**
- Very severe
- Paroxysmal causing anxiety and agitation
- Unilateral predominantly lumbar
- Inguinal Irradiation
- Sometimes triggered by a trip

**Macro-or microscopic hematuria**
± Bladder signs: pollakiuria ,false desires
± Digestive signs: nausea, vomiting, transit stop

B- Imaging
- Ultrasound shows the gallstones and objectifies its impact, but the detection of lumbar or pelvic lithiase might be delicate. It is also the best way to affirm, locate and quantify nephrocalcinosis.
- The abdomen cliche without preparation is essential and complementary to recognize a radiopaque lithiase and identify unusual locations (retro-bladder ureter, bladder, urethral).
- The uroscan has a higher sensitivity to ultrasound but its use is limited in pediatrics.

At the end of these investigations in the North African experience, the location is pyelocaliceal in 65 to 78% of cases, ureteral or bladder in 19 to 35% of cases (1,2).

III- CONDUCT OF ETIOLOGIC ASSESSMENT

A- Urinalysis

**Table 2: Diagnostic orientation according to the stone composition**

<table>
<thead>
<tr>
<th>Gallstone Composition</th>
<th>Affection in question</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phospho-ammonium magnesium (struvite, type IV)</td>
<td>Urinary tract infection in germ urease</td>
</tr>
<tr>
<td>Calcium phosphate (brushite, type IV) Calcium carbonate (carbapatite)</td>
<td>Hypercalciuria Tubular acidosis</td>
</tr>
<tr>
<td>Calcium oxalate dihydrate (Weddelite, type II)</td>
<td>Urease germs infection</td>
</tr>
<tr>
<td>Calcium oxalate monohydrate (whewellite, type I)</td>
<td>Hyperoxaluria</td>
</tr>
<tr>
<td>Cystine (type V) Cystinuria</td>
<td>Cystinuria</td>
</tr>
<tr>
<td>Uric acid (type III) Hyperuricosuria Purine metabolism anomaly</td>
<td></td>
</tr>
<tr>
<td>2.8 Dihydroxyadenine Deficiency in adenine phospho-ribosyl transferase</td>
<td></td>
</tr>
<tr>
<td>Xanthine Xanthinuria</td>
<td></td>
</tr>
<tr>
<td>Drugs Precipitation of the parent drug or metabolite</td>
<td></td>
</tr>
</tbody>
</table>
With dipstick is essential, sometimes supplemented by a bacteriological examination. Lithiasis morphological analysis (binocular) is essential and efforts must be made to collect the gallstones or their debris (2). Crystalluria study –when possible- should be conducted on freshly voided urine and infrared spectroscopy provides precise results regarding the composition (Tables 2 and 3), while other investigations are limited to specific tests of the mentioned etiology. If the nature of the lithiasis is not identified, guided biochemical tests are to be undertaken.

B- Affections in question

Table 3: Distribution (%) of major stone constituents in North Africa (2,3)

<table>
<thead>
<tr>
<th>Major Constituent (%)</th>
<th>Tunisia (N = 187)</th>
<th>Egypt (N = 100)</th>
<th>Morocco (N = 222)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Both sexes</td>
<td>Both sexes</td>
<td>Boys</td>
</tr>
<tr>
<td>Calcium oxalate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- whewellite</td>
<td>61,5</td>
<td>47,7</td>
<td>34</td>
</tr>
<tr>
<td>- weddelite</td>
<td>49,2</td>
<td></td>
<td>9</td>
</tr>
<tr>
<td>Phosphates</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- carabapatite</td>
<td>18,8</td>
<td>21,4</td>
<td>11</td>
</tr>
<tr>
<td>- brushite</td>
<td>10,7</td>
<td>8,7</td>
<td>19</td>
</tr>
<tr>
<td>- struvite</td>
<td>0,6</td>
<td>0,6</td>
<td></td>
</tr>
<tr>
<td>Purines</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- uric acid</td>
<td>13,3</td>
<td>2,9</td>
<td>3</td>
</tr>
<tr>
<td>- ammonium urate</td>
<td>6,4</td>
<td>8,7</td>
<td>17</td>
</tr>
<tr>
<td>- xanthine</td>
<td>1,0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- cystine</td>
<td>6,4</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>- proteins</td>
<td>5,3</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>- drugs</td>
<td>1,1</td>
<td></td>
<td>2</td>
</tr>
</tbody>
</table>

Lithiasis secondary to tubulopathies or to inborn errors of metabolism are rarer than lithiasis occurring in the context of infection, malformation or nutritional disorder, but they are generally more serious, their identification has essential therapeutic and genetic consequences (Table 4). Bladder lithiasis «endemic» has a special place in pediatrics (1,2,3), representing up to one third of lithiasis cases in developing countries, while it has almost disappeared in the developed countries. It mainly affects children, especially boys, aged one to five years. The gallstones, which can reach 4 cm diameter, consist essentially of ammonium urate and some calcium oxalate. Their origin lies in malnutrition, particularly in phosphate deficiency (no dairy, no animal protein), diverting the renal elimination of the acid load to the kidney ammoniagenesis which combines with physiological hyperuricosuria the process is often favored by insufficient hydration or by dehydration repeated episodes.
In addition, it seems that the phenomenon of land global warming significantly increases the global prevalence of nephrolithiasis (4). In addition to the affections specifically responsible for lithiasis, we can observe toxic lithiasis, either drug-induced or non drug-induced one (Table 5). In some cases, urinary calculi may reveal a Munchausen syndrome (5).

In practice, what should be done is simple initial diagnosis (Table 6). After this disentangling, management requires a specialized environment.

**IV- PROGNOSIS**

The main prognostic factors with regard to the risk of chronic renal failure are the presence of nephrocalcinosis and repeated obstruction and/or infection episodes. Therefore, the risk is particularly found in certain diseases, including the genetic ones: primary hyperoxaluria, cystinuria, Dent disease, family hypomagnesemia-hypercalciuria-nephrocalcinosis syndrome, Bartter syndrome, 2.8 deficit-dihydroxyadenine (6). An early and effective management can differ and even prevent the renal function deterioration.

**V- MANAGEMENT**

Most child lithiases belong to a specific treatment of the causal affection, but several aspects of treatment are common to all etiologies.

**A- Urgent treatment of nephritic colic**

This treatment is based on a consensus established in adults and is effective in less than an hour:
- Venous route as long as there is pain
- Ketoprofen: 1 mg / kg every 8 hours without exceeding 48 hours
- Paracetamol 15 mg / kg
- If insufficient analgesia: nalbuphine 0.2 mg / kg every 6 hours
- Free drinks, to adapt to thirst and diuresis
- Filter the urine.

**Table 4: Hereditary diseases that cause stones: guidance material**

- Early start
- Family history of renal lithiasis, parental consanguinity
- Bilateral and multiple gallstones
- Frequent recurrences
- Nephrocalcinosis often associated
- Tubular damage
  - Clinical syndrome polyuriodipsie, stature delay
  - Organic syndrome: metabolic acidosis, impaired concentration
- Sometimes non-specific renal signs
B- Major Principles of Preventive and Maintenance Regimen

The lithiasic risk is directly related to the urinary concentration of a component (normal or abnormal), expressed by the connection of a numerator (mass mg, mmol, etc.) to a denominator (urine volume L, mL, etc.). To reduce this connection, the numerator should be reduced (specific treatment: reduction in urinary calcium with a thiazide and / or a reduction in sodium intake) whereas the denominator should be increased (urine volume, thus hydration). Certain crystallization thresholds are, therefore, identified, eg 0.4 mmol / L for urinary calcium and 4 mmol / L for oxaluria.

1- Urine dilution

The base treatment of any lithiasis is the solutes dilution contained in the urine by increasing urine output, and thus, the hydration. Therefore, diuresis should be at least 2 to 3 L / m² per 24 hours in a lithiasic patient. Drinks are taken at regular intervals throughout the day, plus taking at bedtime and during all awakenings at night to ensure urine dilution throughout the nychthemeron. In some specific affections (primary hyperoxaluria), the conduct of hydration in young children may require the use of enteral feeding.

2- Hp Control

The importance of urinary Hp should not be neglected as it determines in part the lithiasic risk. When it is less than 5.3, it favors the crystallization of uric acid, cystine, xanthine, when above 6.5, it favors the crystallization of calcium phosphate and phosphoric complex – ammonium magnesium.

Table 5: Lithiasis and toxic crystalluria (9,10)

<table>
<thead>
<tr>
<th>Drug-induced Lithiasis</th>
<th>Non drug-induced Toxic Lithiasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug-induced medicine precipitation</td>
<td>Induction of hyperoxaluria</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>Vitamin D</td>
</tr>
<tr>
<td>Triamterene</td>
<td>Furosemide</td>
</tr>
<tr>
<td>Gelopectose</td>
<td></td>
</tr>
</tbody>
</table>

3- Role of surgery

Extracorporeal lithotripsy should be the first therapeutic option it requires general anesthesia in young children and requires an experienced team. Other techniques are sometimes used, either as part of the emergency, or cold: ureteroscopy, percutaneous nephrolithotomy, J double probe, etc.. However, regarding problems of access to technical equipment which is expensive, the use of open surgery is still common, especially for staghorn calculi that are usually infectious by origin (2). Similarly, bladder stones usually justify percutaneous cystolithotomy (7). The ureteric stones, depending on their size, can be removed by ureteroscopy, if a non-invasive removal is not possible (8).
Table 6: Conduct of the disentangling etiological investigation

<table>
<thead>
<tr>
<th>Clinic</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Clinical examination (growth, hearing, blood pressure, neurological examination)</td>
</tr>
<tr>
<td>• Personal history (drugs, nutrition, hydration)</td>
</tr>
<tr>
<td>• Family history (gallstones, consanguinity)</td>
</tr>
<tr>
<td>• Ultrasound + abdomen cliché without preparation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Biology</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Diuresis, crystalluria, gallstones morphological analysis, infrared spectrometry</td>
</tr>
<tr>
<td>• Dipstick: blood, protein, nitrite, leukocytes, Hp, glucose, density</td>
</tr>
<tr>
<td>• Plasma Na, K, Cl, bicarbonate, Ca, P, Mg, creatinine, osmolality, uric acid, PTH</td>
</tr>
<tr>
<td>• Urine: urine culture, osmolality, Ca, Na, P, Mg, sometimes: cystinuria, oxaluria, urinary citrate</td>
</tr>
</tbody>
</table>

VI- CONCLUSION

Nephrolithiasis and nephrocalcinosis are symptoms and not a disease in itself. In children, the etiology is often available on the basis of available diagnostic tools. It is essential to have access to early diagnosis, especially in case of tubular or metabolic abnormalities. The management always involves hyperhydration and generally specific treatment. The renal prognosis depends mainly on the presence or absence of nephrocalcinosis, the observance degree of infection repeated episodes and obstruction, sometimes repeated surgical procedures and therefore the overall available resources. Sometimes, the overall prognosis also depends on the severity of extra-renal signs.

References

7) Melouet F, El Kabbaj F. Apport de l’analyse morpho-constitutionnelle des calculs dans le diagnostic étiologique de la lithiase urinaire chez l’enfant marocain (soumis pour publication).
CHAPTRE 16

URINARY LITHIASIS IN MOROCCO
EPIDEMIOLOGY AND BIOLOGICAL EXPLORATION

Faïza Meiouet, Saâd El Kabbaj, Rabat - Morocco
HIGHLIGHTS

✓ The urolithiasis is much less common in children than in adults.
✓ The main causes are essentially: urinary infections, malformative uropathies and metabolic causes.
✓ Children urinary lithiasis poses specific problems that are frequently difficult, which make it advisable to manage it by specialized nephro-urological and biological teams.
✓ A thorough biological exploration is essential in children since the first lithiasic occurrence.
✓ The morpho-constitutional analysis of gallstones and the study of the crystal are crucial to the etiologic diagnosis.

I- FREQUENCY AND EPIDEMIOLOGY

Urolithiasis is much less common in children than in adults. Its prevalence is inversely related to the socioeconomic status of the population (1). In industrialized countries, the frequency of children urolithiasis has significantly decreased compared to what it used to be before and the bladder lithiasis has become scarce (2).

In all European series, 50 to 60% of lithiasis in children occur before the age of 5, half of which before the age of 2 years (2). The main causes are urinary tract infections, malformative uropathies and metabolic causes (1). In France, Daudon (3) observed an increase in frequency of children lithiasis, slight but significant: from 2.8% in the period between 1980 and 1989 to 3.6% in the period between 2000 and 2009.

II- DEMOGRAPHIC CHARACTERISTICS

Of our 310 analyzed gallstones serie, 90 belong to girls (29%) and 220 come from boys (71%) (5). Extreme ages range from 3 months to 17 years for boys with an average age of 7.2 years and between 1 and 17 years for females with an average age of 9.2 years. This prematurity of urolithiasis observed in infants in Morocco is also found in a study in Tunisia (6). As in other countries, the male predominance in Morocco, is still relevant with a male / female ratio (G / F) of 2.4.

This report is similar to the one observed by Osama (7) in the Middle Atlas in Morocco (G / F = 3) and is higher than the one observed by Daudon (8), France (G / F = 1.8) and Tunisia (9) (G/F = 1.5). Our results are in concordance with all pediatric studies conducted in developed as well as developing countries. They all converge towards the male preponderance.

III- CHEMICAL COMPOSITION OF GALLSTONES

In our study, 37.4% account for pure gallstones, largely dominated in children by oxalate monohydrate calcium, whereas in infants, ammonium urate gallstones of pure acid are the most dominant.

A- Influence of gender

The oxalate and calcium composition of gallstones is predominant with a considerable difference between boys and girls. Indeed, an increased frequency of whewellite (monohydrate calcium oxalate) was observed in females: 68% against 35% in boys. Weddellite or oxalate ofdehydrate calcium is not very common in Moroccan children: 8% in males and 3% in females.
B- Influence of age

1- In Males
In male infants, gallstones of ammonium acid urate predominate acid followed by phosphatic
gallstones composed primarily by carbapatite with urinary tract infections urease germs. The
proportion of these two types of constituents decreases with age later on. Conversely, there was a
significant increase in calcium oxalate monohydrate or whewellite with age.

2- In Females
The monohydrate calcium oxalate or (whewellite) becomes dominant at the age of 2 years and
reaches very high levels between 5 and 15 years. The struvite, which is a marker of urinary tract
infection with urease germs is also observed in all age groups.

IV- MONOGENIC LITHIASES IN MOROCCO
They are the result of monogenic hereditary anomalies and appear in early childhood. In our
study, 23.22% is due to metabolic diseases in which 18.7% caused by primary hyperoxaluria and
4.5% by cystinuria (5).

A- Geographic variations of urolithiasis
The examination of the data shown in table 1 highlights significant geographical variations. It is
clear that calcium oxalate is the dominant component in all countries except Sub-Saharan Africa.
Thus, whewellite gallstones are particularly common in Algeria (12), Tunisia (9) and Morocco (5)
with a very high proportion exceeding six to nine times that of weddellite, while in France (8)
whewellite and weddellite are in similar proportions.
The majority calcium phosphate gallstones occur more frequently in France (8) and particularly
in males 44% against 27.8% in females. The ammonium urate is responsible for nearly half of
the gallstones observed in Sudan (10) and the third of pediatric gallstones in the three countries
studied (11) (Cameroon, Senegal, Mali). As for the gallstones mainly composed of the struvite,
their frequency is variable: 2.26% in China (14), 25% in Croatia [13] with a proportion of struvite
gallstones containing up to 41.2% in (Cameroon, Senegal, Mali) (11), 24.6% in Algeria (12) and
22.9% in France (8).

B- Etiology of urolithiasis

1- Gallstones of calcium oxalate
Gallstones made of calcium oxalate are substantially the majority in all countries. However, crystal
phases constituting them have different etiologies: monohydrate calcium oxalate or whewellite is
oxalo-dependent while weddellite or dihydrate calcium oxalate is calcium-dependent.

a- Weddellite gallstones or dihydrate calcium oxalate
In the series analyzed in Morocco, Tunisia (9) and Algeria (12) (Table 1), the weddellite is
significantly less frequent compared to France. We can deduce that hypercalciuria is a less common
cause of lithiasis in the Maghreb countries compared to the industrialized ones where idiopathic
hypercalciuria is the most common cause of urolithiasis in children noted in 50 to 80% of cases
(3). The idiopathic hypercalciuria associates in varying proportions, intestinal hyperabsorption and
urinary leakage of calcium (19,20). It may be accompanied by bone loss (21, 22) that may be the
result or conversely the cause of renal calcium leak (23).
The hypercalciuria may also be secondary to monogenic diseases that are more rare (Dent disease, Lowe syndrome, familial hypomagnesemia) (24, 25, 26). In these diseases, the gallstones are made mostly of calcium phosphate in the form of carapatite of usual morphology with low carbonation rate while gallstones morphology type IVa2 towards a distal renal tubular acidosis.

b- Whewellite gallstones or monohydrate calcium oxalate

Table 1: Comparison of the frequencies of the main constituents lithiasic observed in children in countries grouped by geographical region

<table>
<thead>
<tr>
<th>Country</th>
<th>Calcium Oxalate</th>
<th>Calcium Phosphate</th>
<th>Presence of struvite</th>
<th>Purines</th>
<th>Cystine</th>
</tr>
</thead>
<tbody>
<tr>
<td>North of Africa or Maghreb</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tunisia [8] N = 310</td>
<td>52.6%</td>
<td>45.8%</td>
<td>6.8%</td>
<td>14.2%</td>
<td>9.7%</td>
</tr>
<tr>
<td>Algeria [11] N = 61</td>
<td>60.6%</td>
<td>50.8%</td>
<td>9.8%</td>
<td>19.8%</td>
<td>………</td>
</tr>
<tr>
<td>Study Morocco N = 310</td>
<td>57%</td>
<td>51.3%</td>
<td>5.5%</td>
<td>4%</td>
<td>20.3%</td>
</tr>
<tr>
<td>Sub-Saharan Africa</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cameroon Senegal Mali [10]</td>
<td>23.5%</td>
<td>23.5%</td>
<td>0%</td>
<td>5.9%</td>
<td>17.7%</td>
</tr>
<tr>
<td>Chadian [10] N = 175</td>
<td>55.4%</td>
<td>………</td>
<td>………</td>
<td>11.4%</td>
<td>15.9%</td>
</tr>
<tr>
<td>Europe</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>France [8] N = 1449</td>
<td>38.5%</td>
<td>17.25%</td>
<td>21.25%</td>
<td>31.15%</td>
<td>6.3%</td>
</tr>
<tr>
<td>Croatia [13] N = 146</td>
<td>48.7%</td>
<td>………</td>
<td>………</td>
<td>13.7%</td>
<td>25%</td>
</tr>
<tr>
<td>Asia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>China [14] N = 189</td>
<td>64.97%</td>
<td>49.72%</td>
<td>15.25%</td>
<td>9.04%</td>
<td>2.26%</td>
</tr>
<tr>
<td>West Asia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Armenia [15] N = 198</td>
<td>62%</td>
<td>………</td>
<td>………</td>
<td>7%</td>
<td>17%</td>
</tr>
</tbody>
</table>

The frequency of monohydrate calcium oxalate or whewellite in the Moroccan child is very high (5): 51.5%, and also in Algeria (12): 50.8% and Tunisia (9): 45.8%, in contrast to France (8) where it represents only 17.25%. This crystalline form is essentially oxalate-dependent and its origin in the gallstones is made up primarily of four mechanisms (3):
- Insufficient diuresis, which is a common cause of hyperoxaluria concentration.
- Excess intake of foods rich in oxalates (chocolate, spinach, beets, pepper...)
- Digestive hyperabsorption oxalate which can result trigger:
  - Low calcium intake
  - A high-fat diet may bind calcium in the intestinal lumen and promote secondary free oxalate absorption.
- Inflammatory diseases such as Crohn's disease or celiac disease
  - Irritation of the digestive mucosa linked to infectious or parasitic and endemic diseases and spice consumption increasing permeability to oxalate ions.
- An endogenous oxalate overproduction of genetic origin.
2- Gallstones of ammonium acid urate

In our series, this type of lithiasis is observed with a frequency of 9% and is specific to certain regions of Morocco. In the countries of Sub-Saharan Africa, the lithiasis is found at much higher frequencies: 48.6% in Sudan (10) and 29.4% in (Cameroon, Senegal, Mali) (11). It has become very rare in industrialized countries. This is an endemic lithiasis from disadvantaged backgrounds of developing countries (27, 28) and its occurrence is due to two factors (3).

a- Dietary factors

Throughout the duration of breast-feeding, infants receive an adequate intake of calcium, phosphorus and water. Nevertheless, after weaning, children living in these poor rural areas receive food mainly made of grains, low in phosphorus. In addition, this food is usually free of dairy and animal protein and therefore delivers a very low intake of phosphorus. Under these conditions, the excretion of H+ ions through kidneys is carried out predominantly by increasing ammonuria that promotes the precipitation of the ammonium acid urate in the presence of hyperuricosuria (due to immaturity tube) (28).

b- Factors associated with infectious diarrhea

These children suffer from frequent episodes of infectious diarrhea of bacterial or viral origin, leading to acute dehydration due to loss of bases, electrolytes and water. The kidneys compensate for the loss of a base by stimulating ammoniogenesis. This results in an increase in the concentration of ammonium and urine uric acid, without increasing urinary pH and thereby promoting the precipitation of the ammonium acid urate (29).

In both contexts, the ammonium acid urate may either compose completely the gallstone or be associated with a variable amount of monohydrate calcium oxalate.

Another pathological context may generate ammonium acid urate is the urinary infection with urease germs, where the high urinary pH and the urinary ammoniogenesis are caused by the local decomposition of urea (3).

3- Struvite gallstones

In our series, the struvite gallstones or infection lithiasis occupy the second position with 20.5% after the whewellite ones. They are significantly more frequent in boys with 29% than in girls with 12%. This lithiasis has considerably decreased in industrialized countries, reflecting the improvement in their health care level. It is observed at high rates in some countries such as Croatia 25% (13), Armenia 17.5% (15) and in Sub-Saharan Africa (Cameroon, Senegal, Mali) (11) where it accounts for 17.7%.

It requires medical treatment to eradicate completely and permanently the urinary infection and to stop this recidivism. Even a small proportion of struvite in a gallstone is evocative of a urinary tract infection with β urease germs. The major urinary germs producing urea are: D2 Corynebacterium, Ureaplasma urealyticum, Proteus, Staphylococcus epidermidis, Staphylococcus aureus and Klebsiella (3).

4- Gallstones of calcium phosphate

Calcium phosphates in the form of carbapatite are very uncommon in the Moroccan child with only 4%. These results are consistent with those of Daudon (11) who observed a proportion of calcium phosphate with 5.9% in African countries while in France (8), the calcium phosphates are sharply increasing in both sexes. However, a high incidence of urinary tract infections with non-urease germs such as Escherichia coli (30, 31) was observed in patients with phosphatic lithiasis.
5- Gallstones of uric acid
It is rare in our series (2%), as in most pediatric series (8.13). The pure uric lithiasis can be due to an important hyperuricemia as seen in Lesch-Nyhan syndrome, hematological malignancies and tumor lysis. Similarly, the risk of uric or urate acid lithiasis is higher in the first years of life due to the excretion of uric acid resulted from the higher neonatal tubular immaturity (32).

6- Medicated gallstones

Figure 1: Etiological directions of morpho-constitutional analysis calculations (3)

The drug that is most in question is the antibiotic: ceftriaxone, which promotes the formation of gallstones directly precipitating as crystals in the urinary tract.

7- Hereditary lithiases originally metabolic

a- Primary or Oxalosis Hyperoxaluria (POH)
This is the main cause of oxalate and calcium lithiasis in children in Morocco (18.7%). The prevalence of primary homozygotes hyperoxaluria is significantly higher in North Africa than in industrialized countries (11). Due to its scarcity, Primary Hyperoxaluria is often unrecognized or diagnosed late. It is responsible for less than 1% of end-stage renal failure (ESRD) in children
in Western populations, but represents more than 10% of ESRD children in countries with high consanguinity (3).

b- Cystine lithiasis
Lithiasis composed of cystine constituted 4% of gallstones, an incidence comparable to 5.3% found in a Tunisian study (34) with a male predominance also noted contrary to the French series (8) where there is a higher incidence of cystine in females.

V- CONDUCT OF BIOLOGICAL EXPLORATION
A thorough biological exploration is essential in children since the early lithiasic occurrences. The morpho-constitutional analysis of gallstones and the study of crystalluria are essential for the etiologic diagnosis.

A- Clinical benefits of the gallstones analysis
The gallstone is the key element of the etiological diagnosis because it is a pathological product, reflecting diverse cristallogenes process whose crystalline species composing it move towards the biochemical abnormalities that led to its formation.

B- Methods of gallstone analysis
1- Structural and morphological analysis
This step serves to identify the structural information of the gallstone. This can be obtained by optical methods from the binocular loupe to the scanning electron microscopy. Routinely, the examination of the binocular loupe is quite sufficient from a clinical perspective. At first, the surface of the gallstone is observed in details (color, texture, aspect) and its structural features such as crystalline conversion, the presence of abutment faces or papillary umbilication with Randall plate. Then, examining the gallstone section enables to assess the organization of the structural layers and to identify a zone of potential nucleation that is the starting point of lithogenesis.

2- Molecular and crystal Identification
This step can be performed by the crystallographic methods such as X-ray diffraction which was one of the first global physical used methods (39) or the spectral methods of molecular spectroscopy namely Infrared Spectroscopy and Raman Spectroscopy. The technique of choice is Infrared Spectrophotometry (IRSP), it can identify organic or mineral compounds, crystalline or amorphous, drugs and false gallstones.

C- Morpho-constitutional classification
Morpho-constitutional classification, structure and pathology are summarized in table 4.

D- Study of crystalluria
In the absence of analyzable gallstone, the crystalluria study is particularly valuable. The existence of crystalluria is one of the best reflections of the metabolic activity of the lithiasis, as there is in fact an excellent concordance between the nature of urinary crystals and biological abnormalities or the lithogenic composition of the gallstone. This etiological exploration permits (42,43):

• to screen genetic cristallogenic diseases.
• to screen mediated crystalluria.
• to identify risk lithogenic factors.
• to identify clinical risk factors of recurrence.
• to provide therapeutic monitoring.
• to immediately provide the diagnosis when identifying cystine crystals, 2.8-dihydroxyadenine, xanthine, struvite or medication.

The study of crystalluria is carried out on the first morning urine, because they correspond to urine issued overnight containing the solute concentration and therefore have a greater probability of containing crystals (43). The main etiological orientations according to the characteristics of crystalluria are summarized in Table 2.

VI- HEREDITARY AND METABOLIC DISEASES AT THE ORIGINE OF URINARY LITHIASES

In case of nephrocalcinosis, multiple bilateral calcium lithiasis or of particular extra-renal clinical signs (auditory, ocular, cerebral ...), some genetic diseases generating lithiasis must be systematically sought by some blood and urine tests often specific.

A- Primary hyperoxaluria,

By mutation of AGXT gene (type 1) or, more rarely, the GRHPR gene (type 2) should always be suspected in populations with high consanguinity. At the biochemical level, they are characterized by a significant rise in oxaluria accompanied by an increase in urinary excretion of glyoxylate, glycolate (AGXT gene mutation) or L-glycerate (GRHPR gene mutation) (53, 56,57). The dosage of these oxalate metabolic precursors allows to orientate the diagnosis towards the genetic form involved in the majority of cases, but provides no information about the nature of the mutations in question and, in case of AGT anomaly on the sensitivity to pyridoxine, which must always be tested in these patients a priori.

AGXT genotyping is, henceforth, sufficient to confirm the diagnosis when it identifies one of the recognized characteristic mutations in the target population, thus avoiding the use of liver biopsy (58, 59). Genotyping can also predict the response to pyridoxine the patients that are homozygous for Gly170Arg or Phe152Ile mutation are good responders (60). Primary hyperoxaluria type I is the most common and the only one that is likely to become more complicated to visceral manifestations of oxalosis. The mechanism of lithogenesis in hyperoxaluria is monofactorial: it takes a considerable increase in the oxalate concentration in urine.

B- Distal tubular acidosis

By mutation of the SLC4A1 gene, the autosomal dominant acidosis triggers, in patients, hypercalciuria, nephrocalcinosis and nephrolithiasis without neurosensory impairment. The distal tubular acidosis with an autosomal recessive transmission is due to some mutations in the genes: ATP6V0A4 without deafness or with late deafness and ATP6V1B1 accompanied in the latter case by early deafness (61).

C- Bartter syndrome

The cause of severe hypokalaemia, of which there are five types according to the mutated genes: type I (prenatal) (62) by mutation of the SLC12A1 gene type II (prenatal) (62) by mutation of the KCNJ1 gene type III (63) by mutation of the CLCNKB gene Type IV (Infant) (64) by mutation of the BSND gene Type V (65) by mutation of the CaSR gene (A).
Table 2: Relationships between morphological types, composition and causes of the associated calculations (37).

<table>
<thead>
<tr>
<th>Type Morphologique</th>
<th>Composition usuelle</th>
<th>Principales causes du calcul</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia Whewellite (C1)</td>
<td>Intermittent Hyperoxalurie with or without hyperuricurie. Randall’s plaque (umbilication) - Cacchi-Ricci disease</td>
<td></td>
</tr>
<tr>
<td>Ib Whewellite</td>
<td>Hyperoxaluria - Stasis</td>
<td></td>
</tr>
<tr>
<td>Ic Whewellite</td>
<td>Primary hyperoxaluria I, II, not I not II</td>
<td></td>
</tr>
<tr>
<td>Id Whewellite</td>
<td>Hyperoxaluria + multiple stones + anatomical confinement</td>
<td></td>
</tr>
<tr>
<td>Ie Whewellite</td>
<td>Absorptive hyperoxaluria (inflammatory bowel diseases, steatorrhea, extensive resection of the small intestine)</td>
<td></td>
</tr>
<tr>
<td>IIa Weddellite (C2)</td>
<td>Hyperoxaluria</td>
<td></td>
</tr>
<tr>
<td>IIb C1 + C2 through loss H2O or mixed crystallization</td>
<td>Hypercalciuria + moderate or intermittent hyperoxaluria</td>
<td></td>
</tr>
<tr>
<td>IIc Weddellite</td>
<td>Hyperoxaluria + multiple stones + anatomical confinement</td>
<td></td>
</tr>
<tr>
<td>IIIa Anhydrous uric acid (AU0)</td>
<td>Stasis - acid urine pH - prostatic adenoma</td>
<td></td>
</tr>
<tr>
<td>IIIb Uric acid dihydrate (AU2) and / or by AU0 (H2O loss)</td>
<td>Hyperuricosuria - ammoniogenesis renal failure (metabolic syndrome) - type 2 diabetes - hyperuricemia - ileostomy - myelo-lymphoproliferative syndrome - HPRT deficiency.</td>
<td></td>
</tr>
<tr>
<td>IIIc Various urate Ammonium acid urate</td>
<td>Hyperuricosuria + alkaline urine + excretion of excessive cation present Hyperuricosuria + urinary tract infection germs</td>
<td></td>
</tr>
<tr>
<td>IIId Ammonium acid urate</td>
<td>Hyper renal or urinary ammoniogenesis (infectious, nutritional or therapeutic) - Infectious diarrhea and malnutrition (phosphorus deficiency) - anorexia nervosa - laxative abuse.</td>
<td></td>
</tr>
<tr>
<td>IVa1 Carbapatite (CA) ± oxalates</td>
<td>Non urease urinary infection germs - hypercalciuria - phosphate diabetes - abnormal urinary acidification - primary hyperparathyroidism</td>
<td></td>
</tr>
<tr>
<td>IVa1 Carbapatite + struvite</td>
<td>Chronic urinary tract infection by urease germs</td>
<td></td>
</tr>
<tr>
<td>IVa2 Carbapatite</td>
<td>Congenital or acquired tubular acidosis (Sydrome Sjögren, chronic hepatitis) - intratubular calculations focal disorder acidification (Cacchi-Ricci)</td>
<td></td>
</tr>
<tr>
<td>IVb Carbapatite ± struvite</td>
<td>Recurrent urinary infection with urease microbes - primary hyperparathyroidism (+ struvite if infection)</td>
<td></td>
</tr>
<tr>
<td>IVc Struvite</td>
<td>Infection of the urinary tract by urease germs</td>
<td></td>
</tr>
<tr>
<td>IVd Brushite</td>
<td>Primary hyperparathyroidism - hypercalciuria - phosphate diabetes</td>
<td></td>
</tr>
<tr>
<td>Va Cystine</td>
<td>Cystinurie-lysinurie</td>
<td></td>
</tr>
<tr>
<td>Vb Cystine + traces CA</td>
<td>Cystinurie + therapeutic alkalizing and poorly balanced diet</td>
<td></td>
</tr>
<tr>
<td>VIa Protéines</td>
<td>chronic pyelonephritis</td>
<td></td>
</tr>
<tr>
<td>Vlb Proteins + compound metabolic or iatrogenic Proteins + CA (± struvite)</td>
<td>Protein origin (clot, or primitive reaction proteinuria) + metabolic or drug cause (triangulene, quinolones, ....) Infection of the urinary tract</td>
<td></td>
</tr>
<tr>
<td>VIc Protein + C1</td>
<td>End stage renal disease - chronic dialysis</td>
<td></td>
</tr>
<tr>
<td>IV Urinary infection HO</td>
<td>hyperoxalurie</td>
<td></td>
</tr>
</tbody>
</table>
D- Tooth Disease
By mutation of the CLCN5 gene, reflected biologically by a low weight molecular proteinuria (made of β2-microglobulin), hypercalciuria, hypophosphatemia and hyperphosphaturia (64). It is accompanied by nephrocalcinosis, a calcium phosphate lithiasis and renal failure progressing to ESRD (67).

E- Ocular Cerebral Renal Syndrome of Lowe
By mutation of the OCRL1 gene, which can give birth to the same abnormalities as the tooth disease or be accompanied by ocular (cataracts) and cerebral (mental retardation) problems and, at the biological level, by a hyperchloremic acidosis, a low weight molecular proteinuria, hypercalciuria and aminoaciduria (68).

F- Family Hypomagnesemia
With hypercalciuria and nephrocalcinosis by mutation of CLDN16 gene, which results in normocalcemic hypermagnésurie and hypomagnesemia with hypercalciuria (67, 69).

G- Hypophosphatemic rickets (RHH)
By mutation of PHEX, FGF23 or SLC34A3 genes [70], resulting biologically in hypophosphatemia and hyperphosphaturia and can lead to lithiasis and hypercalciuria with nephrocalcinosis when children are supplemented with vitamin D (67).

H- Phosphated Diabetes
By mutation of the NPT2a gene that is responsible, according to mutations, for lithiasis or osteoporosis, which is reflected biologically by hypophosphatemia with renal phosphate leak with hypercalciuria and increased circulating calcitriol (67).

---

Table 2a: Morphological main associations

<table>
<thead>
<tr>
<th>Type Morphologique</th>
<th>Composition usuelle</th>
<th>Principales causes du calcul</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia + IIa</td>
<td>Whewellite + weddellite</td>
<td>Intermittent hypercalciuria + Intermittent hyperoxaluria</td>
</tr>
<tr>
<td>Ia + IIa + IVa</td>
<td>Whewellite + weddellite + carbapatite</td>
<td>Intermittent hypercaliciuria + hyperoxaluria - Cacchi-Ricci disease</td>
</tr>
<tr>
<td>IIa + IVa</td>
<td>weddellite + carbapatite</td>
<td>Hypercalciuria - primary or secondary hyperparathyroidism</td>
</tr>
<tr>
<td>Ia + IIIb</td>
<td>Whewellite + uric acid</td>
<td>Hyperuricemia/Hyperuricosuria + intermittent hyperoxaluria</td>
</tr>
<tr>
<td>Ia + IVa</td>
<td>Whewellite + carbapatite</td>
<td>Cacchi-Ricci - Intermittent hyperoxaluria + urinary infection</td>
</tr>
<tr>
<td>IVa + IVc</td>
<td>Carbapatite + struvite</td>
<td>Infection of the urinary tract by urease germs</td>
</tr>
</tbody>
</table>
I- Anomalies of purines track

- Lesch-Nyhan syndrome, which is revealed by choreoathetosis, a mental retardation and self-harm behavior, is due to a complete deficiency of hypoxanthine guanine transferase phosphoribosyl (HGPRT) (67, 71). This affection, whose transmission is linked to the X, affects therefore mostly boys.

In case of partial deficiency (Kelley-Seegmiller syndrome), neurological signs are absent. At the biochemical level, the two syndromes result in hyperuricemia with Hyperuricosuria, which can bring about gout crises, urate nephropathy, and a risk of uric lithiasis. Another rare cause of hyperuricemia with hyperuricosuria and lithiasis of uric acid is the hyperactivity of the phosphoribosylpyrophosphate synthase (PRPPS) (67).

- Mutations in the gene encoding the URAT1 transporter, which provides the tubular reabsorption of the uric acid, result in hyperuricosuria with hypouricemia which creates a risk of lithiasis, particularly when the urinary pH is mildly acidic (67).

- The glycosogenoses diseases type I, type III or type V (67).

J- Cystinurie

Cystinuria is a hereditary aminoaciduria transmitted as an autosomal recessive mode, which explains the supporting role of consanguinity. It is caused by a hereditary anomaly in the intestinal and renal transport of cystine and dibasic amino acids: arginine, lysine and ornithine, and this
<table>
<thead>
<tr>
<th>Nature crystals</th>
<th>Characteristics of the crystalluria</th>
<th>Pathology or abnormality associated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whewellite</td>
<td>Presence</td>
<td>Hyperoxalurie de débit ou de concentration</td>
</tr>
<tr>
<td></td>
<td>Number of crystals &gt; 200/mm³</td>
<td>Massive hyperoxaluria =&gt; search primary hyperoxaluría</td>
</tr>
<tr>
<td></td>
<td>Facies crystals shuttles and stretched hexagons</td>
<td>Ethylene glycol poisoning</td>
</tr>
<tr>
<td></td>
<td>Crystal volume &gt; 1000 mm³</td>
<td>In renal transplant patients, the risk of impaired graft Intratubular crystallization</td>
</tr>
<tr>
<td>Weddellite</td>
<td>Mere presence</td>
<td>Hypercalciurie concentration</td>
</tr>
<tr>
<td></td>
<td>Facies dodecahedral crystals</td>
<td>Hypercalciurie major metabolic</td>
</tr>
<tr>
<td></td>
<td>Crystal size &gt; 35 microns</td>
<td>Hypercalciurie + hyperoxalurie + Hypocitraturia relative or absolute</td>
</tr>
<tr>
<td>Brushite</td>
<td>Mere presence</td>
<td>Hypercalciurie ± hyperphosphaturie</td>
</tr>
<tr>
<td></td>
<td>Number of crystals &gt; 500 / mm³</td>
<td>Primary hyperparathyroidism</td>
</tr>
<tr>
<td></td>
<td>Heterogeneous nucleation with weddellite</td>
<td>Calcium lithiasis recurrence risk</td>
</tr>
<tr>
<td>Cystine</td>
<td>Mere presence</td>
<td>Cystinurie</td>
</tr>
<tr>
<td></td>
<td>Cristallin volume &gt; 3000 µ3/mm³</td>
<td>Gallstone recurrence likely</td>
</tr>
<tr>
<td>2,8-Dihydroxyadenine</td>
<td>Mere presence</td>
<td>Homozygote adenine phosphoribosyl transferase deficiency</td>
</tr>
<tr>
<td>Struvite</td>
<td>Mere presence</td>
<td>Urease germs infection</td>
</tr>
<tr>
<td>Ammonium acid urate</td>
<td>If pH &gt; 7</td>
<td>Hyperuricosuria + Infection with urease germs</td>
</tr>
<tr>
<td></td>
<td>If pH &lt; 7</td>
<td>Hyperuricosuria + Chronic Diarrhoea + phosphorus deficiency</td>
</tr>
<tr>
<td>Uric acid</td>
<td>If pH &lt; 5.3</td>
<td>Risk of lithiasis by hyper urinary acidity</td>
</tr>
<tr>
<td></td>
<td>If pH &gt; 5.3</td>
<td>Hyperuricosuria</td>
</tr>
<tr>
<td>Medicine</td>
<td>Needle crystals, sticks or strips aggregated by big dimensions ( &gt; 50 microns)</td>
<td>Risk of acute renal failure or stones</td>
</tr>
<tr>
<td>All crystals</td>
<td>Crystalluria frequency &gt; 50% of the samples examined</td>
<td>Major risk gallstone recurrence</td>
</tr>
</tbody>
</table>
defect of proximal tubular reabsorption leads to increased urinary excretion of these amino acids. Since cystine is the least soluble of the amino acid, it precipitates and forms very recurrent cystine stones that may destroy the kidneys (1).

1- Biochemical classification of cystinuria
It is based on the combination of disorders of the intestinal and renal transfer observed in heterozygous and homozygous cases (2). In homozygous cases, the three types have a cystine excretion (MW = 240 Da) superior than 2.5 mmol / d (> 600 mg / day) and result in lithiasis. In heterozygous cases, the urinary excretion of cystine has variable degree:

- In type I: it is normal and the heterozygous never become lithiasic.
- In type II: it can reach 2.5 mmol /d and some of these heterozygotes may develop lithiasis.
- In type III: it is moderate and these heterozygotes do not develop stones.

2- Genotypic classification of cystinuria
The new cystinuria classification distinguishes three types (A, B and AB).

- In type A: homozygous cystinuria results in mutations affecting both alleles of SLC3A1. Heterozygous have a normal excretion of amino acids
- In type B: homozygous cystinuria results in mutations affecting both alleles SL7A9. Heterozygous have a normal or increased cystinuria
- In the AB type, cystinuria results in a mutation in one allele of SLC3A1 and SL7A9 allele. Urinary excretion of cystine is 30% lower than the one observed in homozygous types A and B [73].

VII- PREVENTION OF URINARY LITHIASIS
It aims at:
- Avoiding the appearance of the lithiasis in people previously untouched, mainly in the case of heritable lithiasis.
- Avoiding the recurrence of gallstone formation.
- Preserving the renal function of patients with lithiasis especially in the severe forms of the lithiasis.

A- Primary hyperoxaluria
Conservative treatment consists of: A quantity of drink > 3l/day well distributed over the nycthemeron, removal of oxalate-rich foods, Vitamin B6 (100-300 mg /day), thiazide diuretics, magnesium, itrate potassium.

Pyridoxine should be routinely tested in all patients even in end-stage renal failure. Genetic testing can identify potentially responsive patients to pyridoxine. In addition, molecular genetics allows prenatal diagnosis of the disease, provided you have the DNA of other family members, especially both parents (67).

B- Lithiasis of acid ammonium urate
The lithiasis of ammonium urate acid depends mainly on environmental conditions and nutritional habits. It is associated with an ammoniogenesis exess that may be of renal origin (phosphorus deficiency, loss of digestive bases by chronic diarrhea) or urinary one (ammoniogène infection).
1- Promoting factors

- Nutrition: very low in phosphorus (low in dairy and animal protein) and high in grain or vegetarian with high purines.
- Dehydration: insufficient water intakes and chronic diarrhea.
- Loss of digestive bases: chronic infectious diarrhea.
- Urinary infections with urease germs.

2- Treatment

- Rebalance the dietary intakes
- Remove the causes of the digestive bases losses,
- Rebalance the fluid or electrolyte balance,
- Restore alkali intake, including supplements citrate,
- Increase water intake,
- In case of infectious etiology, appropriate antibiotic treatment should be undertaken.

C- Cystine lithiasis

1- Basic Measurements

- Quantity of drink > 3 l / d well distributed over 24 hours (alkaline drinking water last dose before bedtime and in severe cases, a new dose around 2 or 3 am).
- Alkalinization of urine: objective: pH of about 7.5 not exceeding 8: Vichy water or Sodium Bicarbonate: 8-12 g / day but may increase natriuresis or tripotassium citrate: 6-9 g / day diluted in 2 to 3 liters of water.
- Restricting foods rich in methionine (sardines, gruyere and cheese with and cooked pasta and all the preparations rich in eggs) (limiting intakes to 1000 mg / day).
- Avoiding drinks high in phosphoric acid (eg colas).
- Reducing high sodium intake.
- Limiting intakes of meat, poultry and fish between 120-150g / day and no more than one egg per week.

2- Medical treatment

- D-penicillamine (300 mg Trolovol): 600-1200 mg / day.
- Tiopronine (Acadione 250 mg): 500-1500 mg / d.

D- Infectious Lithiasis

Eradicating the infection with prolonged antibiotic treatment (several weeks) adapted to the antibiogram after urine culture and removal of gallstones. Also, correcting sometimes anatomic abnormalities and diuresis > 2 liters / day.

E- Oxalate calcium lithiasis

1- General Measures

Amount of drink > 2 l / well distributed over the nycthemeron day (think to drink a large glass of water at bedtime).
• Normal calcium intakes: 800 -1000 mg /day.
• Limiting animal protein intake to 1.2 g /kg /day.
• Reducing sugar intake rapid absorption (sugar, honey, chocolate, jam...)
• Reduce salt intake (less than 9 g /day).

Oxalate and calcium lithiasis with hyperoxaluria
• Calcium intake should be> 800 mg / day (take dairy products).
• Avoid foods high in oxalates (chocolate, sorrel, beets, pepper...)
• If insufficient ==>medical treatment: Vitamin B6 ±Mg, or Allopurinol (200 mg / day) or Thiazide (<25 mg / day) + potassium chloride or Moduretic.

Oxalate and calcium lithiasis with hypercalciuria
The calcium intake should be: 800 - 1000 mg / day. If insufficient, medical treatment Thiazide based.(<25 mg / day), potassium citrate (6-8 g / day diluted in the 2 liters of drinking water), Allopurinol (200 mg / day).

VIII- CONCLUSION
The composition of children's urinary gallstones in Morocco is characterized by the predominance of monohydrate calcium oxalate, where a high proportion is due to an overproduction of endogenous oxalate genetic due to primary hyperoxaluria. The high content of struvite gallstones indicates that infection with urease germs is the main cause.

In many African countries, there is an absence of metabolic investigation which may lead to a delay in diagnosis with deleterious consequences for kidney function, especially in the case of hereditary lithiases and secondary lithiases that require an etiologic management. In all cases, the morpho-constitutional analysis of the gallstones allows to orientate very usefully the etiological diagnosis and further investigation. When there is no gallstone, the study of crystalluria is a clinically useful test that orientates or affirms a diagnosis.

We would like to warmly thank Dr. Michel Daudon, a biologist in Paris Hospitals, who has allowed us to benefit from his long insightful expertise in the field of lithiases at the Necker Hospital and Tenon Hospital. His photos and date have been our reference while editing this chapter.
References

PART V

ARTERIAL HYPERTENSION

CHAPTER 17

CHILDREN’S HIGH BLOOD PRESSURE IN AFRICA

Adonis-Koffy Laurence, Abidjan - Côte d’Ivoire
HIGHLIGHTS
✓ High blood pressure (hypertension), which is a major public health problem affecting nearly 20% of adults, is a dreadful cause of morbidity and mortality. This is why taking the blood pressure should be part of routine examinations in children in general, and in any child affected with heart or kidney disease, with a prematurity history, who underwent body transplantation, or finally those who have received drugs that could cause hypertension.
✓ The prevalence of hypertension in children is much lower than in adults (1% to 3%), but its consequences can be equally devastating.
✓ The younger the child, the more high blood pressure becomes the result of renal parenchymal or vascular disease or an endocrine abnormality.
✓ The frequency of idiopathic hypertension becomes significant only in adolescence, and it remains a diagnosis of exclusion.
✓ The pharmacological treatment of hypertension in children is still characterized by limited studies on the use of antihypertensive drugs in this age group.

I- INTRODUCTION
High blood pressure in children can be treated as an orphan disease because its prevalence remains unknown to this day, while in adults, it is a real public health problem exposing each year nearly 180,000 people to cardiovascular and kidney complications (1). This is a so serious and frequent condition that the systematic control of blood pressure has become a compulsory act of adult’s consultation for early screening. While in children it seems to be rare, there is a vicious circle of its underestimation. Its relatively low prevalence does not generally trigger, as in adults, primary preventions reactions. Thereby taking the blood pressure (BP) in a paediatric setting is not yet systematic and does not reflect the full extent of the problem (2).

In Africa, this difficulty is increased due to the fact that the prevalence of high blood pressure in children is not known at all, but also because it remains an adult disease to the public opinion. Furthermore, taking the BP in children requires special equipment including a blood pressure cuff size varying according to age. These cuffs are not available in the most common maternal and infantile prevention centres (MIP). Thus, in our environment, only high quality paediatric hospital are equipped with tailored cuffs, which does not allow an early and widespread screening of blood pressure in children. The disease is often discovered in case of a major complication. Also, in order to organize primary prevention in our environment, paediatricians should be alarmed at signs, to refer the child to a paediatric hospital department for his PB control.

II- DEFINITIONS
High blood pressure is defined as the elevation of blood pressure percentile compared to a standard combined curve age / size. This definition makes it difficult to provide real estimation of high blood pressure because this assumes, first, the establishment of standard values varying according to sex, race, age and size. Currently, the curves used are those set in the United States and Europe (3, 4) (Appendices 1, 2).
A- BP taking conditions and HBP diagnosis

Blood Pressure Conditions

Blood pressure should be estimated in a bedridden child lying at rest outside screaming (which is sometimes difficult in infants). It deserves to be read in the light of the child’s state. The cuff should be adapted to the arm circumference, which requires the use of at least four different types of cuff according to the child’s age. The cuff should cover 2/3 of the member’s length and must surround the entire circumference (5). There are two methods of BP taking:

- The auscultatory method that requires the use of a cuff and stethoscope for which the BBP and DBP are identified from the appearance and disappearance of arterial sounds.

- The automated oscillometric method, which is not reliable in children according to some authors (5), but the devices are more efficient with sphygmomanometer type and have the advantage to more easily estimate the BP measurement in neonates and infants. In practice, we may retain the following figures as normal:
  - before 1 year: 8/5
  - from 1 to 2 years: 9/6
  - from 2 to 4 years: 10/6.5
  - from 4 to 5 years: 9/6
  - from 5 to 10 years: 10/6
  - from 10 to 14 years: 11/6.

B- Diagnosis of high blood pressure in children

The children classified as hypertensive are the ones in which BBP and / or DBP are higher at the 95th percentile, according to U.S. curves and 97.5th percentile, according to the French SNP. The boundary between a HBP and normal pressure is arbitrary. In case of the suspected HBP, confirm it by taking at least 3 BP certifying all three of the latter’s elevation, but we should quickly categorize it in order to provide appropriate therapeutic management. Three HBP levels should be distinguished:

- Limited or moderate HBP: 97.5th percentile<BP <97.5th percentile 10 mmHg
- Confirmed HBP: 97.5th percentile 10 mmHg <PA <97.5th percentile + 30 mmHg
- Immediately threatening HBP: 97.5th percentile 30 mmHg

Some nomograms designed from children’s height and for each sex are proposed taking into account the threshold definitions (Appendix 2), but they are for children from 95 cm in size. For younger children, HBP can be defined as follows:

- In the new-born: BP> 9/6
- 1 month- 2 years: BP> 11/7

With the aim of primary prevention of HBP complications and an etiological research, a newclassification has been recommended by the ESH (6) based on a U.S. study as follows:

- NormalBP if BP <90th percentile
- High normal BP (prehypertension) if 90 <BP <95th percentile, above 12/8 adolescents
- BP Stage 1 if 95 <BP <99th percentile
- BP Stage 2 if BP> 99th percentile over 5 mmHg.
Outside this definition derived from the BP figures, some clinical signs move towards a BP diagnosis. These include headaches, blurred vision, sudden decrease in visual acuity, vertigo, tinnitus, epistaxis, abdominal pain, fatigue, weight loss, isolated agitation, coma, status epilepticus and heart failure. In general, it is the combination of a good history taking, a thorough clinical examination and taking of the BP at least 3 times in conditions that will establish a diagnosis of BP. However, the context of sub-medicalization and poverty in the tropics are such that most diagnoses are made in extreme urgency as evidenced by the data in the following figure from a paediatrics CES dissertation on HBP in children in the service of Yopougon paediatric medical UHC (7).

In our countries, HBP is most often diagnosed in the presence of complications putting at stake the child's vital prognosis with PAO type or control seizures of cerebral oedema (7). In children, in 70% of cases, HBP is secondary, which justifies an etiological research as soon as it is confirmed.

Figure 1: Distribution of patients according to the severity of HBP with admission to the paediatric medical service UHC in Yopougon.

<table>
<thead>
<tr>
<th>Type of HBP</th>
<th>Size</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe HBP</td>
<td>19</td>
<td>60 %</td>
</tr>
<tr>
<td>Confirmed HBP</td>
<td>5</td>
<td>16.7 %</td>
</tr>
<tr>
<td>Limited HBP</td>
<td>7</td>
<td>23.3 %</td>
</tr>
</tbody>
</table>

III- HBP CAUSES AND RISK FACTORS

In practice, searching for risk factors and elements moving towards an etiology of HBP is carried out at the same time through an anamnestic, clinical and paraclinical investigation.

A- Importance of history taking

Personal and family history of kidney, cardiac or hormonal disease, specifically a family HBP, a family nephropathy will be sought. In the child's history, we will search for laying of an umbilical catheter in the neonatal period, the concept of drug intake during childhood, such as corticosteroids, the occurrence of recurrent pyelonephritis. In the more recent past, we seek a mucoid-bloody diarrhea, issuing abnormal urine coloration, the occurrence of oedema and the presence of HBP signs. As for adolescents, we must learn about the concept of smoking and oral contraceptives in young girls. The anamnestic investigation must end with a good exploration of health records in search of history raised by the analysis of the weight curve. The latter is indeed a monitoring tool widely used in developing countries for the prevention of protein-energy malnutrition. Medical staff and health workers are trained to carry out the record and its analysis. The weight curve could also be used for early HBP.

This curve would be of its value in HBP screening if a failure to thrive is seen outside a nutritional defect and any dietary error. In this case, the delay could be attributed to organ dysfunction, such as the heart or the kidney, necessitating a referral in to a paediatric service for the BP measurement and other explorations.

B- Physical examination

It allows examining the main bodies involved in the HBP occurrence:
1- Examination of the kidneys and excretory system

It is usually poor, but we must look for the presence of oedema, a lumbar mass, ureteral painful points, and we must watch genitals to look for defects. During this examination, it is imperative to observe urination to assess the coloration, the urinary stream. Diuresis should be evaluated.

2- The cardiovascular examination

Blood pressure should meet the level at the four members, as well as peripheral pulses are palpated to detect coarctation of the aorta, which is a relatively common cause of HBP in children. In addition, we also seek a heart murmur, hepatomegaly, and tachycardia.

3- Other

The scrutiny of the skin provides arguments in relation to hormonal causes and systemic diseases of HBP. We seek spots «coffee-colored» meaning neurofibromatosis, fibroids for a phacomatose, malar erythema associated with arthritis pleading willingly to erythematous lupus. In any case, all devices must be examined for signs of tumor, such as pallor, purpura, abdominal mass, the presence of bone pain evoking a neuroblastoma.

In our context of developing countries, where the technical platform does not always allow a good investigation and where low-income families limit the explorations, the time of the history and physical examination is of an inestimable value. A good examination, combined with a clinical examination, leads to a better etiological approach that allows not only to obscure the diagnostic tests, but also to better target and prioritize them based on the suspected etiology.

C- Complementary examinations

Apart from the hemogram that explores the body in general terms and urine test strips that are easy to perform in our environment and in order to save health, paraclinical examinations should not be a systematic application to any HBP. In case of a suspected renal disease, we will require a hierarchical manner:

- Looking for hematuria, proteinuria by urine dipstick, and if positive, quantification of proteinuria by 24 hours and Addis Hamburger account.
- A blood electrolytes, urea and creatinine dosage. Urinary electrolytes examination is difficult of access and interpretation
- On radiographs, renal and urinary tract ultrasound is a first line test. A Doppler ultrasound will be done in case of suspicion of stenosis of the renal artery or vein
- Due to ANG prevalence as an etiology of HBP in children in sub-Saharan Africa, the search for ASLO and the determination of complement C3 and CH50 fraction may contribute to the etiological diagnosis (7)
- Depending on the etiological orientation, some second-line tests may be required such as IVU, UCR, scintigraphy, which is not available in certain developing countries.

- When the anamnesis and physical examination guide towards a cardiac cause:
  - ECG, echocardiography should allow the etiologic diagnosis - Finally, in the presence of tumor and hormonal causes, we require: A complete blood count, chest radiography, urinary catecholamines, the dosage of valique mandelic acid (VMA) and more specifically, depending on the suspected tumor, tumor markers.
D- The causes of HBP in children (features in sub-Saharan Africa)

Etiologies, which vary depending on the environment and lifestyle, can take a genetic trait. Very few studies on the HBP etiology in Africa are available in Africa. However, a study conducted in the paediatrics service of Yopougon University Hospital in Ivory Coast, and submitted during the Paediatrics Ivorian Days in 2009, shows the following etiologies based on a number of 30 children (7).

Table 1: Distribution of hypertensive children according to etiologies (Abidjan)

<table>
<thead>
<tr>
<th>Organs in question</th>
<th>Etiologies</th>
<th>Nb: 30</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney</td>
<td>Acute glomerulonephritis</td>
<td>11</td>
<td>36.7</td>
</tr>
<tr>
<td></td>
<td>Kidney Failure</td>
<td>07</td>
<td>23.3</td>
</tr>
<tr>
<td></td>
<td>Nephrotic Syndrome</td>
<td>03</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Polycystic kidneys</td>
<td>01</td>
<td>3.3</td>
</tr>
<tr>
<td></td>
<td>Renal Burkitt</td>
<td>01</td>
<td>3.3</td>
</tr>
<tr>
<td>Heart</td>
<td>Global Failure</td>
<td>02</td>
<td>6.7</td>
</tr>
<tr>
<td></td>
<td>Right IC</td>
<td>01</td>
<td>3.3</td>
</tr>
<tr>
<td></td>
<td>Left IC</td>
<td>01</td>
<td>3.3</td>
</tr>
<tr>
<td>Others</td>
<td>Rheumatic disease with cardiac injury</td>
<td>01</td>
<td>3.3</td>
</tr>
<tr>
<td></td>
<td>Undetermined HBP</td>
<td>02</td>
<td>6.7</td>
</tr>
</tbody>
</table>

Thus, in Ivory Coast, renal causes appear to be the most common aetiologies, as evidenced by the data in Europe, Asia and the USA (8,9). The main causes of HBP in children are as follows:

- Renal causes are the most common (80 to 90% of cases, excluding the aortic coarctation):
  - Hypertensive acute glomerulonephritis
  - Chronic glomerulonephritis
  - Acute or chronic terminal renal failure
  - The renovascular causes: congenital anomalies of the renal pedicle, kidney segmental hypoplasia,
  - Renal tumors: nephroblastomas, sympathoblastome etc.

- Non-renal causes are rare:
  - Transient HBP:
  - Intracranial hypertension
  - Poliomyelitis
  - Guillain-Barré syndrome
  - Hypercalcemia
  - Poisoning: Lead, mercury, vitamin D, liquorice, nasal drops containing sympathomimetics, corticosteroids, etc.

- Permanent or paroxysmal HBP:
  - Of vascular origin: coarctation of the aorta
  - Of tumor origin: pheochromocytoma.
  - Of endocrine origin: Cushing’s syndrome, hyperthyroidism, Conn’s syndrome, Turner syndrome.
Essential HBP in children and adolescents in which the exact cause is unknown, but where obesity and family history play a primordial role, is increasingly common.

III- MANAGEMENT OF HBP IN CHILDREN

It is conceived in two ways: curative and preventive treatment. But the major problem of HBP in Africa is represented by the difficulty of access to care. The VITARAA study (AT visit and associated risk in Africa), which analysed 10 countries, shows that HBP affects 11% of the population and the major mortality factor is the lack of access to care. For example, Amlodipine 5 mg is prohibitively expensive for most countries. In Malawi, the treatment costs 18 working days per month, while it represents only 1.5 days in Sri Lanka (10).

A- Curative treatment (11,12)

It consists of lowering blood pressure levels that have become abnormal, which is the treatment of hypertensive crisis, but it will also allow, through a thorough treatment to maintain these numbers to normal values.

1- Treatment of hypertensive crisis

Regardless of the cause treatment (medical or surgical), treatment of acute exacerbation of HBP is not early conceived unless in hospitals. The antihypertensive are the recommended drugs:

- Nifedipine (Adalat), calcium inhibitor: 0.5 to 1 mg / kg / dose sublingual
- Nicardipine (Loxen IV) calcic inhibitor in a progressive and flexible action

In case of severe HBP or suspected renal artery stenosis: 10 to 20 mcg / kg slow 10 minutes then 1 mcg / kg / min in continuous IV infusion

- Labetalol (Trandate), alpha, beta-blocker, bolus: 0.2 mg / kg IVD to be renewed after 10 minutes to 1 mg / kg. Even in case of pheochromocytoma. Cl: BAV, asthma, heart failure
- The dihydralazine (Nepressol): peripheral vasodilator: 0.5 mg / kg IM or IVL about 30 minutes
- Sodium nitroprusside (Nipride) of an exceptional indication
  - Furosemide (Lasix) is used in case of fluid overload: 0.5 to 2 mg / kg over 30 minutes IVL
  - The renal replacement is necessary in case of anuric renal failure.

Medical treatment of pheochromocytoma is based on prasozine (Minipress) orally or via IV labetalol before surgery.

2- Disease-modifying drug of HBP in children

Disease-modifying drug of HBP in children is based on lifestyle changes (too often neglected in our environment, because of nutritionists) and medication.

- The lifestyle measures
  The fight against weight excess and physical inactivity is essential.
  A moderate exercise is usually possible and even recommended. Restricting salt intake appears to be effective, but is not always easy to enforce (13).

- Drug treatment (14)
  Due to the high costs of the medications prescription and chronicity of the disease, we deplore a relatively high rate of non-therapeutic compliance to the HBP treatment in Africa. In fact, most African countries have no social security system and only a very small proportion of the population
### Table 1: Main antihypertensive medication in children

<table>
<thead>
<tr>
<th>Class</th>
<th>ICD</th>
<th>Generic name</th>
<th>Specialty</th>
<th>Daily dose</th>
<th>Number of single dose</th>
<th>maximal dose</th>
<th>precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE-inhibitors</td>
<td>Captopril</td>
<td>Captopril 12,5-25-50mg</td>
<td>Lopril 25-50mg</td>
<td>0,3-0,5mg/kg/dose</td>
<td>2-Mar</td>
<td>6mg/kg/d of 450mg/d</td>
<td>S: Renal function</td>
</tr>
<tr>
<td></td>
<td>Enalapril</td>
<td>Enalapril 5-20mg</td>
<td>Renitec 5-20mg</td>
<td>0,8mg/kg/d</td>
<td>1</td>
<td>0,6mg/kg/d of 40mg/d</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fosinopril</td>
<td>Fozitec 10-20mg</td>
<td>0,1mg/kg/d of 10 mg/d</td>
<td>1</td>
<td>0,6mg/kg/d of 40mg/d</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lisinopril</td>
<td>Lisinopril 5-20mg</td>
<td>Zestril 5-20mg</td>
<td>0,07mg/kg/d of 5 mg/d</td>
<td>1</td>
<td>0,6mg/kg/d of 40mg/d</td>
<td>E: Cough and angioedema</td>
</tr>
<tr>
<td></td>
<td>Ramipril</td>
<td>Ramipril 1,25-2,5-5-10mg</td>
<td>Triatec 1,25-2,5-10mg</td>
<td>2,5mg/d</td>
<td>1</td>
<td>20mg/d</td>
<td>Cl: Pregnancy</td>
</tr>
<tr>
<td>Antagonist of angiotensin receptors</td>
<td>Losartan</td>
<td>Cozaar 50-100mg</td>
<td>0,75 mg/kg/ of 50mg/d</td>
<td>1</td>
<td>1,4 mg/kg/d of 100 mg/d</td>
<td>S: Renal function</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Irbesartan</td>
<td>Aprovel 75-150-300mg</td>
<td>75 of 150 mg/d</td>
<td>1</td>
<td>300mg/d</td>
<td>Cl: Pregnancy</td>
<td></td>
</tr>
<tr>
<td>Blockers</td>
<td>Labetalol</td>
<td>Trandate 200mg</td>
<td>2 of 3 mg/kg/d</td>
<td>2</td>
<td>10-12mg/kg/d of 1,2g/d</td>
<td>Cl: Heart failure</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Carvedilol</td>
<td>Carvedilol 5-25-50mg</td>
<td>Kredex 5-2,5-12,5-25mg</td>
<td>0,01mg/kg/dose of 12,5mg/d en 2 prises</td>
<td>2</td>
<td>0,5 mg/kg/dose of 25mg/d en 2 prises</td>
<td>Asthma, diabetes, sports</td>
</tr>
<tr>
<td></td>
<td>Acebutolol</td>
<td>Sectral 200-400mg</td>
<td>Sectral 40mg/ml</td>
<td>5-10mg/kg/dose</td>
<td>2</td>
<td>20mg/kg/d</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Atenolol</td>
<td>Atenolol 50 and 100mg</td>
<td>Tenormin, Betatop 50 and 100mg</td>
<td>0,3-1mg/kg/d</td>
<td>1-Feb</td>
<td>2mg/kg/d of 100mg/d</td>
<td>Cl: Heart failure</td>
</tr>
<tr>
<td></td>
<td>Bisoprolol/hydrochlorothiazide</td>
<td></td>
<td></td>
<td>0,04mg/kg/d of 2,5/6,25mg/d</td>
<td>1</td>
<td>10mg/6,25mg/d</td>
<td>Asthma, diabetes, sports</td>
</tr>
<tr>
<td></td>
<td>Metoprolol</td>
<td>Mandoprol 50 and 100mg</td>
<td>Lopressor, Seloken 100mg</td>
<td>1-2 mg/kg/d</td>
<td>2</td>
<td>6mg/kg/d of 200mg/d</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Propranolol</td>
<td>Propanolol 40mg</td>
<td>Avocardyl 40mg</td>
<td>1mg/kg/d</td>
<td>2-Mar</td>
<td>16mg/kg/d of 640mg/d</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Syprol 5mg/5ml, 10mg/5ml, 50mg/5ml</td>
<td>0,25 of 0,5mg/kg/ dose</td>
<td>3-Apr</td>
<td>3 of 4 mg/kg/d</td>
<td></td>
</tr>
<tr>
<td>CCBs</td>
<td>Amlodipin</td>
<td>Amlodipin 5 and 10 mg</td>
<td>Amlor 5 et 10 mg</td>
<td>0,06 mg/kg/d of 5mg/d</td>
<td>1</td>
<td>0,06 mg/kg/d of 10mg/d</td>
<td>E: Tachycardia, flushing, headache, peripheral edema, gingival hypertrophy Interactions, anticalcineurins and nicardipine (risk of overdose)</td>
</tr>
<tr>
<td></td>
<td>Niledipin</td>
<td>Niledipin 10mg</td>
<td>Adalate 5 et 10mg</td>
<td>0,25-0,50mg/kg/d</td>
<td>3-Apr</td>
<td>3mg/kg/d of 120 mg/d</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Adalate LP 20mg</td>
<td>1-Feb</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Chronodulate LP 10mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nicardipin</td>
<td>Loxen 20mg</td>
<td></td>
<td>0,33 mg/kg/dose</td>
<td>3-Apr</td>
<td>3 of 4 mg/kg/d</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Loxen LP 50mg</td>
<td>1-Feb</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>α-blockers</td>
<td>Prazosin</td>
<td>Minipress 1-5 mg</td>
<td>Alpress LP 2,5-5mg</td>
<td>0,05-1mg/kg/d</td>
<td>3</td>
<td>0,5 mg/kg/d</td>
<td>E: Orthostatic hypertension</td>
</tr>
<tr>
<td></td>
<td>Terazosin</td>
<td>Terazosin 1 and 5 mg</td>
<td>Dysalant, hytrine 1-5 mg</td>
<td>1mg/d</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
has health insurance. Thus, chronic diseases represent a real problem for families.

In more affluent countries, it is recommended that treatment should be as simple as possible, compliance being inversely proportional to the number of drugs and doses per day. Treatment is, therefore, implemented through stages and, except in very severe cases, it always starts with a single drug.

All classes of antihypertensive drugs can be used and are available in African hospitals. Inhibitors of converting enzyme (ICE) and calsec inhibitors, due to their high tolerance and manoeuvrability, have become hypotensive of a first-line treatment in children. When a drug is not enough to normalize blood pressure, another drug is preferentially associated to it in which mechanism of action is different, taking care to use the so-called synergistic combinations. But it is worth noting that the therapeutic noncompliance rate is proportional to the number of prescribed antihypertensive drugs. The surgical treatment, which is possible in some aetiologies, has benefited from advances in vascular surgery and new techniques.

B- Preventive Treatment (3)

1- Primary prevention

Blood pressure levels according to height in boys

Systolic (mmHg)

Blood pressure levels according to height in girls

Diastolic (mmHg)
It consists of early HBP screening that requires systematic monitoring of the BP during the child’s routine visits. Children’s HBP is secondary in most cases, prevention also consists of properly managing the streptococcal supplier diseases of the HBP such as angina and superinfected dermatosis of the child, main factors triggering glomerulonephritis in our environment. It also relates to improving lifestyle and promoting practices that reduce HBP prevalence in a population. It is the reduction of excessive sodium intake in the diet, regular practice of moderate exercise. According to U.S. studies, the black population has a greater willingness to make more HBP and severity of the latter is higher than the white population’s (15).

2- The secondary prevention
Secondary prevention is to screen cases prehypertension cases to offer early treatment to prevent installation of HBP itself. But all these preventive measures require the provision of BP taking equipment in the main paediatric services.

References
3) André JL. Hypertension artérielle chez l’enfant et l’adolescent. EMC, cardiologie, 11-940-I-40,2005
PART VI

ACUTE KIDNEY FAILURE

CHAPTER 18

ACUTE RENAL FAILURE IN LIMITED RESOURCES COUNTRIES

Amal Bourquia, Casablanca - Morocco
Felicia Eke, Ifeoma Anochie, Port Harcourt - Nigeria
HIGHLIGHTS

✓ The acute renal failure (ARF) is a crash within hours or days of renal function with variable diuresis.

✓ The RIFLE classification classified the ARF patients in several stages.

✓ Whatever the cause of ARF, reducing the DSR is the common pathological cause reduction of glomerular filtration rate (GFR).

✓ The ARF is a major cause of morbidity and mortality in children from poor countries.

I- INTRODUCTION

A- Worth knowing

The kidneys are selective regulators organs that excrete and retain water and many chemicals to ensure the constancy of the internal environment. They receive 20 to 25% of cardiac output, namely 700 liters of blood / 24 h. every day, 170 liters of filtrate devoid of cells and proteins are formed.

1- The excretory function

The kidney, through the process of filtration, reabsorption and secretion, shape, through blood, the final urine comprising only 1% of salt and of the filtrate water.

2- Endocrine functions

- The renin-angiotensin system, essential for the blood pressure regulation, potassium and sodium balance sheet
- Hydroxylation of D3 vitamin, necessary for the phosphocalcic homeostasis
- Some prostaglandins
- Erythropoietin stimulating red blood cell formation.

B- Definitions

Acute renal failure (ARF) is defined as a rapid and acute deterioration of the renal function with an accumulation of nitrogenous waste in the human body (1). The symptoms related to this disease are spread over a period of less than three months. According to the urine volume, there are two clinical types: oliguric ARF where urine output is less than or 1ml/kg/hr. 300ml/m² / per day, and non-oliguric ARF with normal urine output (1). It is an abrupt discontinuation, within a few hours or days, of the renal function with a variable diuresis.

Diagnostic criteria, introduced by the network of acute kidney injury (NAKI), are defined as an increase in creatininemia spreading over 48 hours (4). ARF definition was the cause of considerable confusions, both clinically and in the medical literature. The ARF has recently been replaced by the term Acute Kidney Injury (AKI) to include any type of kidney failure, since a simple change in creatininemia influences the results (2,3). In 2004, the RIFLE classification was published ranking ARF according to the variations of the patient’s reference level, the creatinine serum concentration, the glomerular filtration rate (GFR) or the urine output (ADQI) (4). The RIFLE classification assists AKI patients in several stages, namely the risk, injury, failure, loss of kidney function, and end stage renal disease, according to the serum creatinine or the rapid decrease urinary output (3.5). The RIFLE classification of the ARF has been modified for the pediatric population (Table I).
The ARF has one biological definition, but an inhomogeneous set with etiologies, comorbidity and different complications from one patient to another.

II- EPIDEMIOLOGY

The exact incidence is difficult to define because there is no consensus definition and unnoticed forms are numerous. It varies depending on the definition of the developed or developing countries and the type of the center or the care hospitals. It is estimated at 1 to 3% in the neonatal units and 4 to 30% in intensive care units. The ARF is secondary in 60% of cases.

The ARF is the major cause of morbidity and mortality in children from poor countries, in addition to the lack of hospital equipment, unaffordable prices set for dialysis and inadequate health facilities able to cover the huge population that represent children in these countries, ignorance also contributes to delay access to medical care. The ARF represents 1 to 2% of pediatric admissions in developed countries, while in developing countries, widely variable statistics are emphasized. In Nigeria, Port Harcourt, a hospital study showed a prevalence of 11.7 cases with ARF of which only 2% received a pediatric admission and Morocco, AKI was reported in 1.2% of pediatric admissions and 11% of kidney diseases.

Due to poor and / or non-declarations of ARF cases found in these poor countries, these recorded statistics underestimate the percentage of patients with ARF in hospitals. Unlike developed countries, where cases contracted to the hospital fully contribute to the onset of the ARF causes, the ARF cases, occurring in poor countries, are in their majority, community-acquired.

III- PATHOPHYSIOLOGY

Glomerular pressure, which depends mainly on the renal blood flow (RBF), is controlled by the combined resistance of the renal afferent and efferent arterioles. Whatever the ARF cause might be, reducing the RBF is the common pathological cause of reduced glomerular filtration rate (GFR).

Table: Pediatric-modified RIFLE (pRIFLE) criteria

<table>
<thead>
<tr>
<th>Risk</th>
<th>Estimated CCI</th>
<th>Urine output</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injury</td>
<td>eCCl decrease by 50%</td>
<td>&lt;0.5 ml/kg/h for 16 h</td>
</tr>
<tr>
<td>Failure</td>
<td>eCCl decrease by 75% or eCCl &lt; 35 ml/min/1.73 m²</td>
<td>&lt;0.3 ml/kg/h for 24 h or anuric for 12 h</td>
</tr>
<tr>
<td>Loss</td>
<td>Persistent failure&gt;4 weeks</td>
<td></td>
</tr>
<tr>
<td>End stage</td>
<td>End-stage renal disease (persistent failure&gt;3 months)</td>
<td></td>
</tr>
</tbody>
</table>

*CCl, estimated creatinine clearance pRIFLE, pediatric risk, injury, failure, loss and end-stage renal disease.
ARF etiology contains three main mechanisms

A- Pre renal ARF
In the ARF pre-renal stage, there is a decrease in the glomerular filtration rate (GFR) that occurs due to renal hypoperfusion or hypoxia. This is defined by normal glomerular and tubular functions and a depressed GFR by renal perfusion. In infants, any decrease in the renal perfusion following sepsis, hypovolemia, hypotension, or hypoxia can quickly complicate an ARF making the management of the patient more difficult. Restoration of blood volume usually allows restoring the kidney function.

The prerenal ARF can be the first step leading to an organic ARF.

B- Intrinsic ARF
In the renal intrinsic stage, renal parenchymal aggression affecting vessels, glomeruli and tubules are detected. This includes diseases of the kidney itself, affecting mainly the glomerulus or tubule, associated with the release of vasoconstrictors. Ischemic lesions, which are the most common causes, may be:
- Secondary to an acute renal hypoperfusion
- Of toxic origin
- Linked to glomerular and / or vascular nephropathies.

In case of an intrinsic renal failure, eliminating tubular toxins and initiating glomerular kidney disease treatment decreases the afferent vasoconstriction.

C- Obstructive ARF
The ARF post-renal stage experiences obstruction of the urinary tract, pelvis to the urethra, which increases the hydrostatic pressure in Bowman's capsule, accompanied by changes in capillary blood flow and a decrease in glomerular filtration. The obstruction of the urinary tract is the result of congenital anomalies or acquired disorders.

The obstructive ARF is first caused by an increase in tubular pressure and a decrease in the filtration power. The pressure gradient is quickly equalized and maintaining a glomerular filtration rate is thus dependent on efferent renal vasoconstriction. Rapid relief of urinary obstruction can induce a result in decreasing the vasoconstriction.

Ischemic initial attack triggers a cascade of events including a production of free radicals, cytokines and enzymes, endothelial activation, leukocyte adherence, activation of the coagulation and the initiation of apoptosis. These events continue to cause damage to cells, even after the restoration of the GFR. This result in damage to tubular cells with disruption of tight junctions between cells, allowing a return and leakage of glomerular filtrate and reduced GF. In addition, the dying cells in the tubules can form a barrier that further weakens the GFR and leads to oliguria.

An ARF leads to a progressive increase in the plasma concentration of urea, creatinine, potassium and hydrogen ions ... The immediate risk is represented by the possibility of death from hyperkalemia, convulsions and / or acute pulmonary edema. Mortality is 30 to 73%, the major mortality factors being anuria, sepsis, and a hemopathy. The long-term risk is related to the sequelae with the possibility of progression to chronic renal failure.
IV- POSITIVE DIAGNOSIS

Pediatricians can play a crucial role in the reversal of many underlying causes and prevent further iatrogenic renal damage if the ARF is identified too early.

A- Symptoms

ARF symptoms and signs vary according to the child’s age and etiology. Unfortunately, in the newborn, it is often asymptomatic and is particularly suspected in a newborn who had no urine in the early hours or when the serum creatinine is increased (17). In the resource-limited settings, it is often difficult to conduct a detailed evaluation in newborns with ARF, due to the lack of adequate equipment and infrastructure. The child may present with diarrhea, vomiting, gastroenteritis fever and an infection such as malaria. Some symptoms that may evoke ARF:

- Oligo-anuria, high blood pressure, pallor linked to anemia, edema, vomiting, lethargy
- The hydroelectrolytic disorders, particularly sodium and hydric retention, can cause convulsions, behavioral disorders, cardiac decompensation or coma
- Bloody saddles can evoke a hemolytic uremic syndrome and an infection with Shigella
- Streptococcal sore throat history, skin rashes, haematuria and swelling suggesting a glomerulonephritis.
- Improper urine flow and subpubic swelling explain the triggering causes of post-renal stage
- The pre-renal stage is marked in dehydrated patients, while there are signs of fluid overload with hypertension in the ARF intrinsic stage
- The presence of a distended bladder and enlarged kidneys leads to a post-renal stage. The ARF should be suspected whenever we find oliguria or anuria, hyperventilation caused by acidosis or high blood pressure.

Table 2: Symptoms may evoke an acute renal failure (ARF)

- An oligoanuria, high blood pressure, pallor associated with anemia, edema, vomiting and lethargy.
- Fluid and electrolyte disturbances, particularly sodium and water retention can lead to seizures, behavioral disorders, heart failure or coma
- Bloody stools may evoke a hemolytic uremic syndrome or Shigella infection
- A history of strep throat, rash, hematuria and swelling are reminiscent of glomerulonephritis.
- Poor urine flow and a sub-pubic swelling explains the causes of the occurrence of the post-stage renal
- The pre-stage renal is marked in dehydrated patients, while there has fluid overload features with hypertension in the intrinsic stage of ARF
- The presence of a distended bladder and enlarged kidneys leads to a post-stage renal. The ARF should be suspected whenever we see oliguria or anuria, hyperventilation caused by acidosis or hypertension.

B- Biology

Laboratory investigations include urinalysis and microscopy for hematuria, proteinuria and tubular cells. Serum electrolytes, urea and creatinine cause hyponatremia, hyperkalemia, and high levels
of urine and creatinine. Hemoglobin, a numeration in the blood count, white blood cells and platelets should be performed. In HUS, thrombocytopenia, schistocyte and an ARF are detected.

- Accumulation of nitrogenous waste: ↑ urea and plasma creatinine
- Other metabolic disorders:
  - Hyperkalemia
  - Metabolic acidosis
  - A hypocalcemia and hyperphosphatemia.

Table 2 shows the diagnostic clues to differentiate between the pre-renal stage and renal stage of the ARF. This includes measurements of urine osmolality, the ratio of serum osmolality urine, the ratio of creatinine of serum osmolality, urinary sodium concentration, the fractional excretion of sodium (FE Na) and the index of renal failure (RFI) (1, 6).

Formula: \[ RFI = \frac{ Una \times SCr}{RCU} \]

Formula details: \( RFI = \) Renal Failure Index \( Una = \) Urine Sodium in mEq / L = UNA urinary sodium in mEq \( SCr = \) Serum Creatinine in mg / dl \( RCU = \) Urine Creatinine in mg / dl \( UCR = \) Urine Creatinine urine DUC in mg / dl.

<table>
<thead>
<tr>
<th>PARAMETERS</th>
<th>PRE-RENAL</th>
<th>RENAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine Osmolality (mOsmol/kg)</td>
<td>&gt;500</td>
<td>&lt;350</td>
</tr>
<tr>
<td>Urine Sodium (mEq/L)</td>
<td>&lt;20</td>
<td>&gt;40</td>
</tr>
<tr>
<td>Urine Density</td>
<td>&gt;1.020</td>
<td>&lt;1.020</td>
</tr>
<tr>
<td>Plasma Urine/Urea</td>
<td>&gt;8</td>
<td>&lt;3</td>
</tr>
<tr>
<td>Urine/plasma osmolality</td>
<td>&gt;1.15</td>
<td>&lt;1.1</td>
</tr>
<tr>
<td>BUN/Creatinine</td>
<td>&gt;20</td>
<td>&lt;10</td>
</tr>
<tr>
<td>(Na FE) (%)</td>
<td>&lt;1%</td>
<td>&gt;3%</td>
</tr>
<tr>
<td>RFI</td>
<td>&lt;1</td>
<td>&gt;3</td>
</tr>
</tbody>
</table>

Unfortunately, in poor countries, most laboratories are unable to carry a urine chemistry, which prevents them to provide diagnostic clues to make the difference between the pre-renal and renal stage of the ARF.

**C- Radiology**

Ultrasound upon admission even at the bedside, in addition to the fact that it allows to specify the size, the echo structure of the parenchyma and anomalies, also helps in the etiologic diagnosis. Other explorations, such as chest radiography and occasional kidney biopsy may be needed.

**Ultrasound**

- pylocaliciele dilatation or gallstone
  - Refer to urologist
- Increased kidney size, hyperechogeneous
  - Acute renal failure
- Small kidneys or multicystic
  - Chronic renal failure
V- ETIOLOGIES

The causes of ARF in developed countries are mainly related to hypoperfusion of the intrinsic renal disease, including hemolytic uremic or nephrotoxic syndrome, and congenital and urine anomalies (1,3). However, in tropical areas, especially in poor countries, ARF causes are often associated with the pre-renal stage conditions such as the manifestation of asphyxia in newborns and gastroenteritis in young children (6,7). The increase in the ARF incidence in poor countries is mainly due to ignorance, poverty, infections, certain traditional practices and religious character. The frequent consultation of traditional birth attendants by pregnant mothers may delay access to these hospitals with their newborns affected with asphyxia.

The list of ARF causes in children, identified in hospitals varies according to the endemy of certain endemic diseases in the area, and depending on the availability of medical care and referral system. The causes are compiled according to the pathophysiology and ARF stages, pre-renal, intrinsic and post-renal (1,3,6). Pediatric patients with ARF are a heterogeneous set of etiologies with an average mortality rate of 25%. The patient’s age has significant implications for the differential diagnosis of ARF.

A- The newborn

Neonatal ARF has seen its incidence increase with advances in resuscitation (8 to 24% with a mortality of 10 to 61%). But these figures are probably still underestimated as some definitions are not well adapted to this period of life. The ARF is rarely oliguric during this period, resulting in ignorance of a significant number of cases. We must better recognize most of these situations, in order to limit the damage and monitor these children long after their discharge from hospital.

The RF neonatal causes are often intertwined or in continuity to each other (Table II). The most common of these is perinatal asphyxia, which may complicate antenatal pathology already at risk of neonatal RF (bilateral multicystic dysplasia, bilateral renal dysplasia or hypoplasia of the posterior urethral valves, or congenital pathology nephrology, prenatal exposure to ECI...), the diagnosis is often earlier. Renal ultrasound examination is essential for diagnosis, if possible with a Doppler associated with the dipstick seeking blood (consider arterial thrombosis) or protein (kidney damage control). Every hospitalized newborn should be considered at risk with ARF, which implies monitoring of blood pressure, urine dipstick and diuresis, the only daily available markers. Situations with anuria, which are rare, do not pose diagnostic difficulties, but they already suggest a risk of severe nephron loss, especially when anuria is prolonged. In the absence of anuria, recent use (in ante and post-natal) of nephrotoxic drugs, congenital heart disease, situations of severe dehydration (severe prematurity, loss of salt) and septic shock. The most common ARF cause is represented by pre-renal etiologies.

1- Pre renal ARF
- Perinatal hemorrhage, complications of amniocentesis, placental abruption, birth trauma
- Neonatal hemorrhage, severe intraventricular hemorrhage, adrenal hemorrhage
- Perinatal asphyxia and hyaline membrane disease (respiratory distress syndrome of the newborn).

2- Intrinsic ARF
- Acute tubular necrosis (ATN), which can occur in the context of perinatal asphyxia or be secondary to drugs (aminoglycosides, NSAIDs) given to the mother during the perinatal period.
- Conversion inhibitors of enzyme angiotensin can cross the placenta and cause an ARF.

3- Post-renal ARF
It still requires the search for a congenital malformation..

B- The child
- Before 4 years, the ARF predominant causes are the syndromes of renal hypoperfusion linked to gastroenteritis and the hemolytic uremic syndrome (HUS)
- After 4 years, the majority of ARF cases are related to glomerular nephropathies, especially post-infectious acute glomerulonephritis (AGN).

1- Pre-renal causes
This is an ARF secondary to acute renal hypo-perfusion secondary to a hypovolemia and / or to a state of shock IRA.
- The anamnesis:
It can help to classify the ARF pathophysiology as renal, post-renal functional or intrinsic ARF, and can suggest specific etiologies.
- Private hospital
Patients usually have symptoms related to hypovolemia. Learn about volume loss after vomiting, diarrhea, sweating or bleeding.
The causes are numerous, but the most common ones are as follows:
• Severe acute dehydration (collapse and profound acidosis)
• Severe septic shock.
Functional ARF is a rapidly resolutive ARF through restoring effective blood volume and includes hydroelectrolytic disorders that differentiate it from an organic ARF (table).

2- The intrinsic ARF
Patients can be divided into those with a glomerular etiology and those with tubular etiology of the IRA.
- The glomerular diseases:
We have to consider them in case of a nephrotic syndrome, hematuria, edema and hypertension moving towards a glomerular etiology. It is important to seek a possible infection of the throat or skin.
- Tubular diseases
They should be suspected in any patient after a period of hypotension following cardiac arrest, hemorrhage, sepsis or surgery.
Allergic interstitial nephritis should be suspected in the presence of a fever, rash, arthralgia, and exposure to certain medications, including NSAIDs and antibiotics.

a- Acute glomerulonephritis (AGN)
It is common and occurs at a school age (> 3 years).

a-1- Clinic
- Occurrence usually 1 to 3 weeks after infection by hemolytic streptococcus group A. Other
microbial or viral agents may also be involved. Find a history of pharyngitis, tonsillitis, cellulitis or other streptococcal infections, but also viral infections (MNI, Varicella), endocarditis or an infected ventriculo-cardiac shunt.
- The onset is sudden with:
  - Macroscopic hematuria (urine dirty broth)
  - An oligoanuria
  - Sodium and water retention with weight gain, edema and occasionally nephrotic syndrome. If severe sodium and water retention, risk of cardiac decompensation, convulsions and pulmonary edema
  - HBP sometimes revealing and often severe (headache, convulsions)
  - An APO and / or heart failure sometimes inaugural.

**a-2- Complementary examinations**
- They objectify the urine output fall by the diuresis measurement.
- Urinalysis allows to search for:
  - Hematuria with red blood cell casts
  - Constant proteinuria, non-selective, usually mild, but sometimes with a real nephrotic syndrome
  - Concentrated urine with a low natriuresis.
- Blood tests look for:
  - Transient renal failure with a high urea and a variable creatinine
  - Hyperkalemia, hyperphosphatemia, hypocalcemia
  - Tests for etiological purposes find:
    - A total hemolytic complement (CH50) and especially C3 lowered (early fall, but transient)
    - Serology may find an increase in ASLO
    - Bacteriological analysis allows to search streptococcus.

**a-3- Histology**
Renal biopsy in this typical form is not necessary, if practiced, it would reveal a proliferative endocapsular glomerulonephritis.
The indications for renal puncture biopsy are:
  - Anuria> 2-3 days or oliguria> 4-5 days.
  - An IRA> 10-15 days.
  - Nephrotic syndrome> 2 weeks.
  - A low C3 after 3 months.
  - Persistent hematuria beyond 12-18 months.

**b- Infectious Causes**
Infections are a major ARF cause in children from tropical areas (3, 6, 8). They increase the ARF through immune mechanisms and renal hemodynamic changes. Infections are parasitic, viral and bacterial. Malarial infection is endemic in some parts of Africa, Central America, Latin America, India, Southeast Asia and the Middle East. Approximately 40% of the world population, including
people from poor countries, is at risk of Malariae (8, 9).

b-1- Malaria
It contributed by 13.7% to the ARF causes in Port Harcourt, Nigeria (7). Renal involvement of malaria is found in cases of vomiting and diarrhea leading to dehydration, hypovolemia, and pre-stage renal ARF. In addition, infections with malaria can cause intravascular hemolysis and renal failure, a condition called ‘hemoglobinuric fever’ (6).

b-2- Infection with human immunodeficiency virus (HIV)
It is a major cause leading to the outbreak of acute renal failure in children aged between 10 and 12 years. The infection was considered as an epidemic in developing countries such as Nigeria and South Africa. The ARF, occurring in patients testing positive for HIV, can be triggered from a glomerular disease and acute disorders in the renal function related to the infection. The pre-renal azotemia is the most common cause, while the tubulointerstitial nephritis and crystalluria may occur after taking medicaments treating HIV infection. Other viruses are involved, including hepatitis B and C and cytomegalovirus infections.

Bacterial infections are often among the ARF causes, including streptococci, cholera, salmonellosis, shigellosis, tetanus, diphtheria, sepsis, etc.. Acute renal failure, generated by contaminated drugs, was found in poor countries such as India, Bangladesh, Nigeria because of poor regulatory agencies authors in this area (13,14). In 1998 and 2008, children in India and Nigeria respectively had suffered outbreaks of the ARF as a result of ethylene glycol poisoning. Powder baby teething ‘My Pikin’ has been contaminated in Nigeria, thus affecting 60 children, aged less than two years, with ARF. Medicinal herbs, commonly used in poor countries, especially in Nigeria, were considered triggers of ARF.

c- Toxins caused by snake bites
Scorpion stings or other insects are the causes in Port Harcourt, Nigeria (7), 4.7% of ARF cases are due to birth congenital malformations. The causes of post-renal stage, especially the posterior urethral valves, are not detected early in poor countries, which highly contributed to discover ARF in children.

Labial adhesions, caused by congenital adrenal hyperplasia, not watched, as a result of ignorance and poverty are preventable causes of ARF in the Nigerian teenager.

d- The Hemolytic Uremic Syndrome (HUS)
The most common ARF cause in infants (75%), it often occurs in the summer, due to gastroenteritis (role of consumption of undercooked meat contaminated by verotoxin producing E. coli (VTEC) strain 0157: H7, Salmonella, Shigella, enteropathogenic Coli ...). It is estimated those one in ten children with gastroenteritis Coli 0157: H7 present HUS. HUS occurs about 8 to 10 days later. This disease is associated with a renal thrombotic microangiopathy with arteriolar and capillary endothelial injuries, thickening of the walls of fibrin deposition, thrombosis, and sometimes, cortical necrosis.

d-1- Definition
HUS associates:
- Hemolytic anemia
- Glomerular renal impairment with hematuria
- Thrombocytopenia.
**d-2- Clinic typical HUS**
- The most common, especially in infants
- Find digestive prodromal vomiting, abdominal pain, and recent bloody diarrhea
- Moderate fever for a few hours to a few days
- Clinical symptoms: sudden pallor linked to hemolytic anemia, oligoanuria, weight gain, convulsions, lethargy, irritability, jaundice or subicterus
- Hemorrhagic disorders with thrombocytopenia
- An ARF with hematuria
- Frequently, hypertension
- Neurological signs like convulsions.

**d-3- Paraclinical**
- Examinations of urine (if available) in which we find hematuria and proteinuria
- A blood workup
  - An increase in urea, creatinine, hyperkalemia, with signs of hemolytic anemia or other signs of ARF
  - Severe and regenerative hemolytic anemia
  - A schizocytosis: constantly found (1-10% of cells), early and ephemeral. They are red blood cells, jagged and deformed by their passage to the obstructed vessels. To be searched for at the blood smear.
  - Elevated unconjugated bilirubin with LDH
  - Thrombocytopenia (<100000 plaquettes/mm^3)
  - A DIVC syndrome sometimes associated
  - Signs of ARF.

**d-4- Treatment**

**Symptomatic**
- Renal failure, with recourse, if necessary, peritoneal dialysis
- Hypertension
- Anemia, which may require red blood cell transfusion.

**Specific**
Fresh frozen plasma with or without immunoglobulin.

**Monitoring**
The prognosis is related to the importance and duration of the oligoanuric phase in case of prolonged duration, there may be ESRD, or at least a permanent hypertension and proteinuria. Mortality is 3 to 5%.

**e- The renal vein thrombosis**
It is rare and occurs in neonatal period due to a shock, asphyxia, and sepsis. Later, it is associated with nephrotic syndrome and cardiopathy.

The clinic
- A sudden macroscopic haematuria, nephromegaly and pain in the flanks, unilateral sometimes
bilateral, recovery is possible in the older child.

f- Acute Interstitial Nephritis

f-1- Clinical
A rise in temperature, a skin rash, hyperesinophilia, an ARF by tubulonephritis.

f-1- Causes
• Toxic: - Endogenous: hemoglobin, myoglobin, uric acid.
  - Exogenous: nephropathies medicated (aminoglycosides).
• Heavy metals
• Drugs
• State of shock
• Acute, viral infections
• Metabolic: hypercalciuria, uric acid, oxalic acid, cystinosis, nephronophthisis
• Idiopathic.

3- Post-renal causes

Table 3: Renal failure causes in children

<table>
<thead>
<tr>
<th>Pre-renal stage:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Volume depletion of severe hypovolemia</td>
</tr>
<tr>
<td>• Hypotension, sepsis</td>
</tr>
<tr>
<td>• Hypotension, sepsis, asphyxia at birth, severe heart failure</td>
</tr>
<tr>
<td>• Hypoxia - Respiratory Distress Syndrome</td>
</tr>
<tr>
<td>• Intravascular hemolysis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Renal stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Glomerulonephritis</td>
</tr>
<tr>
<td>• Vascular and thrombotic diseases</td>
</tr>
<tr>
<td>• Hemolytic uremic syndrome, renal vein thrombosis or embolism</td>
</tr>
<tr>
<td>• Renal artery stenosis</td>
</tr>
<tr>
<td>• Interstitial nephritis, infection, crystals</td>
</tr>
<tr>
<td>• Nephrotoxicity</td>
</tr>
<tr>
<td>• Antibiotics, aminoglycosides</td>
</tr>
<tr>
<td>• Heavy metals mercury, lead</td>
</tr>
<tr>
<td>• Toxins snake venom, hemoglobin, myoglobin</td>
</tr>
<tr>
<td>• Phytotherapy / Herbal remedies</td>
</tr>
<tr>
<td>• Papillary nephritis</td>
</tr>
<tr>
<td>• Acute tubular necrosis</td>
</tr>
<tr>
<td>• Hereditary kidney disease</td>
</tr>
<tr>
<td>• Autosomal recessive and dominant polycystic kidney disease.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Post-renal stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Obstructive uropathy</td>
</tr>
<tr>
<td>• Posterior urethral valve, obstruction of the ureteropelvic junction bilaterally</td>
</tr>
<tr>
<td>• Neurogenic bladder, urethral obstruction, restriction</td>
</tr>
<tr>
<td>• Abdominal tumors, retroperitoneal.</td>
</tr>
</tbody>
</table>
ARF secondary to acute obstruction of the excretory system:
- In children, this case is rare (5%), it is either:
  • An obstacle compression or lithiasis, bilateral or solitary kidney
  • Neurogenic bladder or acute retention.

VI- THERAPEUTIC MANAGEMENT
ARF treatment includes control of fluid and electrolyte balance, acid alkali, protein restriction diet, aggressive treatment of hyperkalemia and dialysis when medical intervention does not lead to positive results (1, 6, 15, 17). A careful assessment of intravascular volume is deemed important to determine whether the ARF is reversible by fluid administration. The protection of the intravascular volume’s status may hinder the progression of renal stage to acute tubular necrosis.

The dialysis efficiency varies in pediatric nephrology centers according to availability of funds and trained personnel. Acute peritoneal dialysis, which is the most common type of dialysis in Africa, is easily accessible compared to an acute hemodialysis (18). However, dialysis is still very expensive because of the high price of fluid and peritoneal catheters since they are not easily accessible. In most poor countries, peritoneal fluids are not produced, which requires their importation and influences their cost and availability. In Benin, Cotonou, as in most poor countries, we underline the unavailability of alternative renal replacement therapy which led to a conservative management of patients with ARF (16) points. Nigeria, Port Harcourt, the rate of access to dialysis is 22.2%, of which 108 patients are included in the needs analysis (7).

Most centers in poor countries have hemodialysis machines that cannot take care of children and the majority of them do not put these machines (HD) available to HIV patients with HIV and infections linked to hepatitis B.

Management requires a well detailed record, a physical examination and laboratory investigations to determine possible ARF causes, as well as treatment in adequate time (1.6, 15). Particular problems affecting management arise in poor countries because of the patients’ late presentation, due to ignorance, poverty and transportation constraints, in addition to the poor referral systems, the insufficient number of pediatric nephrologists, the lack of laboratory equipment and the unaffordable prices of renal replacement therapies, if available.

Many children with kidney disease do not receive adequate medical care. There is a critical shortage of pediatric nephrologists (PN) and resources in many African countries. In Egypt, we have a PN for 500 000 children. In Nigeria, a PN for 4.5 million children, while there is no pediatric nephrologist in Cotonou, Benin (8,16). Due to the limited resources in these areas, most hospitals are not equipped with dialysis equipment.

Treatment goals until recovery of renal function are:
• The correction and prevention of threatening conditions such as metabolic disorders
• Treatment of causal disease and aggravating factors
• Support or replacement of renal function
• Prevention of any additional injury or complication
• General mesure:
  - Symptomatic in the acute phase
    - Put the patient at rest and sodium restriction observe a restriction of fluid intake
- Administer diuretics (furosemide), at 1-2 mg / kg every 2-3h (maximum 10mg/kg/d in the absence of RF if not 5mg/kg).
- Administer antihypertensives as needed
- If inefficiency, peritoneal dialysis.
- Resins in case of threatening hyperkalemia (kayexalate).

• Specific
- Antibiotic, Penicillin: no absolute evidence
- Treatment of the entrance: stomatologic and dermatologic ORL
- Specific treatment may be necessary if the form is severe.

• Monitoring the evolution

Monitoring the evolution includes:
- The weight, diuresis
- The cardiovascular status and hypertension
- Biology.

Generally, a rapid correction can be observed:
- From complementemia (1 month)
- From proteinuria (3 months)
- From the hematuria (in years).

Recovery was noted in 95% of cases.

The criteria for poor prognosis are:
• Persistence of hypocomplementaemia > 4 weeks
• Persistence of proteinuria (> 1g/24 h) beyond 3 months
• Persistence of hematuria beyond 1 year.

A- Pre renal ARF
The treatment of hypovolemia

1- The fluid management

Patients with ARF have difficult problems of fluid management. The hypovolemia potentiates and exacerbates all ARF forms. The recovery of blood volume by rapid fluid infusion is often sufficient to treat many ARF forms. However, the rapid liquid infusion may cause a fatal fluid overload.

The accurate determination of the patient’s volume status is essential and may require invasive hemodynamic monitoring, regular physical examination and monitoring of laboratory results

- Vascular filling
  - 9 %o serum salt 20 ml / kg over 15 minutes up to 60 ml / kg
  - Macromolecules if septic shock
  - Albumin 4% if hypoalbuminemia.

- If insufficient: monitoring of CVP

Transfusion is required if bleeding.

Diuretics are illogical and even dangerous, before the restoration of blood volume.

In this type of ARF, the kidney tissue is healthy and usually the response to the filling is adequate. Evolution is favorable in the majority of cases (64% of cases in our group), however, a delay in diagnosis increases the mortality and the risk of transition to organicity.
B- Post-renal ARF
- To remove the obstacle
- Fluid and electrolyte monitoring is necessary to prevent secondary disorders for the resumption of diuretic + + C/

C- Organic ARF

1- General measures of conservative treatment
- Maintain vital functions
- Maintain normovolemia and renal perfusion
- Transform a low output ARF to a high output ARF
- Correct and prevent hydroelectrolytic disorders
- Control blood pressure
- Treat anemia
- Adjust the dosage of drugs (or avoid them)
- Ensure proper nutrition
- Treat eventual cause
- Initiate dialysis if necessary.

For this, a monitoring is sometimes required:
- Arterial catheter if hypotension or high blood pressure
- Central venous catheter if overload and hemodynamic monitoring
- Indwelling catheter.

2- Inputs adaptation to water loss and ion
This requires close monitoring with a rigorous inputs / outputs record, a twice-daily control weight and CVP, where necessary. Fluid restriction is required: 20 ml / kg / d + + diuresis digestive losses Consider fever: 10 ml / kg level> 37.5, and polyuria during recovery.

3 - Hyperkalemia treatment
- Frequent and dangerous, increased by acidosis and certain medications
- Bicarbonate: 0.5 to 1 mEq / kg / dose in 20 minutes)
- Potassium exchange resins: Kayexalate (exchange K → Na) or Sorbisterit (exchange K → Na): 1 to

---

**table 4: Maintaining the fluid and electrolyte balance**

<table>
<thead>
<tr>
<th>Weight (Kg)</th>
<th>Daily Intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td></td>
</tr>
<tr>
<td>&lt; 10</td>
<td>1 – 20</td>
</tr>
<tr>
<td>1 – 20</td>
<td>20 &gt; 20</td>
</tr>
<tr>
<td>Sodium</td>
<td></td>
</tr>
<tr>
<td>&lt; 110</td>
<td>2.5mmol/Kg</td>
</tr>
<tr>
<td>Potassium</td>
<td></td>
</tr>
<tr>
<td>11 – 30</td>
<td>30 &gt; 30</td>
</tr>
</tbody>
</table>

---
2g/kg/d orally or intra rectal.
- If emergency: Calcium and vitamin D or dialysis

4- **Hyponatremia treatment**
   - Usually due to a dilution in most cases, more or less to a depletion
   - A fluid restriction is usually sufficient
   - If depletion => correction always progressive
   \[ Q \text{ in mmol} = \text{desired increase (mEq / L)} \times 0.6 \times \text{weight}. \]

   In practice...
   - Perfusion of base considering treatment: glucose + equal volume of insensible losses ions
   - Hourly diuresis compensation, volume for volume
   - Composition of compensation appropriate to ionicU, Ssalé 50%, 25% and 25% SG5 Bicar14 %
   - Compensate for other losses: drains, saddles...
   - Stimulation of diuresis has no effect truly demonstrated on the evolution. However, it greatly facilitates the management.

   Furosemide is given at 0.5 to 5 mg/kg per dose, 2 mg/kg IV or IM, repeat after 6-8h. Beware, if hypovolemia, only start after filling. The risk of hearing doses grows continuous use. If ineffective, it must be stopped.

5- **Ensure diet**
   - The diet has a prognostic value, early nutritional support is essential right from the second or third day.
   - If there are some problems, take into account the volume, ionic and nutrition composition, digestive tolerance and the patient’s appetite.

   Via the oral route: 60 - 120 cal/kg (carbohydrates, lipids) eventually using a probe.
   - Dialysis is sometimes needed
   - Resort to milk low in phosphorus and potassium
   - In older children: hyper caloric (120% RDI)

6- **Extrarenal dialysis (ERD)**

   The main methods of renal replacement therapy are intermittent hemodialysis, continuous venovenous hemodiafiltration and peritoneal dialysis. Each of these therapies has its advantages and limitations.

   **Indications**
   - Overload, heart failure.
   - Hypertensive crisis.
   - Symptomatic uremia (pericarditis, encephalopathy, bleeding, nausea, vomiting, pruritus).
   - Hyperkalemia> 7 mmol/L
   - Severe acidosis resistant to conservative management
   - Pulmonary edema
   - Severe dysnatremia (<115 or> 165)
A need for transfusion in an auric child
- Convulsive seizure, resistant tetany
- Neurological signs
- Hypocalcemia, hyperphosphatemia
- Insufficient nutritional intake
- Significant poisoning with dialysable agent (methanol, ethylene glycol, theophylline, aspirin, lithium).

The selection criteria
- Age of child => opportunities vascular
- Hemodynamic => tolerance.
- Etiology.

Techniques
- Peritoneal dialysis used in 30 to 60% of cases
- Discontinuous hemodialysis, 10 to 20% of cases
- Continuous hemofiltration AV or VV, 15 to 40% of cases
- Possibility of hemodiafiltration.

Hemodialysis (HD)
Widely available, it is less expensive and more efficient, but it requires significant experience and an essential hemodynamic stability. Requiring first the right route, it is mainly used in older children.

Peritoneal dialysis (PD)
The easiest and best tolerated of renal replacement techniques in the child, it is a technique of choice in infants. Inexpensive, widely available, it does not entail hypotension. However, it is unable to remove large amounts of liquids or solute. Its use may be more common in children and in developing countries.

Catheter placement increases the time for implementation and treatment is relatively slow.

The risk of infection is the most important complications. The PD is contraindicated in case of a digestive surgery.

The quantity to be infused is 20 to 50 ml / kg / cycle from 45 to 60 minutes.

Prevention
Important cause of morbidity and mortality, 80% of ARF cases can be avoided through:
- Improvement of basic care
- A timely and appropriate treatment of infections
- Educating mothers to prevent dehydration (gastroenteritis)
- Avoiding toxic products, including contained in traditional decoction.

ARF RESULTS
ARF results are deemed unfavorable in poor countries compared to developed ones (6, 7, 8). The high poverty rate indicates that 982 million of 4.8 billion people, constituting the population of
developing countries, earn a dollar a day, while 2.5 billion people earn less than two dollars a day, which influences their behavior regarding care and preservation of their health. Late patient access to the hospital, the use of herbal medicines as well as the inaccessibility of dialysis increased the mortality rate caused by the ARF. In Nigeria, the hospital mortality rate caused by the ARF varies from 40.5% to 46.2% compared to 25% recorded in the United States (1,7), which shows the firm belief that the ARF is the main cause of morbidity and mortality among children from poor countries around the world.

VII- CONCLUSION
The ARF is a rare disease that requires adaptation to pediatric constraints. Its prognosis is variable depending on the initial pathology, and long-term monitoring is still required. The lack of dialysis opportunities and the remoteness of centers may worsen the prognosis. In order to enhance the ARF management in Morocco, it is necessary to implement preventive measures quite early and work at the PD generalization.

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7) A. Bourquia
CHAPTER 19

NEPHROPATHY SECONDARY TO TYPHOID SEPTICAEMIA

Odetunde Odutola Israel, Enugu - Nigeria
HIGHLIGHTS

✓ Typhoid sepsis remains common in Africa.
✓ Renal complication is an unusual manifestation of typhoid fever. Transient proteinuria is the most common renal manifestation.
✓ In some cases, acute renal failure or nephrotic syndrome with a poor prognosis.
✓ Proper hydration can prevent the development of acute tubular necrosis.
✓ Besides the treatment of sepsis, hydrolelectrolytique disorders, dialysis may sometimes be necessary.

I- INTRODUCTION

Improvement in the standard of living has reduced the incidence of typhoid enteritis in the developed countries but this condition remains common in underdeveloped parts of the world, namely Africa, where outbreaks and epidemics continue to occur in both urban and rural areas. One of the unusual manifestations of typhoid fever is kidney failure complication. Although 25% of patients excrete salmonella typhi in the urine during the acute illness, renal complication may occur from ischemic damage resulting from inadequate perfusion induced by severe diarrhoea dehydration and septic shock systemic release of endotoxin or other toxin and activation of inflammatory cascade during septicaemia activation of the immunologic pathway or immune complexes resulting from salmonella infection and rarely direct invasion of the renal tissues and collecting system. In many condition a combination of these mechanism may occurred. Another factor to be considered is the nephrotoxic effect of some antibiotics the use of antimicrobial agents for the treatment of infection may trigger a renal complication.

II- PATHOGENESIS AND PATHOLOGY

A- Pathogenesis

It may be explained by inflammatory and necrotic changes in the intestinal node, liver, spleen and lymph node, which would result in pyrexia, toxaemia, pathologic changes and function derangement in the kidneys. Where typhoid nodule and salmonella typhi are generally not found.

B- Pathology

The most common lesions found in the kidney are swelling and albuminus degeneration of the proximal tubular epithelium, but interstitial nephritis, glomerulonephritis, and pyelonephritis have been noticed as well. Histopathological findings include focal proliferation of mesangial cell, hypertrophy of endothelial cell and congested capillary lumina. Immunofluorescent studies show IgM, IgG, and C3 deposition in the glomeruli with salmonella antigens detected within the granular deposit in the mesangial area. Salmonella antigens have been found within the glomeruli in IgA nephropathy following salmonella septicaemia.

III- CLINICAL PRESENTATION

- Transient proteinuria, which is the most frequent renal manifestation, is sometimes caused by an immune complex-mediated glomerulonephritis.
- In certain cases the glomerulonephritis may present itself as an acute kidney failure or a nephrotic
syndrome with poor prognosis. In severely ill children, acute tubular necrosis may develop. Among patients with intravascular haemolysis associated or not with glucose–6-phosphate dehydrogenase deficiency may evolve into an acute kidney injury. Symptoms of pyelonephritis and cystitis may also occur in children with typhoid septicaemia.

IV- TREATMENT
The treatment is usually divided into three major components, which are specific treatment of salmonella sepsis with sensitivity antibiotics, treatment of secondary renal pathology and supportive care. With renal diseases, supportive care involves managing hypertension, fluid, and electrolyte abnormalities as well as managing decreased renal function. Nephrotoxic agents, which may worsen the renal injury and delay recovery of function, are to be avoided. Such agents include contrast media, aminoglycosides, and NSAIDs.

A- Acute tubular necrosis (ATN) secondary to typhoid septicaemia
1- Prevention of ATN
In the case of severely ill children with typhoid septicaemia, administration of fluids, diuretics, mannitol, and low-dose dopamine have been used to prevent or reverse renal injury. Vigorous prophylactic fluid administration has proven to be successful in the prevention of ATN in the author's experience.

2- Fluid management
The main objective of fluid management is to restore and maintain intravascular volume. ATN may manifest itself with hypovolemia, euvolemia, or volume overload. Moreover, estimation of fluid status is a prerequisite for initial and ongoing therapy. This is accomplished by measuring input and output, serial body weights, vital signs, skin turgor, capillary refill, serum sodium, and Fractional excretion of sodium (FeNa). Critically ill children diagnosed in our centre with typhoid septicaemia with intravascular volume depletion usually receive prompt and vigorous fluid resuscitation. Initial therapy includes isotonic sodium chloride solution or lactated Ringer solution at 20 mL/kg over 30 minutes. It can be repeated twice if necessary, after careful monitoring to avoid possible fluid overload.

Potassium administration is contraindicated until urine output is established. If anuria persists after 3 fluid boluses (confirmed by bladder catheterization), in the presence of volume overload, fluid restriction and possibly intravenous administration of furosemide are required. Children with established ATN may not respond to furosemide, in which case it would be judicious to consider fluid removal by dialysis, especially if signs of fluid overload are evident. Supportive management includes input and output records, daily weights, and blood pressure monitoring. During the recovery phase, children develop significant polyuria and natriuresis and may become dehydrated if appropriate adjustments in fluid requirements are not made.

3- Electrolytes and acid-base balance
a- Hyperkalemia
If serum potassium levels exceed 5.5–6.5 mEq/L, eliminate all sources of potassium from the diet or intravenous fluids and administer a cation exchange resin such as sodium polystyrene sulfonate (Kayexalate). Emergency treatment of hyperkalemia is indicated when serum potassium exceeds 6.5 mEq/L or tall peaked T waves are evident on the ECG, this includes administering intravenous
sodium bicarbonate, infusion of glucose and insulin, by beta-agonists (albuterol by nebulizer),
administration of calcium gluconate (with continuous ECG monitoring) to counter the effects of
hyperkalemia on the myocardium. The definitive therapy for significant hyperkalemia in oliguric
ATN often includes dialysis. Once the mentioned conservative measures are taken, arrangements
are subsequently made for dialysis.

b- Hyponatremia

The primary treatment of hyponatremia is free water restriction. Serum sodium of less than120
mEq/L may require hypertonic (3%) sodium chloride infusion, especially if CNS dysfunction is
noted. Because the administration of hypertonic sodium chloride is likely to precipitate CNS
dysfunction, it should be contemplated with extreme caution in intensive care services. Notice the
author seldom resorts to this particular treatment.

c- Hyperphosphatemia

Management of hyperphosphatemia includes dietary restriction and oral phosphate binders
(calcium carbonate or calcium acetate). Hypocalcemia usually responds to oral calcium salts
used for control of hyperphosphatemia but may require 10% calcium gluconate infusion in severe
cases. Metabolic acidosis of ATN is usually benign and requires no treatment. Moderate acidosis
should be treated with oral sodium bicarbonate or sodium citrate. Severe acidosis, especially in
the presence of hyperkalemia, requires intravenous bicarbonate therapy.

4- Dialysis

The purpose of dialysis is to remove endogenous and exogenous toxins and to maintain fluid,
electrolyte, and acid-base balance until the renal function returns. Indications for acute dialysis
are not absolute the decision to use this therapy depends on the rapidity of onset, duration,
and severity of the anomaly to be corrected. The choice between haemodialysis and peritoneal
dialysis depends on the overall clinical condition, availability of technique, aetiology of the ATN,
institutional preferences, and specific indications or cons-indications. Reports from most centres
in the region showed the peritoneal dialysis is a gentler and preferred method in infants and
younger children and it is becoming more readily available. Paediatric haemodialysis facilities
are scarcely emerging in Nigeria renal health care while continuous veno-venous haemofiltration
(CVVH) is not available yet in the region. Peritoneal dialysis therefore remains the only renal
replacement therapy option for children.

- Common indications for dialysis in ATN secondary to typhoid septicaemia
- Fluid overload that is unresponsive to diuretics
- Fluid overload that hinders adequate nutritional support
- Hyperkalemia with oliguria
- Symptomatic acid-base imbalances
- Refractory hypertension
- Symptomatic uremia (pleuritis, pericarditis, CNS symptoms)

B- Nephritis secondary to typhoid septicaemia

Treatment must address typhoid septicaemia with antibiotics because spontaneous remission
may occur following the treatment of the primary disease. Treatment of secondary renal pathology
ranges from watchful waiting to the use- actually rare- of immunosuppressive medication, such as
steroids or cyclophosphamide. Aggressive therapies, which may introduce additional risk, are not indicated for children suffering from mild or benign disease. Risk factors for progressive renal disease include heavy proteinuria (protein excretion >2 mg/kg/d), reduced renal clearance function (estimated GFR or measured CrCl<75% normal), and hypertension have seldom been identified. Hypertension when it occurs can be managed with antihypertensive, such as calcium channel blocking agents, angiotensin-converting enzyme inhibitors, angiotensin receptor blocking agents, peripheral vasodilators, and diuretics. The most common fluid anomaly is hypervolemia, it is treated with fluid restriction and diuretics or dialysis if renal function is too poor to respond to diuretics. Hyponatremia usually is dilutional and will respond, at least partially, to removal of excess fluid. Hypocalcemia may respond to oral or intravenous calcium depending on the gravity. Light metabolic acidosis may occur but would seldom require primary treatment.

**C- Pyelonephritis and cystitis secondary to typhoid septicaemia**

Pyelonephritis and cystitis secondary to typhoid septicaemia respond well to specific treatment of salmonella sepsis with sensitivity antibiotics with remission of symptoms and signs.

**References**

5) Srivastava RN. Acute glomerulonephritis in salmonella typhi infection. Indian Pediatr. 1993: 30: 278-279
CHAPTER 20

THE HEMOLYTIC UREMIC SYNDROME

Hesham Safouh, Cairo - Egypt
**HIGHLIGHTS**

✓ **Hemolytic Uremic Syndrome** is a leading cause of acute renal failure in children less than three years.

✓ **HUS** is characterized by the association of hemolytic anemia with schistocytes, thrombocytopenia and renal failure secondary to thrombotic microangiopathy.

✓ The typical form is the most common (90%) in children, occurring after an episode of diarrhea in enteropathogenic *Escherichia coli*.

✓ Kidney failure is reversible in the majority of cases, but long-term renal sequelae may be observed.

✓ The treatment is purely symptomatic typical HUS (transfusion of packed red blood cells, treatment of acute renal failure).

✓ Atypical forms are rarer but often poorer prognosis.

✓ Recurrence after renal transplantation is exceptional in post infectious forms but common in atypical forms.

I- **INTRODUCTION**

The hemolytic uremic syndrome (HUS) is characterized by three main features: non-immune microangiopathic hemolytic anemia, thrombocytopenia and renal injury secondary to the development of platelet thrombi and intravascular coagulation in small vessels, particularly in the kidney. It is part of a broader group of disorders characterized by capillary thrombosis in many organs, known as thrombotic microangiopathy (TMA). The latter includes both HUS and thrombotic thrombocytopenic purpura (TTP) which are characterized by capillary thrombosis and associated organ dysfunction. Lesions typically affect the kidney (mainly glomeruli and arterioles), although the brain, heart, lungs, gastrointestinal tract, and pancreas all may be involved. TTP has been reported in children, but is more common in adults. In contrast, HUS is more common in children (1,3).

HUS is the most common cause of acute renal failure in childhood. It leads to significant morbidity and mortality during the acute phase. In addition to acute morbidity and mortality, long-term renal and extrarenal complications can occur years after the acute episode (4).

II- **CLASSIFICATION AND ETIOLOGY**

In children 90% of patients have the so-called typical or post-diarrheal (D+) HUS. Karmali et al. established that D (+) HUS was attributable to infection with shiga toxin producing *Escherichia coli* (STEC). This form occurs mainly in children 6 months to 3 years of age, and has a relatively favorable outcome, as rapid progression to end-stage renal failure (ESRF) is not common and many patients make a long-term full recovery (4).

The other form, called atypical or D (-) HUS (aHUS) (10% of children), occurs at any age, may be sporadic or familial, and has a worse prognosis, as about 50% of patients progress to ESRF. Less than 20% of cases of atypical hemolytic–uremic syndrome are familial. Both autosomal dominant and recessive patterns of inheritance have been reported. Atypical HUS that develops in patients who do not have a family history of the disease is classified as sporadic. Triggers for the sporadic form are mentioned in Table 1 under Etiology (pathogenesis) unknown and many of these triggers
have been related to complement abnormalities as well. HUS can be classified according to the etiology of the different disorders from which it is composed as well as the pathogenesis of the microangiopathy (Table 1) (6).

Table 1: An Etiological / Pathogenetic classification of HUS

<table>
<thead>
<tr>
<th>1. Etiology (pathogenesis) known</th>
</tr>
</thead>
<tbody>
<tr>
<td>a - Infection induced</td>
</tr>
<tr>
<td>• Shiga and shiga-like toxin-producing bacteria enterohemorrhagic Escherichia coli (EHEC, STEC), Shigella dysenteriae type 1, Citrobacter freundii</td>
</tr>
<tr>
<td>• Streptococcus pneumoniae, neuraminidase and T-antigen exposure</td>
</tr>
<tr>
<td>b - Disorders of complement regulation</td>
</tr>
<tr>
<td>• Genetic disorders of complement regulation</td>
</tr>
<tr>
<td>• Acquired disorders of complement regulation, e.g. factor H antibody</td>
</tr>
<tr>
<td>• Genetic or acquired disorders of von Willebrand proteinase, ADAMTS13</td>
</tr>
<tr>
<td>• Defective cobalamin metabolism</td>
</tr>
<tr>
<td>• Quinine induced</td>
</tr>
<tr>
<td>2. Etiology (pathogenesis) unknown</td>
</tr>
<tr>
<td>• Human immunodeficiency virus (HIV)</td>
</tr>
<tr>
<td>• Malignancy, cancer chemotherapy and radiation</td>
</tr>
<tr>
<td>• Calcineurin inhibitors and following transplantation</td>
</tr>
<tr>
<td>• Pregnancy, and oral contraceptive pills</td>
</tr>
<tr>
<td>• Systemic lupus erythematosus and antiphospholipid syndrome</td>
</tr>
<tr>
<td>• Unclassified</td>
</tr>
</tbody>
</table>

Occasionally, HUS may be brought about by a combination of inherited and environmental factors. Clinicians thus need to be alert to this possibility and should fully investigate any case that falls outside the typical infection-induced pattern of disease.

III- PATHOGENESIS

Shiga toxins have a single A subunit linked to five B subunits. Whereas the gene for shiga toxin is encoded in the chromosome of S. dysenteriae-1, genes for Stx1 and Stx2 are encoded in E. coli by bacteriophages (viruses that infect bacteria). Stx1 is identical to shiga toxin, the product of Shigella dysenteriae type 1, Stx2 is approximately 60% homologous to Stx1. The B subunit recognizes and binds to a cell glycolipid (globotriaosylceramide), expressed on renal tubular and vascular cells in kidney, brain and intestine (7,8).

Humans acquire antibodies to Stx2 during childhood and teenage years, and maybe as a result adults are, to some extent, protected by acquiring anti-Stx2 antibodies (9). Factors implicated in the regulation of the alternative pathway of the complement system such as factor H (CFH) (10) CD46 (or MCP for membrane cofactor protein) (11,12), factor I (CFI)(13,14) and more recently factor B (CFB)(15) and C3 (16) which are implicated in the formation of the alternative C3-convertase have all been linked to the pathogenesis of HUS in familial and even sporadic cases. In addition, acquired cases of atypical HUS associated with CFH dysfunction due to anti-CFH autoantibodies have been identified (17).
Complement protein factor H helps regulate alternative complement pathway activation by inhibiting the formation of the alternative C3-convertase and accelerating its decay as well as serving as a cofactor for the C3b-cleaving enzyme, factor I. Thus in cases with factor H dysfunction, complement deposition on endothelial cells, particularly in glomeruli, can lead to vascular injury and TMA. Several different abnormalities of factor H function and quantity have been described in patients with familial or recurrent HUS (18).

IV- SIGNIFICANCE OF HUS IN AFRICAN COUNTRIES

Reports on the significance of HUS as a cause of ARF in African countries vary and range from 5.5 % up to 76.5 % of causes of ARF. Safouh(19), reported that the HUS accounted for 23 cases (28 %) out of a total of 83 patients presenting with acute renal failure to the Pediatric Nephrology Unit, Cairo University, Egypt during the period from April 2005 till end of 2009. They included 14 females and 9 males and their ages ranged from 2 months to 14 years (mean 46 +/- 48.8 ms). There was positive consanguinity in 7 (30 %), but no family history of similar condition in any of them. Thirteen came from urban and 10 from rural areas. Diarrhea preceding the attack was watery in 6 (26 %), Bloody diarrhea in 11 (48%) and there was a negative history of diarrhea in 6 (26 %). Additional presenting symptoms are shown in Table 2.

Table 2: Additional presenting symptoms in HUS

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>19 (83 %)</td>
</tr>
<tr>
<td>Edema</td>
<td>17 (74%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>17 (74%)</td>
</tr>
<tr>
<td>Fever</td>
<td>13 (56.5%)</td>
</tr>
<tr>
<td>Lethargy</td>
<td>7 (30 %)</td>
</tr>
<tr>
<td>Lethargy</td>
<td>4 (17 %)</td>
</tr>
<tr>
<td>Oliguria</td>
<td>15 (65 %)</td>
</tr>
<tr>
<td>Anuria</td>
<td>8 (35 %)</td>
</tr>
<tr>
<td>Jaundice</td>
<td>4 (17%)</td>
</tr>
<tr>
<td>Petechiae</td>
<td>6 (26%)</td>
</tr>
<tr>
<td>Bleeding</td>
<td>6 (26%)</td>
</tr>
</tbody>
</table>

Admission creatinine and urea were 7.1 +/- 3.41 and 121.8 +/- 47 mg/dl, respectively. Proteinuria and hematuria were universally found. Admission Hb was 5.8 +/- 1.6 mg/dl, platelets 188000 +/- 126/mm3. Fragmented RBCS were seen in all but 2 cases. Treatment included antihypertensives in 14, steroids in 3, blood transfusion in 18, plasma transfusion in 15, plasmapheresis in 3, acute peritoneal dialysis in 15 and hemodialysis in 8. Four patients fully recovered, 5 died and 14 ended up with CKD. Four of the 5 cases (80 %) that died vs. 3/18 (17 %) who survived had significant CNS symptoms on admission (lethargy, stupor)(p < 0.01). There was no significant difference between survivors and non-survivors as regards age, D- or D+ HUS, initial plasma creatinine (mean 7.089 vs. 7.120 mg/dl), initial Hb values (mean 5.611 vs. 6.700 g / dL), platelet count (mean 203,670 vs. 136,000 / mm3 nor initial systolic or diastolic blood pressures.In a retrospective chart review by
Van Biljon(20) of 102 children (mean age 37 months) to determine the causes of ARF in children admitted to the Pretoria Academic Hospital from 1986 to 2002, the most common single cause was HUS (35.3%).

A prospective study, from March 1994 through February 2000 was carried out by Olowu and Adelusola (21) to determine the prevalence of ARF clinical types, etiology, comorbidities, and outcome in Nigerian children. There were 78 boys and 45 girls (M: F 1.73:1) mean age was 6.28 +/- 4.0 years. The HUS accounted for only 5.5% of cases of ARF.

Shimelis and Tadesse(22) analyzed the case records of 30 pediatric patients with the diagnosis of ARF admitted to Tikur Anbessa Hospital in Addis Ababa between October 1997 and October 2001. There were 15 females and 15 males. Twenty-three patients (77 %) had post-diarrheal hemolytic uremic syndrome. The age ranges of post-diarrheal hemolytic uremic syndrome cases were between 0.6 years and 7 years with a median age of 2.2 years. Fourteen patients died of acute renal failure among this hemolytic uremic syndrome contributed to the death of 9 patients. From stool cultures of 16 patients with hemolytic uremic syndrome, there were five isolates of Shigella species, two isolates of E. coli, and two isolates of Salmonella species. They concluded that the HUS was the leading cause of acute renal failure in infants and young children in their series.

V- EPIDEMIOLOGY

The most prevalent form of HUS is that induced by STEC and, in some tropical regions, by Shigella dysenteriae type 1. STEC cause a zoonosis in which hemorrhagic colitis and HUS are the most severe expression in humans. Animals, particularly ruminants such as the cow, may be colonized by organisms that are clearly pathogenic in humans without expressing disease themselves. Fluctuations in incidence may occur, with local epidemics sometimes linked to a common source of infection. It has been estimated that one in ten exposed to the infection develops symptoms of colicky abdominal pain and diarrhea, and 15% of children with diarrhea or bloody diarrhea will develop HUS. Outbreaks may be biphasic, a second wave occurring 2 weeks later from person-to-person transmission. The time from exposure to onset of diarrhea is usually less than a week, mostly 3–4 days, and the mean interval between onset of diarrhea and presentation of HUS is 4 days, range 1–10 days (23).

The E. coli serotypes that are associated with HUS vary in different parts of the world. In North America and North West Europe the dominant serotype is O157:H7 (24,26), but other serotypes occur, either sporadically or as causes of outbreaks of enterocolitis and HUS. In Southern Europe a high proportion of HUS is associated with O26(25) and, in Australia, O111 is the dominant causative strain. In developed countries, there is a seasonal pattern to the incidence of HUS, being greater in summer than in winter (27). Data from African countries as regards the serotypes of E. coli causing HUS is lacking.

HUS as a complication of Shigella dysenteriae type 1 infection has many features resembling STEC-induced HUS. The age range is wider, the median age of presentation being approximately 3 years, and the median time from the onset of diarrhea to the presentation of HUS is 7 days, compared to 4 for most STEC infections. HUS complicating Shigella dysenteriae is usually more severe, but the condition mostly occurs in developing countries in tropical regions, where children may have co-morbidities and poor access to health care (28).
Olotu et al. (29) studied children admitted to Kilifi District Hospital, Kenya, between 1997 and 2005 with HUS and reviewed their records in order to determine the clinical features and outcomes of the disease. Thirty-one children fulfilled the criteria: 21 (68%) had diarrhea-associated HUS (D+HUS), the remainder did not (D-HUS) five had involvement of the central nervous system. Those with D-HUS had lower hemoglobin and platelet counts when compared with those with D+HUS. The overall mortality rate was 55% (17/31) with no significant difference between the two groups. Severe hyponatremia ([Na+]<120 mmol/L) predicted a poor outcome. Shigella dysenteriae was the most common isolated organism in the stool and E. coli and S. dysenteriae were the most common blood isolates.

An outbreak of dysentery in Zimbabwe was associated with a high mortality, especially in children who developed hemolytic uremic syndrome (HUS). To examine the causes of high mortality from HUS and to suggest measures that could reduce the case fatality rate, clinical and laboratory features of were reviewed. Of 91 children with dysentery, 14 developed HUS. While Shigella dysenteriae type I was responsible for the dysentery outbreak in the community, most stool cultures of children with HUS were negative. Mortality from HUS was high. Late recognition of HUS and a lack of peritoneal dialysis could have contributed to the fatal outcome in some cases. Early recognition of HUS through close observation of children with dysentery and appropriate laboratory investigations with referral to a hospital, where peritoneal dialysis is available, should improve the outcome (30).

Germani et al. reported an increase in the number of reported cases of acute bloody diarrhea in infants and adults in the Central African Republic since 1996. E. coli O157:H7 was isolated from two fatal adult cases. Smoked zebu meat was suspected in several hospital cases (bloody diarrhea, hemolytic anemia, and renal insufficiency) in which non-fermenting sorbitol E. coli O157:H7 was not isolated. In two cases of acute diarrhea, other serotypes of E. coli were indicated by retrospective PCR on stools which were positive for SLT1 (31).

Bhimma et al. reported on 81 of 107 cases of hemolytic uremic syndrome (HUS), admitted between July 1994 and February 1996, following an outbreak of Shigella dysenteriae type 1 dysentery in Kwazulu/Natal. All patients, excluding 1, were black with a mean age of 38 months (range 1-121) 50 (61.7%) were males. The mean duration of dysentery was 11.3 days (range 1-41) and HUS 15 days (range 1-91). Most patients had acute oliguric renal failure (90.1%), 42 (51.6%) required peritoneal dialysis. Complications included encephalopathy 30 (37.0%), convulsions 12 (14.8%) and hemiplegia 2 (2.3%), gastrointestinal perforation 8 (9.9%), protein losing enteropathy 26 (32.1%), toxic megacolon 4 (4.9%), rectal prolapse 5 (6.2%), hepatitis 11 (13.6%), myocarditis 5 (6.2%), congestive cardiac failure 3 (3.7%), cardiomyopathy 3 (3.7%), infective endocarditis 1 (1.2%), septicemia 15 (18.5%), disseminated intravascular coagulation 17 (21%). Leukemoid reactions were found in 74 (91.3%) patients, hyponatremia in 56 (69.1%), and hypoalbuminemia in 67 (82.7%). Stool culture for Shigella dysenteriae type I was positive in only 7 (8.6%) patients Shiga toxin assays were not performed. Recovery occurred in 32 (39.5%), impaired renal function in 8 (9.9%), chronic renal failure in 26 (32.1%), end-stage renal disease in 1 (1.2%), and death 14 (17.3%) patients (32).

VI- CLINICAL PRESENTATION

Signs of GI illness characterized by abdominal pain, vomiting, and diarrhea precede the onset of HUS in D+ disease. In some cases, the GI manifestations may be minimal. More commonly, the
diarrhea is pronounced and bloody. Following this prodrome, anorexia, weakness, pallor, and jaundice are the resenting symptoms in many children with HUS. Oliguria and/or hematuria are the first manifestations of renal involvement in these patients. These manifestations may evolve over hours to a few days, depending on the severity of the disease. Hyponatremia due to fluid overload (dilutional hyponatremia), high anion gap metabolic acidosis, and hyperkalemia may be seen at initial presentation in some patients (33,34). Central nervous system symptoms, such as lethargy, irritability, seizures, cortical blindness, paresis, and coma occur in up to 30% of affected children (35).

In atypical HUS, preceding GI symptoms may or may not be seen. Most of these children present with a history of a prodromal respiratory illness, such as otitis, sinusitis, or pneumonia, which may still be present at the time of recognition of HUS (34).

VII- COMPLICATIONS
Organ dysfunction in acute illness may result from vascular thrombosis and infarction of the CNS (lethargy, coma, seizures, stroke) myocardium (infarction, congestive heart failure), GI tract (colonic perforation or stricture), and/or pancreas (diabetes mellitus). Such manifestations are usually seen in patients with severe disease (36,37).

Evidence of chronic renal damage (proteinuria, hypertension, and/or renal insufficiency) may be seen in up to 30–50% of children who recover from HUS. Significant hypertension may be present after recovery from HUS and may require multiple medications for control. Long-term follow-up for children with any evidence of chronic renal sequelae is essential (38,40).

VIII- LABORATORY INVESTIGATIONS:
Any child with HUS, especially those with atypical forms of the disease, should be thoroughly investigated, since accurate diagnosis can significantly therapy (41).

Investigations usually include:

A- Urinalysis
Typical findings include hematuria, proteinuria, and cellular casts.

B- Hematology
- Low hemoglobin, and evidence of RBC damage such as burr cells, and schistocytes (fragmented RBCs) are characteristic.
- Thrombocytopenia (as low as 5000/mm3.) is common but platelet numbers may be low normal early in the course of the disease.
- The reticulocyte count is typically elevated in response to intravascular hemolysis, although, as renal insufficiency develops, the reticulocyte count will be low.

C- Normal direct and indirect coombs tests
- The haptoglobin is low and indirect bilirubin high. Plasma lactate dehydrogenase (LDH) is high due to RBC lysis.
- The prothrombin and partial thromboplastin times are normal.
- The leukocyte count is often elevated early in the course of HUS.
D- Stool culture
O157 STEC are cultured from stools on sorbitol MacConkey agar enriched with tellurite. Because this serotype is usually unable to ferment sorbitol, colonies can be inspected, picked, and then tested specifically for O157 by agglutination or enzyme immunoassay (EIA). However, often in D+ HUS, by the time the child presents with signs of HUS, the diarrheal illness is resolving and stool cultures are often negative. Urine cultures may occasionally grow E. coli in cases with negative stool culture results (23).

E- Shiga toxin assay
Detection of Stx in stool, will allow more rapid detection of Stx-mediated HUS.42

F- Renal function
Renal insufficiency may manifest itself over 5–7 days after first evidence of renal involvement. Elevated blood urea nitrogen (BUN) and creatinine, hyperkalemia, metabolic acidosis, hypocalcemia, hyperphosphatemia, and hyperuricemia may all be found.

G- Renal biopsy
It is indicated usually only in atypical cases. The lesions of Stx-related hemolytic–uremic syndrome, which are indistinguishable from those of its atypical form on the basis of standard histologic analysis, are characterized by thickening of arterioles and capillaries, endothelial swelling and detachment, and subendothelial accumulation of proteins and cell debris. Platelet thrombi obstruct vessel lumina (43).

H- Further investigations in atypical cases
For children with atypical HUS, (D-) HUS, or familial or recurrent HUS, careful consideration of the previously mentioned unusual etiologies must be considered. Adequate investigation of such cases requires advanced lab services and is quite expensive and thus African centers may require support from Western or other advanced centers to assist in the diagnosis and accept samples for analysis.

Determination of C3, C4, C1q, CFH, CFI and CFB levels, expression of MCP and screening for anti-CFH antibodies is indicated for all patients with aHUS. A low C3 level reflects complement activation and consumption. Patients with the hemolytic–uremic syndrome who have low C3 levels have high levels of activated complement components, including C3b, C3c, and C3d. The C3 convertases of the classic and lectin pathways are formed by C2 and C4 fragments, whereas the alternative pathway convertase cleaves C3 but not C4. Thus, a low serum C3 level in a patient with atypical HUS who has a normal C4 level indicates selective activation of the alternative pathway. Normal C3 level does not eliminate the presence of CFH or CFI mutation or of anti-CFH antibodies. Genotyping of CFH, CFI and MCP, and if possible CFB and C3, is indicated for all patients with aHUS, even if plasma levels are normal. Since a post-diarrheal onset of HUS has been observed in all groups, genotyping must be performed for patients with uncertain diagnosis of D+ /STEC+ HUS, especially before transplantation (44).

I- Thrombotic thrombocytopenic purpura
If TTP is a diagnostic consideration, assays of ADAMTS 13 activity and antibodies directed to ADAMTS 13 should be obtained (45).
IX- TREATMENT

Many children with HUS recover spontaneously with appropriate supportive care and management of acute renal failure.

- Antibiotic therapy is not indicated in STEC HUS or idiopathic HUS and has been associated with worse outcome in a few series. However antibiotics may be indicated in Shigella induce HUS since in contrast to STEC they are invasive organisms (46). Careful volume expansion early in the course of HUS may attenuate the degree of renal impairment (47). Serum albumin is often low in these children and replacement with intravenous albumin may be useful (48).

Treatment of anemia with RBC transfusions is done to keep the hemoglobin >8.0 mg/dl. During the latter stages of severe HUS with renal insufficiency, erythropoietin administration may be useful (49). Platelet transfusions do not provide prolonged improvement in the platelet count and might even worsen the TMA process (50).

Management of acute oliguric renal failure requires:

- Strict attention to fluid balance
- Treatment of hypertension
- Correction of metabolic disturbances such as hyperkalemia, metabolic acidosis, hypocalcemia, and hyperphosphatemia.

When dialysis is required, whether PD, HD or CRRT, it is generally needed for 5–7 days, although some patients have recovered after more than 1 month of dialysis. For all subjects with HUS, provision of adequate nutrition is important and may require TPN until the GI tract has recovered (51).

Other therapies For D+ HUS, such as intravenous streptokinase (52), plasma infusions or plasmapheresis (45), intravenous γ-globulin (53°), Stx-binding antitoxins (54) and corticosteroids (55) have not been shown to have an impact on outcome.

Patients with genetic HUS that result from congenital deficiencies of complement pathway regulators, or congenital TTP that result from a congenital deficiency of ADAMTS13, may benefit from the replacement of these factors through plasma infusions (45).

In atypical HUS due to factor H abnormalities, plasma exchange or infusion started within 24 hours after diagnosis, with an exchange of one to two plasma volumes per day or an infusion of 20 to 30 ml per kilogram has been associated with a decrease in mortality from 50% to 25%. Plasma exchange has shown to be superior to plasma infusion for remission and prevention of recurrences, possibly through the removal of mutant dysfunctional CFH molecules as well as anti-CFH antibodies (56,57). The combination of plasma exchange with the use of immunosuppressant drugs (e.g., corticosteroids and azathioprine or mycophenolate mofetil) and an anti-CD20 antibody (rituximab) resulted in long-term dialysis-free survival in 60 to 70% of patients. CFH concentrate offers hope for the future (58).

Patients with CFI mutations have only a partial response to plasma therapy and since MCP is a cell-associated protein, plasma exchange or infusion is unlikely to be effective in patients with MCP mutations, and spontaneous remission generally occurs in the latter group (58).

There is no proven benefit for plasma infusions or plasmapheresis in HUS/TTP associated with autoimmune disorders, human immunodeficiency virus (HIV) infection, transplantation, malignancy, or medications (45). A humanized anti-C5 monoclonal antibody, eculizumab, is being
recently reported as promising in patients with typical and atypical HUS. It blocks complement activity by cleavage of the complement protein C5 and prevents the generation of the inflammatory peptide C5a and the cytotoxic membrane-attack complex C5b-9 (59,62).

HUS recurs in around 50% of patients who undergo renal transplantation, and graft failure occurs in 80 to 90% of those with recurrent disease. The risk of graft loss due to HUS recurrence or graft thrombosis is high in patients with CFH and CFI mutations, while it is very low in patients with MCP mutations. Family living donor transplantation is contraindicated, because of the risk of graft loss due to recurrence and the risk that donors themselves might have HUS after donation, due to unknown genetic factors shared with the recipient. Kidney transplantation under pre-, intra- and postoperative intensive plasmatherapy may be successful in some patients. Combined liver and kidney transplantation has been successful in a few patients with CFH mutation (63,64).

**X- PREVENTION**

Strategies to minimize exposure to STEC include improved meat processing, food handling, and preparation. Simple measures, like hand- and food-washings as well as avoidance of ingestion of raw and rare beef are important aspects of prevention especially in African countries.

**References**


CHAPTER 21

RENAL REPLACEMENT THERAPY IN ACUTE KIDNEY INJURY IN CHILDREN

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HIGHLIGHTS
✓ The acute renal injury is an important factor for morbidity and mortality in infants.
✓ Renal replacement therapy starting in patients with ARI prevents the occurrence of complications and immediate death.
✓ The choice of RRT mode is linked to the clinical picture, to the presence or absence of multi-organ failure and to the indication of renal replacement therapy.
✓ The prognosis of the AKI depends on the etiology, age of the patient and the clinical presentation, infants under 1 year is present a higher mortality rate

I- INTRODUCTION
Acute renal failure (ARF) is defined by a rapid decline in glomerular filtration rate, resulting in the disturbance of renal physiological functions including (1,2,3): Impairment of nitrogenous waste product excretion Loss of water and electrolyte regulation Loss of acid-base regulation. ARF is an important contributing factor to the morbidity and mortality of critically ill infants and children (4).
The management of patients with acute renal failure or acute kidney injury (AKI) is principally supportive, with renal replacement therapy (RRT) indicated in patients with severe kidney injury. Multiple modalities of RRT are currently available. These include peritoneal dialysis, intermittent hemodialysis (IHD), continuous renal replacement therapies (CRRTs), and hybrid therapies, such as sustained low-efficiency dialysis (SLED). Despite these varied techniques, mortality in patients with ARF remains high, greater than 50 percent in severely ill patients.
The initiation of RRT in patients with AKI prevents uremia and immediate death from the adverse complications of renal failure. It is possible that variations in the timing of initiation, modalities, and/or dosing may affect clinical outcomes, particularly survival. However, there is a paucity of studies in which these issues have been addressed directly.

II- INDICATIONS FOR AND OPTIMAL TIMING OF DIALYSIS INITIATION
Renal replacement therapy in children with ARF should be initiated for the following:
• Signs and symptoms of uremia symptoms that include pericarditis, neuropathy or an otherwise unexplained decline in mental status regardless of the serum BUN or creatinine concentration.
• Azotemia (BUN greater than 29 to 36 mmol/L).
• Severe fluid overload as manifested by hypertension, pulmonary edema or heart failure that is refractory to supportive medical therapy.
• Severe electrolyte abnormalities including hyperkalemia, hypernatremia, hyponatremia, and acidosis that are refractory to supportive medical therapy.
• Need for intensive nutritional support in a child with oliguria or anuria.
The choice of renal replacement modality is influenced by the clinical presentation of the child, the presence or absence of multi-organ system failure, and the indication for renal replacement therapy (2,3).
Available renal replacement modalities for the management of ARF include the following:
A- Hemodialysis
Hemodialysis (HD) is the intervention that most rapidly changes plasma solute composition and removes excessive body water compared to the other modalities. However, this may not be tolerated by hemodynamically unstable patients.

B- Peritoneal dialysis
Although peritoneal dialysis (PD) is less efficient in altering blood solute composition and fluid removal, it can be applied continuously. It is therefore well tolerated by hemodynamically unstable patients. It is the simplest of the modalities to apply and hence is the one most frequently used.

C- Continuous renal replacement therapy
The use of continuous replacement therapy (CRRT) (also referred to as hemofiltration) is increasing in children and includes several modalities (continuous arteriovenous hemofiltration, continuous venovenous hemofiltration, continuous arteriovenous hemodialysis, and continuous venovenous hemodialysis). In patients treated with CRRT, the rate of fluid and solute removal is slow and continuous. As a result, CRRT is better tolerated than hemodialysis in patients who are hemodynamically unstable. The removal of solutes over the course of 24 to 48 hours is as efficient as conventional hemodialysis. In addition, some prefer this technique in patients with sepsis or multiorgan system failure, as it may enhance the removal of cytokines (4,5).

It is impossible to recommend the use of one modality over another because there are few studies that compare the different types of renal replacement therapy in children (5-7). Although retrospective reports have shown decreased survival rate in patients treated with CRRT, the results are inconclusive as patients treated with CRRT also had an increased incidence of hypotension and inotropic pressor support compared to those who received hemodialysis (5,7). One retrospective report of 42 children who underwent surgical repair of congenital heart disease found survival to be the same with either peritoneal dialysis or hemofiltration. Fluid removal, urea and creatinine clearance, and caloric intake were superior in the hemofiltration group (8).

III- ACUTE PERITONEAL DIALYSIS
The choice of modality of managing ARF depends on patient size, availability of vascular access, integrity of the peritoneal membrane and abdominal cavity, and perhaps most importantly, clinical experience and expertise (9,10,11). However, in most developing countries, as in our setting, there are no facilities for paediatric hemodialysis (PD), hence PD remains the only available option for management of ARF.

A- Advantages
 Compared with other available modalities, PD has several advantages as a renal replacement therapy in patients with ARF:
- It is widely available and technically easy to perform.
- Large amounts of fluid can be removed in hemodynamically unstable patients this fluid removal may also permit the administration of parenteral nutrition.
Disequilibrium syndrome is not precipitated because of slow solute removal.
- Easy and gradual correction of acid-base and electrolyte imbalance may be performed.
- PD access placement is relatively easy, particularly in children.
• Arterial or venous puncture and anticoagulation are not required.
• It is a highly biocompatible technique.
• Dosing is easy, particularly in children.

**B- Cons-indications**
Since there are very few absolute cons-indications for acute PD, most of the following conditions are only relative cons-indications to this modality (12):
• Recent abdominal and/or cardiothoracic surgery
• Diaphragmatic peritoneal-pleural connections
• Severe respiratory failure
• Life-threatening hyperkalemia
• Extremely high catabolism
• Severe volume overload in a patient not on a ventilator
• Severe gastroesophageal reflux disease
• Low peritoneal clearances
• Fecal or fungal peritonitis
• Abdominal wall cellulitis

**C- Placement of catheter**
Acute PD access can be achieved without serious difficulty by inserting a semirigid catheter or by placing a single cuff Tenckhoff catheter. The semirigid catheter insertion can be performed at the bedside by a nephrologist or surgeon. The Tenckhoff catheter is usually placed in the operating room by a surgeon this flexible catheter is more comfortable for the patient who is moving around in bed and operative insertion avoids the occasional development of intestinal perforation with percutaneous insertion. Below are some pictures of acute catheters that can be used for acute peritoneal dialysis.

**D- Components of acute peritoneal dialysis**
The standard acute PD prescription includes the following components:
• Length of the dialysis session
• Dialysate composition
• Exchange volume
• Inflow and outflow (drain) periods
• Dwell time
• Number of exchanges
• Dialysate additives
• Monitoring fluid balance

**E- Length of dialysis session**

1- PD session
The total length of an acute PD session averages about 48 to 72 hours since a session usually
consists of 48 to 72 exchanges, each of which lasts approximately half an hour to one hour (13). Nevertheless, the length of the PD session can vary significantly since it is dependent upon the cause and duration of ARF, the amount of solute and fluid removal that is desired, and the risk of infection, particularly with rigid catheters.

To accommodate the unpredictable course of ARF and the overall condition of these critically unstable patients, acute PD orders should only be written for a period of 24 hours. Periodic adjustments may need to be made based upon the patient evaluation and laboratory parameters, which should be performed at least daily.

2- Dialysate composition
PD dialysate is available in standard hydrous dextrose concentrations of 1.5, 2.5, and 4.25 percent. Dialysate solutions should be warmed to body temperature prior to infusion to avoid discomfort and enhance solute transport.

An initial dialysis solution dextrose concentration of 1.5 percent may be more appropriate in children especially since they are usually

Dialysis solutions with higher dextrose concentration can be substituted based upon the amount of fluid removed and the patient's hemodynamic parameters.

The most practical way to achieve adequate fluid removal is by mixing and matching low and high dextrose concentration solutions. Once the patient is euvoleticmic, the dialysis solution should be switched to a dextrose concentration of 1.5 percent and the rate of exchange slowed.

3- Exchange volume
The exchange volume is the amount of dialysate solution instilled into the peritoneal cavity during an exchange. Factors affecting this volume include the peritoneal cavity size, the presence of pulmonary disease and/or hernia(s), and the desire to limit leakage of dialysate. Usually start with 10ml/kg going on to 20ml/kg in next 24 hours maximum not more than 40ml/kg.

a- Respiratory insufficiency
Patients with pulmonary diseases, such as pneumonia, chronic obstructive/restrictive lung disease and respiratory failure requiring ventilatory support, may require smaller exchange volumes to prevent compromise of diaphragmatic excursions and respiration.

b- Hernias
In patients with abdominal wall or inguinal hernias, the exchange volume must be reduced to limit the increase in intraabdominal pressure.

c- Leakage
Most clinicians keep the exchange volume low for the first day to avoid leaks from the new catheter insertion site. The dialysate volume can then be gradually increased over the ensuing three to four days as tolerated by the patient.

4- Inflow time
Inflow time is the time required to instill the dialysate into the peritoneal cavity, a process usually driven by gravity. Inflow usually takes approximately 10 to 15 minutes (14). Factors that determine the inflow time include: The dialysate volume Degree of elevation of the dialysate bag above the patient's abdomen The presence of absence inflow resistance resulting from kinking of the peritoneal catheter or from reduced bowel motility. To maximize the efficiency of dialysis, it is imperative to keep the inflow time to a minimum.
5- Dwell time
The dwell time is the period in which the exchange volume remains in the peritoneal cavity, or the time between the end of inflow to the beginning of the drain period.

The dwell time for standard acute PD is approximately 30 minutes, but initially may start with flushes without dwell time or dwell times of about 15 minutes depending on requirements for solute removal.

6- Outflow time
Outflow time is the time required to drain the effluent dialysate from the peritoneal cavity. The outflow of the dialysate is controlled by gravity and usually takes about 20 to 30 minutes (14). Some of the major determinants of the outflow time include: Volume of the dialysate effluent to be drained, Outflow resistance, which results from kinks in the catheter, decreased bowel motility, and fibrin in the dialysate. The height difference between the patient and the drainage bag. As with the inflow time, it is important to keep the outflow time to a minimum. This can be done by adjusting the height of the drainage bag.

It is extremely important to ensure complete drainage since incomplete drainage can result in progressive accumulation of dialysate in the peritoneal cavity, leading to respiratory embarrassment and/or abdominal discomfort. The PD orders should specify to «continue outflow until drainage stops» to avoid incomplete drainage. However, complete drainage at each exchange is not mandatory, and an alternative is to assure that it occurs after every second or third exchange. This obviates the wasting of crucial dialysis with slow or inefficient drainage.

7- Dialysis solution additives
Drugs can be added to the dialysis solution to treat specific conditions. It is imperative to follow sterile technique when adding additives into dialysate solutions. Some of the commonly used dialysate additives are heparin, insulin, and potassium.

a- Heparin
Heparin is usually added to dialysate solutions at a dose of 200 to 500 units per liter to prevent fibrin clot formation, which can obstruct the peritoneal catheter (13). Although it is usually added when plugs or strands of fibrin are visible in the drained fluid, heparin is more beneficial when added prophylactically. Once outflow obstruction is established, there is usually a poor response to heparin. Instillation of fibrinolytic agents would be necessary. Since neither heparin nor fibrinolytic agents are absorbed through the peritoneum, neither produce systemic anticoagulation.

b- Potassium
Since standard PD solutions do not contain any potassium, potassium chloride should be added to the dialysate (usually 3 to 4 mmol/L) in hypokalemic patients. In patients with cardiac disease, particularly if treated with digoxin, the serum potassium should be closely monitored and the intraperitoneal potassium added to the dialysate to maintain the serum potassium at about 4 meq/L (13).

8- Monitoring fluid balance
It is essential to maintain accurate flow sheets, monitor intake and output records, and document net ultrafiltration in patients on acute PD. Daily intake and output charting and weights need to be incorporated into acute PD orders.
F- Complications
Acute PD is associated with complications, some of which are serious and potentially life-threatening (15,16). Many are preventable. A brief listing of these complications is found in this section. The approach to the diagnosis and management of peritonitis is presented separately.

1- Mechanical complications
Most of the mechanical complications are not a serious threat to life, but may result in reduced dialysis efficiency. These include the following:

a- Abdominal pain or discomfort
Mild abdominal pain or discomfort is common and is usually secondary to abdominal distention. By comparison, moderate to severe pain may be due to a catheter-related complication and warrants investigation.

b- Intraabdominal hemorrhage
Mild bleeding is frequent and can be observed with catheter placement. However, severe intraabdominal hemorrhage has been reported from catheters, particularly semirigid acute catheters.

c- Leakage
Leakage around the PD catheter site is a common occurrence, which can be managed by reducing the exchange volume for the first 24 hours. In some cases, temporary cessation of PD may be necessary.

d- Inadequate drainage
Inadequate drainage is usually due to decreased bowel motility. Administration of bowel cathartics will improve drainage in most situations, while manipulation of the catheter may occasionally be necessary.

e- Bowel perforation
Bowel perforations may be observed, particularly with the placement of semirigid acute PD catheters. Patients may have severe abdominal pain, blood-tinged peritoneal effluent, intraabdominal hemorrhage, and (rarely) shock. Therapy consists of the cessation of acute PD treatments, catheter removal, intravenous antibiotics, and bowel repair.

2- Others complications

a- Infectious complications
Infectious complications are common, particularly peritonitis. The incidence of peritonitis can be significantly decreased by maintaining sterile precautions during the placement of acute PD catheters and by preventing contamination during exchanges.

In addition, a puncture site abscess can result from the bedside placement of acute PD catheters, particularly if meticulous attention is not given to sterile technique.

b- Pulmonary complications
- Basal atelectasis and pneumonia: Atelectasis and pneumonia can result from the increase in intraabdominal pressure associated with acute PD treatments.
• Pleural effusion: Migration of fluid into the thoracic cavity, hydrothorax, can occur via a defect in the diaphragm or diaphragmatic lymphatics. A right sided effusion is most common. Decreasing intraabdominal pressure by lowering exchange volumes and performing acute PD in a supine position may help in most situations. Pleurodesis is rarely required.

• Aspiration: Increased intraabdominal aspiration may result in the aspiration of gastric contents, the incidence of which may be reduced with the use of a lower exchange volume.

c- Cardiovascular complications

• Hypovolemia: Excessive ultrafiltration \([16]\) or diaphragmatic elevation secondary to increased intraabdominal pressure (resulting in decreased venous return) can reduce effective tissue perfusion.

• Cardiac arrhythmias: Cardiac arrhythmias are common, due most frequently to electrolyte and metabolic disturbances, or diaphragmatic elevation.

d- Metabolic complications

Metabolic complications are common and often preventable complications of acute PD:

• Hyperglycemia: Hyperglycemia can result from the high glucose concentration of the PD fluid.

• Hypoglycemia: Hypoglycemia may occur following the cessation of PD.

• Hypernatremia: Hypernatremia can be induced by the disproportionate loss of free water in the PD fluid when hypertonic exchanges are repeatedly used. Since aquaporin 1 water channels in peritoneal capillaries are activated by the glucose-generated tonicity of the dialysate, free water moves down these channels. Sodium will then diffuse down its diffusion gradient from blood to dialysate through the small intercellular «pores.» However, if the exchange is short in duration, there may be inadequate time for sodium diffusion to occur and the patient slowly becomes hypernatremic. This is best corrected by lengthening the duration of the exchanges so that diffusion can occur and/or using less hypertonic dialysate.

• Hypokalemia: As previously mentioned, hypokalemia may ensue because standard PD solutions do not contain any potassium. This can be corrected by adding potassium to the dialysate.

• Protein losses: Protein losses occur in the dialysate, occasionally exceeding 5 g/day.

IV- HAEMODIALYSIS

Hemodialysis (HD) refers to the transport process by which a solute passively diffuses down its concentration gradient from one fluid compartment (either blood or dialysate) into the other. During HD, urea, creatinine, and potassium move from blood to dialysate, while other solutes, such as calcium and bicarbonate, move from dialysate to blood. The dialysate flows countercurrent to blood flow through the dialyzer to maximize the concentration gradient between the compartments and therefore to maximize the rate of solute removal. The net effect is the production of desired changes in the plasma concentrations of these solutes: a reduction in the blood urea nitrogen and plasma creatinine concentration and an elevation in the plasma calcium and bicarbonate concentrations.

A- Advantages

• Excellent solute clearance

• Bicarbonate as standard

• Can be used to rapidly remove large volumes of fluid e.g. in pulmonary edema
B- Disadvantages
• Requires haemodynamically stable patient
• Vascular access may be difficult

Factors affecting individual haemodialysis prescription:

C- Extracorporeal circuit
Lines and haemodialyzer should be selected bearing in mind that a child can only tolerate 10% of its blood volume in the circuit.
Example: 10kg child has total blood volume of 10x80ml=800ml
Total extracorporeal volume tolerated is 80ml.
Lines selected and haemodialyzer should not exceed this.

D- Haemodialyzer
The surface area should not exceed that of the child (Fresenius F3) has surface area of 0.4, F4 has 0.7, and F5 has 1.0.

E- Length of session
Initial session should be no more than 2 hours to prevent disequilibrium syndrome

F- Blood pump speeds
Speed can be up to body weight x 8ml/min.

V- CONTINUOUS RENAL REPLACEMENT THERAPIES
CRRT represents a family of modalities that provide continuous support for severely ill patients with AKI. These include continuous hemofiltration, hemodialysis, and hemodiafiltration, which involve both convective and diffusive therapies. Although superior clearance of middle and larger molecular weight molecules are associated with convective therapies (hemofiltration) compared with diffusive therapies (hemodialysis), there are no studies clearly showing improved clinical outcomes compared with the type of solute transport.

In the commonest type blood is pumped from a vein, through a filter back into the vein (CVVH) or can be artery to vein (CAVH).
A- Advantages
• Good in haemodynamically unstable patients
• Less episodes of hypotension

B- Disadvantages
• Clearance is poor compared to haemodialysis
• Clotting of the filter

VI- PROGNOSIS

The outcome of ARF depends upon the etiology, age of the patient, and the clinical presentation (17-20). Infants younger than 1 year of age have both the highest incidence and mortality rate (17,21). In a retrospective report of 228 children with ARF, the overall survival rate was 73 percent (22). Failure of three organ systems was associated with more than a 50 percent mortality rate. In another retrospective study of 245 children with ARF, 71 percent of patients survived the initial hospitalization (23). Over the next three to five years after discharge, 35 of 174 initial survivors died 24 within 12 months of discharge. Of the initial survivors, 16 patients progressed to end-stage renal disease, including three who subsequently died.

Outcome of renal replacement therapy

Outcomes among children with acute renal failure who require renal replacement therapy also vary with disease severity, underlying renal process, extra-renal organ involvement, and other factors (21). In a retrospective report of 226 children, the variables associated with survival among patients with acute renal failure were evaluated (7). Renal replacement therapies included hemofiltration, hemodialysis, and peritoneal dialysis.
References

PART VII

UROLOGY

CHAPTER 22

ANTENATAL DIAGNOSIS
I- ANTENATAL DIAGNOSIS IN AFRICA

Amal Bourquia, Casablanca - Morocco
I- INTRODUCTION

The antenatal medicine comprises two separate components: The screening, offered to all pregnant women and the diagnosis allowing medical care. From the medical, social and cultural point of view, antenatal ultrasound has revolutionized the monitoring of pregnancy. Its objectives are diverse and accessibility - very uneven through the world- depends on the economic status of the women concerned. In fact, the antenatal care (ANC) has been exported to developing countries such as conceived in industrialized countries without questioning its efficiency in our countries for decrease of the morbidity and maternal and neonatal mortality. But this advantage could not be effective without an organized maternal health system, containing networking services, good quality care and a good relationship with the population. The extensive use of African women in the ANC, when it is available has to be exploited to implement effective actions.

II- SCREENING MALFORMATIVE UROPATHY

A- Evolution

Before the doctor was most of the time faced with a palpable mass, abnormalities of the urinary stream, or -when the parents presented late their baby or child - to complications. Unfortunately, those situations have not yet disappeared from the African context.

Today, these abnormalities are detected before birth and multidisciplinary care begins at birth. The progress of the medical equipment and training of sonographers have indeed led to an improvement of these anomalies detection rate and an earlier screening. The number of malformatives uronephropathies – which some within the scope of a polymalformative syndrome - is important, since these are approximately 0.2 to 7% during pregnancy, the most common abnormalities detected antenatal reaching 17%.

B- Place of ultrasound

It is relatively efficient in the prenatal diagnosis of renal parenchymal disease. In bilateral grave forms (agenesis, dysplasia, polycystic), the main warning sign is oligohydramnios. The obstructive uropathy is easily suspected prenatally because their warning sign is fluid.

The renal pelvis or renal pelvis dilatation, is the most frequent, isolated, without reaching the bottom device without parenchymal involvement is always a good prognosis. The diagnostic accuracy between high or low uropathy is more relevant in the third quarter. The mechanism of the dilation is generally not identified and vesicoureteral reflux escapes most of the time diagnosis.

The renal functional problem arises when obstructive pathology is bilateral and important. The situations where renal function is compromised definitely result in oligohydramnios progressing to anamnios, signs of parenchymal renal dysplasia.

If the uropathy is unilateral, the ultrasound monitoring of pregnancy aims at detecting the appearance of contralateral kidney pathology in the third quarter. The antenatal screening of a viable uropathy requires a postnatal exploration at the end of the first week of life, except the cases of severe urological distress.

C- Interests of the antenatal care

It has two objectives: the screening of the associated anomalies and attempt to evaluate renal prognosis. The prenatal renal ultrasound examination, as a key of the ANC, allows measuring the anterior-post diameter, the visualization of the ureters, the bladder, the aspect of the renal
parenchyma and the quality of amniotic liquid. If the diagnosis of uropathy is established, a prenatal consultation with pediatric urologist is programmed to:

- Evaluate the long-term prognosis,
- Inform the family,
- Evoke the eventuality of an intervention,
- Eliminate often the Infrared Spectroscopy spectrum which is feared by parents.
- In case of severe uropathy with antenatal renal insufficiency, a proposal for termination of pregnancy is suggested. However, this proposal is often confronted with a set of social and religious factors that complicate this type of decision.

**D- Postnatal follow up**

An early treatment modifies the overall prognosis of uropathy.

- A renal ultrasound is indicated postnatal to assess:
  - The anterior-posterior diameter,
  - Cortical thickness and cortico-medullary differentiation,
  - The kidney size and chalices,
  - The existence of cysts.
- Renal scintigraphy (MAG 3> DMSA) and / or cystography (only indication: posterior urethral valve “PUV”) can be performed thereafter. Obviously, it is important to ensure a long-term monitoring.

**III- AFRICAN REALITY**

Is the prenatal consultations always accessible to all mothers? How do we realize ultrasounds during pregnancy? Are the ANC successful? What is the attendance for these consultations?

The answers to these issues are variable and uncertain, with great disparity of access to the ANC from a country to the other one, according to the health organization and from a region to the other one within the same country. However, we note that personal factors impact the effectiveness of screening and the frequency of these ANC are influenced by the distance with the centers, the quality of the consultations and the follow up.

The antenatal diagnosis of the obstructive uropathy has significantly modified the pediatric care. Arguably, without fear of contradiction, that early diagnosis brings some benefit to the baby through an opportunity to correct any anomalies and / or prevention of complications, hence the need to work in its generalization and in its improvement in Africa.

**References**

CHAPTER 22

ANTENATAL DIAGNOSIS

II- MANAGEMENT OF ANTENATAL DETECTED HYDRONEPHROSIS

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The diagnosis of antenatal hydronephrosis is made on fetal ultrasound performed during pregnancy it is the most frequently diagnosed defect in antenatal ultrasound.

At birth the balance sheet should include malformation after a few days, an ultrasound.

Depending on the expansion of the urinary tract best appreciated by the antero-posterior distance pelvis several approaches are possible: a simple ultrasound monitoring generally every 3 months during the first year of life. Achieving MAG3 scintigraphy (or DTPA), made after the age of 1 month. This review will provide a quantification of the obstacle.

I- INTRODUCTION

Antenatal hydronephrosis is defined as dilatation of the collecting system of the fetal kidney. It is common finding of antenatal ultrasound examination. In nearly 1% of pregnancies, a significant fetal anomaly is detected by ultrasonography. 20-30% of these anomalies are genitourinary in origin. 50% of them manifest as hydronephrosis (1,3).

After introduction of fetal ultrasonography (US), the abnormalities of urinary tract being recognized with increasing frequency due to: the sophistication of ultrasound machines, greater staff expertise and the widespread use of detailed fetal scan at 16 to 20 weeks gestation. Most pelvic dilation is a transient finding however, urinary obstruction can be the cause, which will lead to renal injury and end stage renal disease. If these anomalies are not detected by antenatal US and subsequently managed, many of these abnormalities manifest later in life as pyelonephritis, hypertension and end stage renal disease. A study done in Tripoli, Libya 53% of children with chronic kidney disease were due to congenital nephropathy, 52.2% of them were due to posterior urethral valve with late presentation to pediatric nephrologists (31).

II- DEFINITION

Several systems are used to grade antenatal hydronephrosis. Two main classifications exist (4). The first is grading system developed by the Society of Fetal Urology (SFU) which is based on the long axis sonographic appearance of renal parenchyma and pelvicalyceal system (5) as shown in table 1.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Central renal complex</th>
<th>Renal parenchymal thickness</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Intact</td>
<td>Normal</td>
</tr>
<tr>
<td>1</td>
<td>Slight splitting of pelvis</td>
<td>Normal</td>
</tr>
<tr>
<td>2</td>
<td>Evident splitting of pelvis and calyces</td>
<td>Normal</td>
</tr>
<tr>
<td>3</td>
<td>Wide splitting of pelvis and calyces</td>
<td>Normal</td>
</tr>
<tr>
<td>4</td>
<td>Further splitting of pelvis and calyces</td>
<td>Réduite</td>
</tr>
</tbody>
</table>

The more widely used classification for antenatal hydronephrosis is based on the measurement of the maximum antroposterior diameter of renal pelvis or the renal pelvis diameter (RPD) and the gestational age (6) as shown in table 2.
However mild renal pelvic dilation (RPD = 4-10mm) shows no clinical impact on normal renal development (7,8), while moderate and severe renal pelvis dilation (RPD =10mm and >15mm respectively) associated with increasing risk of significant congenital abnormalities of kidney and urinary tract (9,11). The controversy exists as to the threshold beyond which the fetal RPD is considered abnormal. Most recent studies suggest that antenatal hydronephrosis exist when RPD exceeds 5mm before 24 weeks gestation or when over 7mm beyond 25 weeks of pregnancy (7,12,13).

III- EPIDEMIOLOGY
Antenatal hydronephrosis is more common in boys than girls (2:1). 20-40% are bilateral (14). The reported incidence of antenatal hydronephrosis is ranged from 0.6-4.5% in different studies (7,8,14,15).

A 5 years cohort study (16) compare the incidence of renal abnormalities from 1999 to 2003 with those reported previously from 1989 to 1993. They concluded that there was increased incidence of renal abnormalities detected antenatal. The incidence was 7.6/1000 births in recent cohort study versus 3/1000 live birth of previous one.

IV- CAUSES OF ANTENATAL HYDRONEPHROSIS
Antenatal hydronephrosis may due to obstructive or non obstructive causes. Non obstructive lesions such as primary vesicoureteric reflux (VUR) and multicystic dysplastic kidney (MDK). Obstructive lesions particularly bilateral lesions are more harmful to developing kidneys. These include pelviureteric junction obstruction (PUJO), vesicoureteric junction obstruction (VUJO) and posterior urethral valve (PUV). Transient and physiological hydronephrosis is by far the most common form of antenatal hydronephrosis. It is accounted for 30-50% of cases (9).

In Meta analysis of 1678 infants, the pelviureteric junction obstruction (PUJO) is the most common causes of antenatal detected hydronephrosis. Its frequency is increased with the increase severity of hydronephrosis. The second most common cause of antenatal hydronephrosis is VUR, which was not associated with increased severity of hydronephrosis (8).

A study done in Tripoli-Libya (32) of 90 neonates (125 renal units) had antenatal hydronephrosis from 1995 to 2007. fifty-nine (66%) of them were males and thirty-one (34%) were females. Pelviureteric junction obstruction (PUJO) was found in 25.5% of cases, vesicoureteric reflux (VUR)
are present amniocentesis for karyotyping should be strongly considered (17). As the current consensus if RPD exceed 5mm in the second trimester, a repeat fetal US scan in the third trimester is required to assess its progression. If RPD exceed 7mm in the third trimester, a plane for postnatal management of newborn becomes mandatory (7).

Antenatal intervention either by direct and repeated bladder drainage or placement of vesico-amniotic shunt of infant with antenatal detected hydronephrosis still remain controversial and has failed to improve the natural course of congenital urinary tract obstruction. The main causes of failure of this type of management are renal dysplasia and pulmonary hypoplasia, which are associated with urinary tract obstruction and are irreversibly by the time the urinary dilation is first noticed by antenatal US. The main indication of invasive antenatal management is presence of markers of abnormal renal function. Which include presence of oligohydraminos and poor cortico-medullary differentiation in kidney with increased echogenicity (4).

It is important to counsel the parent when fetal hydronephrosis is detected in sensitive way including reassurance that the majority will turn out to be transient and benign.

If fetal hydronephrosis persistent in the third trimester a multi-disciplinary approach is needed which include neonatologist, pediatric nephrologists, pediatric urologist and geneticist as necessitated by the underlying condition.

B- Postnatal management

Clinical examination will take place after birth to ensure that there are no other associated problems. If baby is well with no evidence of abdominal mass and passing urine with only unilateral lesion then discharge home should not be delayed. The role of prophylactic antibiotics is still controversial. Infants with minor postnatal dilation do not need prophylactic antibiotics, as the urinary tract infection is uncommon in infants with two normal postnatal US examinations (18).

A prophylactic antibiotic is given for those neonates who had evidence of obstruction due to posterior urethral valve. Antibacterial prophylaxis is conventionally given to infants with VUR and for 6 months of life to infants demonstrating moderate to severe hydronephrosis (11).

Renal US should always be performed in neonates who had persistent hydronephrosis in the third trimester (20,21). It should be done after 48 hrs. after birth to ensure that the infant is well hydrated and urine flow is established. However, renal US can be done early when there is severe bilateral hydronephrosis or a palpable abdominal mass at birth. The optimal timing of US at around 7 to 10 days of life, applying the same standard grading system to antenatal scan (22).

Most infants with postnatal hydronephrosis undergo voiding cystoureterogram (VCUG) to exclude VUR and bladder outlet obstruction. It should be performed, usually within 4 weeks in majority of cases (23). However, it must be done within 48 hours of birth in any infant suspected to have posterior urethral valve. Several studies have recently demonstrated that gross degree of VUR can be associated with minimal or no-dilation on post natal US (24,25). Some controversies still exist regarding the need of VCUG for cases of MDK, PUJO and UVJO.

The radionuclide imaging is usually delayed until 3 months after birth unless clinically indicated (palpable mass at birth or severe pelvic dilation). A technetium-99m dimercaptosuccinic acid scan (DMSA) is performed to confirm the non-function kidney and to define the differential function in infants with VUR and MDK.

99mTc mercaptaoacetyltriglycin (MAG3) is radionuclide scan of choice because it’s high initial renal uptake to demonstrate the differential function and excretion in infants with hydronephrosis
and usually associated with diuretic injection. Alternatively 99m-technetium diethyl triamine pentaacetic acid (DTPA) may be used (7).

**Postnatal schema of management of antenatally hydronephrosis as adopted from (29) is shown below:**

*Postnatal scheme of antenatal hydronephrosis (29).*

### C- Common specific etiology of antenatal hydronephrosis

**1- Transient hydronephrosis**

It is the commonest cause of antenatal hydronephrosis (9). The majority will resolve spontaneously either in third trimester or in early infancy (26). No need for prophylactic antibiotics and no further investigation apart from post natal US is needed.

**2- Uretero-pelvic junction obstruction (UPJO)**

Is the most common cause of non-physiological obstruction. Its prevalence is approximately 1 in 2000 children with a male to female ratio in infancy of 3:1. 20-25% of cases had bilateral obstruction (9). Its management depends on the MAG3 renogram, if it is more than 40% a serial follow up US is recommended while when the differential function is less than 40% with poor excretion surgical reconstruction is recommended (27).
3- Posterior urethral valve
It is common cause of antenatal hydronephrosis in Libyan children. It accounted for 17.7% of cases with antenatal hydronephrosis (32). In severe cases with markers of impaired renal function, the bladder is generally decompressed using a percutaniously placed vesicoamniotic catheter or percutaneous endoscopic in utero ablation of the valve. These intrauterine procedures should be carried out in highly specialized center. It carries many risks like fetal injury, intrauterine infection and premature labor. The risk of fetal mortality is 43% of cases (28). After diagnosis is established with postnatal VCUG a small polyethylene tube is inserted. Foley catheter should not be used because the balloon may cause severe bladder spasm and may produce severe bladder obstruction. Early referral to pediatric urologist is recommended.

VCUG showing posterior urethral valve with bilateral VUR

4- Multi cystic dysplastic kidney (MDK)
It is usually unilateral. Bilateral is incompatible with life. It is easily recognized by cystic appearance on pre and postnatal US with no function at all on the DMSA scan. Its management was conservative in (2 approach and they documented progressive involution with time (23% of cases disappear and 33% of cases reduced in size by 2 years of age).
5- Vescicoureteric reflux (VUR)
It constitutes between 10 to 38% of cases of antenatal hydronephrosis (4). When diagnosis is made by postnatal VCUG then the infants require a DMSA scan to define differential renal function and renal scaring. It is predominates in males with high-resolution rate 65% within 2 years (30).

6- Uretero-vesical junction obstruction (UVJO):
It is a rare condition and it is diagnosed when there is a dilated ureter as well as hydronephrosis without VUR on VCUG and it is confirmed by MAG3 renography.

VI- CONCLUSION
Antenatal detected hydronephrosis is commonly associated with significant morbidity in early life. It can lead to parental anxiety extending well beyond the current pregnancy. The indication for choice to evaluate an infants with antenatal hydronephrosis should be based on evidence based protocols and guidelines. Multi-disciplinary approach remains the best way to offer a good care for these children.

Acknowledgment:
Thanks are due to Dr. K.Ben Rahuma Neonatal SpR Salford Royal Hospital, Salford, UK for his, revision and advice.

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CHAPTER 23

URINARY TRACT INFECTION IN CHILDREN

Albert Bensman, Paris - France
HIGHLIGHTS
✓ Urinary tract infection (UTI) is one of the most common pediatric bacterial infections.
✓ Signs and symptoms of UTI (cystitis and pyelonephritis) are often non-specific, especially in infants.
✓ Screening for UTI based on the test strips (leukocytes and nitrites). The diagnosis of UTI is based on clinical and urine cytology examination. We must have a per-void urine sample.
✓ The diagnosis of pyelonephritis should be routinely considered in any fever with no obvious focus of infection. Culture is used to specify the bacterial species and quantify bacteriuria.
✓ The UTI is often associated with an abnormality of the urinary tract the most common is vesicoureteral reflux uretero-renal.
✓ Recurrence is common and renal scars, which are not rare, may cause long-term hypertension and nephron loss.

I- INTRODUCTION
Urinary tract infections UTI are one of the most common causes of bacterial infections. The prevalence of the disease depends on many factors, including age and sex:
In the first three months of life, the prevalence of UTI is higher among boys and among febrile patients aged less than 3 months the risk of UTI is approximately 13% for females, 2% in circumcised boys, 19% of those who are not. It is in the first year of life the incidence of the first episode of UTI is the highest in febrile infants, the risk of UTI is estimated within one year 6% of girls and 3% boys.
After the first year of life, urinary tract infections are much more common in girls than in boys (8% of girls and 2% of boys under the age of 6 years). Vesico-Ureteral-Reflux vesicoureteral reflux is by far (90% of cases) the abnormality most frequently found, but it does not induce a change of management. Much more rarely, other abnormalities of the urinary tract are highlighted: stenosis of the ureteropelvic junction, mega-ureter stones, ureteral duplicity... The lower urinary tract infections (cystitis) recurrent almost exclusively girls, this is attributable in addition to anatomical reasons, to the frequency of bladder instability, major risk factor for recurrence of UTI between 3 and 6 years. The increasing antibiotic resistance of bacteria involved in the UTI limits the choice of antibiotics.

II- POSITIVE DIAGNOSIS OF URINARY TRACT INFECTION
The diagnosis of the urinary tract infection is conducted UTI in presence of a bacteriuria superior to 105 cells /ml. A leukocyturia disease frequently accompanies the bacteriuria. However, in 10 to 20% of authentic infections, no pathological leukocyturia is detected. These criteria are not valid only if requirements of urine sampling and storage prior to examination are perfectly met.

A- Urine tests
Difficult in children

1- In the one with previous voluntary mictions
Urine is collected from the stream, as it is the case with adults, following a local toilet. In uncircumcised boys, a long prepuce may contain large quantities of seeds a reliable data collection
may only be referred to after a prepuce and a gland toilet.

2- In the newborn and infant

Urine collection is obtained through pocket system. After a very thorough local disinfection with an antiseptic (Dakin®, for example), adhesive pocket sterilization is placed. It is actually difficult to avoid the contamination of application connected to the skin. To reduce the maximum risk, it should be removed once the miction takes place. If the child has not urinated while the pocket has been placed for twenty minutes, this pocket should be removed, the skin cleaned and a new sterile pocket is placed.

Despite these precautions, pockets technique cannot be reliable and many hospital teams prefer the suprapubic puncture or bladder catheterization. Urine sample inside the stream in a child with no voluntary mictions is very reliable but requires, after removing stratum and doing a local disinfection, a permanent presence of an adult at the bedside of the child.

Regardless of the sampling type, the urine collected should be cultured as soon as possible. To avoid any microbial growth, urine should be stored at 4° between their issue and examination in the laboratory. If in doubt, do not hesitate to repeat cytology for a second review to confirm the diagnosis.

B- The research of urinary leukocytes and nitrites

In a child with a misdiagnosed fever or bladder symptoms (mictional burn, pollakiuria), a urine dipstick is very useful when screening a urinary tract infection. Urine should be collected with rigor in a sterile manner, as it is the case with cytological examination of urine. The leukocyturia in the strip has a high sensitivity = 67% to 94%, but specificity is poorer. Many strains of bacteria convert urinary nitrate to nitrite urine. Detection of nitrites in the strip has high specificity, 90% to 100%, but lower sensitivity, 16% to 82%. But in case of negativity of leukocytes and nitrites, the negative predictive value was 97% that is to say that the risk of a urinary tract infection is extremely low.

In a huge number of cases, urinary strips (leucocytes, nitrites) avoid repeated cytological examination of urine and even moving children to emergency (2).

However, urine strips have their limits: expiry deadline and storage and use conditions are crucial to know. They are less reliable in infants who are less than 3 months. In these infants, there is less nitrite in the urine for infants are not fed with big quantities. These young infants have frequent mictions, which do not allow a conversion in the bladder from nitrates into nitrites. In case nitrites and leucocytes strip is positive, a cytological examination of urines should follow to detect the germ and the antibiogram. These strips are only an orientation examination.

III- LOCATION OF INFECTION

A- Locating the urinary tract in a child is necessary

Indeed, low infections do not threaten the renal parenchyma. In contrast, infections of parenchyma kidney may be responsible of renal scarring.

B- Semiology of urinary tract Infection and its location

It is often simple, leading to the prescription of urine microscopy and culture.
1- General symptoms
Their presence is suggestive of acute pyelonephritis: increasing fever to 39° - 40°, chills, sweating, and general physical deterioration. These signs are absent in lower urinary tract infections.

2- Functional signs
In case of acute pyelonephritis cases, there may be abdominal pain, sometimes accompanied by digestive disorders. When located in the lumbar region they are suggestive. In case of low infection, symptomatology can be summed up in bladder signs: pollakiuria, burning on miction.

3- Biological signs
Certain abnormalities are very suggestive of acute pyelonephritis: hyperleucocytosis with polynucleosis, inflammatory syndrome (ESR greater than 30 mm in the first hour, C. reactive protein > 30 mg/l, procalcitonin > 0,5ng/ml). These signs can be subtle or differentiated especially in cases of recurrent infection of the urinary tract. They can be misleading in young children, infants and neonates. This can include unexplained bouts of fever, digestive disorders, the fall-off of ponderal curve, weight loss, cyanosis, jaundice, and a hepatomegaly. Lack of fever does not eliminate the diagnosis of acute pyelonephritis. The newborn may sometimes be hypothermic.

In fact, a urine microscopy and culture must be required whenever a symptomatology suggests an infection of unclear origin, and, in the case of a newborn, in the presence of a symptomatology suggesting neonatal infection.

4- Imaging examinations to visualize the source of the infection
- Uro MRI
- Renal scanner with injection (but too irradiant for children)
- DMSA renal scintigraphy

These examinations should exceptionally be performed when encountering diagnostic difficulties. Their high cost does not allow multiplying their prescription.

In a small number of cases, ultrasound of the renal parenchyma can also visualize the outbreak of acute pyelonephritis.

IV- ETIOLOGIC RESEARCH- UROLOGIC INVESTIGATIONS

Infection of the urinary tract is the main mode of revelation of obstructive uropathy, vesicoureteral reflux, lithiasis and bladder dysfunction. It should be emphasized on the need to seek bladder instability through interrogation. This instability is featured through a urinary urgency diurnal urine leakage, sometimes enuresis.

It should push to seek for a constipation that can contribute to this bladder instability.

The other cause is bladder immaturity: the bladder continues to have uninhibited contractions of the detrusor muscle as with a child who has not yet voluntary mictions.

Bladder immaturity warrants a treatment by oxybutynin (Driptan®, Ditropan®).

- Renal ultrasound allows the visualization of obstructive uropathy or lithiasis.
- Retrograde cystography (RCG)

Major consensus conferences recommend the implementation of RCG in case of primary acute pyelonephritis. However, the practice of this examination is only contributory in 30% of cases. In
70% of cases, RCG is normal. When a VUR is emphasized, it is a low-grade reflux that is frequently visualized. Many recent studies have shown that long-term antibiotic prophylaxis is not justified in low-grade VUR (3). This case indicates the implementation of RCG starting from the primary acute pyelonephritis especially if renal ultrasound is normal. RCG, in this case, may have no therapeutic consequence 9 out of 10 times. This is why we may propose, after the first PNA, when the renal ultrasound is normal, not to prescribe RCG, but to remain very alert in case of misdiagnosed fever and to practice a urine cyto-bacteriologic examination in less doubt. In case of a second PNA, RGC should be prescribed (4).

V- TREATMENT
We may distinguish between three different circumstances: low infection, acute pyelonephritis, and prophylactic treatment of reinfection in children with uropathy and/or frequent recurrent infections.

A- Minor infection treatment
This is a minor infection without potential severity in the absence of uropathy. There is no need to use injectable antimicrobials unless they are the only assets of the germ. The products frequently used are: nalidixic acid (Negram) (30-60 mg / g / day) but it cannot be used with newborns or young infants due to the risk of hyper-intracranial pressure: nitrofurantoin (Furadantin, Microdoïne) (3-5 mg/kg/d), cotrimoxazole (Bactrim, Eusa prim) at a dose of 6 mg / kg / day of trimethoprim and 30 mg/kg / day of sulfamethoxazole amoxicillin at a dose of 50 to 100 mg/kg/day. All these antimicrobials are used in monotherapy. The duration of treatment is more or less 7 days.

1- Low, recurrent and asymptomatic infections in a little girl are a particular case. In the absence of an underlying uropathy, these asymptomatic infections have no potential severity. They end up healing spontaneously, they relapse when the antimicrobial treatment is stopped and the total duration of their evolution is not affected by the treatment. For these reasons, it is possible to refrain from any therapy.

2- Low, recurrent and symptomatic infections in a little girl are different. The importance of bladder symptoms requires action. Factors favouring recurrence must be sought and treated: vulvitis, poor local hygiene, and constipation. Bladder instability is a common cause and should be sought routinely. When recurrences are spaced, each one can be treated on an ad hoc basis according to the protocol we have seen. However, if recurrences are too close, it is best to initiate daily prophylactic treatment.

B- Treatment of acute pyelonephritis
Treatment should sterilize the renal parenchyma. Bactericidal antibiotics should be used when faced with high urinary and parenchymatous concentrations.

1- Antibiotics
• Three major groups of antibiotics are mainly used: cephalosporins, aminopenicillins, and aminoglycosides. The choice of antibiotic is guided by the antibioticogram. In renal failure, the dosage should be adapted to the glomerular filtration.
• The aminopenicillins, alone or combined with clavulanic acid (beta-lactamase inhibitor), remain good antibiotic. However, the increasing number of resistant organisms does not permit their first-line use before prior knowledge of the antibiogramme. They must be prescribed 3 or 4 times a day.
• The third-generation cephalosporins are effective on virtually all E. coli and other urinary bacteria. These are the antibiotics of choice when susceptibility testing is not yet known.
• Aminoglycosides: experimental work has shown interest in the sterilization of the renal parenchyma. The key molecules are: netilmicin, amikacin, gentamicin.

a- Use of antibiotics

The potential severity of infections of the urinary tract of the neonatal period, those associated with a sub-uropathy and a severe infectious table necessitate a double-agent therapy consisting of two synergistic and bacterial antibiotics (cephalosporin 3rd generation and aminoglycosides). In other cases, no objective argument can decide between monotherapy and combination therapy. The duration of parenteral treatment is about 3-4 days. It is pursued by an oral treatment for ten days. Studies are in progress on oral treatment from the outset. Early studies concluded that this attitude is possible, but we must remain cautious.

b- Duration of treatment

It is on the order of 10 to 15 days. Upon finishing the antibiotic therapy, with bactericidal dose, a preventive antimicrobial therapy is discussed in order to avoid recurrence.

2- Prophylaxis

Its purpose is to prevent relapse of acute pyelonephritis. It is also prescribed in cases of very recurrent cystitis in the little girl. It was routinely prescribed in cases of vesicoureteral reflux. It is justified in high-grade vesicoureteral reflux and in some obstructive uropathy.

By contrast, recent prospective studies conclude that in case of low-grade VUR, antibiotic prophylaxis has little interest. In boys, the foreskin is a starting point for urinary tract infection. We must therefore treat preputial adhesion and phimosis, possibly through circumcision (5).

Three antimicrobials are predominantly used. These are those already prescribed in the low infection: nitrofurantoin (Furadantin, Furadoine..), cotrimoxazole (Bactrim, Cotrim), cefaclor (Alfatil). However, the dosages are much lower than in cases of infection, in a single dose at night: nitrofurantoin 1 mg/kg/day cefaclor 10 mg/kg/day, cotrimoxazole at a dose of 2 mg/kg/day of trimethy and 10 mg/kg/day of sulfamethoxazole.

References

CHAPTER 24

THE CURATIVE TREATMENT OF THE URINARY INFECTION

Abdeljalil Maoudj, Algiers - Algeria
I- INTRODUCTION AND PROBLEMATICS
Urinary tract infection in Africa is a public health problem. It often reveals the presence of a malformative uropathy. The diagnosis is not always easy, especially in infants, because of the nonspecific clinical presentation and the difficulty to achieve a good bacteriological sampling. The upper urinary tract infection (pyelonephritis) can be dotted with complications by the renal scarring formation risk, that is, itself, generating renal failure or high blood pressure.

Its management is, however, controversial. The various current therapeutic protocols obtained from each other’s experience, are currently being reassessed. New studies results have refined these protocols. The management of urinary tract infection in Africa must be adapted. Implemented protocols must be efficient and take into account different current resources and, above all, be compliant with the bacteriological data specific to each country.

II- TREATMENT GOALS AND PRINCIPLES
The urinary tract infection treatment aims mainly at sterilizing, as quickly as possible, the urinary tract and the renal parenchyma to avoid the scarring injuries formation.

Antibiotics used must be removed through the urinary tract and particularly reach a sufficient intra renal parenchymal and tubular concentration.

This bactericidal activity implies that the bactericidal antibiotic concentration is approximately ten times the minimum inhibitory concentration (MIC) (1).

The inhibitory quotient (IQ) is the ratio between the plasma concentration and the MIC it should be at least higher than 8 (1). The beta-lactams, aminoglycosides and sulfonamides meet the requirements of a good intra-renal circulation in an active form.

Table 1 shows the different inhibitory quotients antibiotics, depending on the route used:

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>Route</th>
<th>QI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicilline</td>
<td>Orale/IV</td>
<td>3/50</td>
</tr>
<tr>
<td>Amo/ A. Clav</td>
<td>Orale</td>
<td>4</td>
</tr>
<tr>
<td>Cefixime</td>
<td>Orale</td>
<td>16</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>IV</td>
<td>1600</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>IV</td>
<td>2500</td>
</tr>
<tr>
<td>Cotrimoxazole</td>
<td>Orale</td>
<td>6-10</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>IM / IV</td>
<td>40</td>
</tr>
</tbody>
</table>

III- WHICH ANTIBIOTICS TO BE USED?
There are many molecules that can be proposed in the treatment of urinary infection.

We distinguish between first-line antibiotics commonly prescribed probabilistically before any antibiotic spectrum and are expected to be active on the presumed bacteria (Enterobacteriaceae)
and second and third line antibiotics, used in particular situations (resistant germs, particular land...).

**A- First-line antibiotics**

The first-line antibiotics are represented by aminopenicillins (ampicillin, amoxicillin), sulfonamides in particular, cotrimoxazole, nitrofurantoin and nalidixic acid (2). Table 2 shows the first-line antibiotics, their dosage and administration route.

**Table 2: First-line Antibiotics**

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>Route</th>
<th>Dosage mg/kg</th>
<th>Nombre de prises</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin</td>
<td>po im / iv</td>
<td>50-100</td>
<td>3-4</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>im / iv</td>
<td>100-200</td>
<td>3-4</td>
</tr>
<tr>
<td>Cotrimoxazole</td>
<td>po</td>
<td>6-7</td>
<td>2</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>po</td>
<td>3-5</td>
<td>3</td>
</tr>
<tr>
<td>Nalidixic Acid</td>
<td>po</td>
<td>30-60</td>
<td>4</td>
</tr>
</tbody>
</table>

**B- Second and third- line antibiotics**

**Table 3: Different antibiotics used in 2nd and 3rd line**

<table>
<thead>
<tr>
<th>2nd line Antibiotics</th>
<th>Route</th>
<th>Dosage (mg/Kg)</th>
<th>Number of intakes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amox / Aclav</td>
<td>po im / iv</td>
<td>40</td>
<td>2-3</td>
</tr>
<tr>
<td>Ampicilline</td>
<td>po</td>
<td>25-50</td>
<td>2-3</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>im / iv</td>
<td>60-100</td>
<td>4</td>
</tr>
<tr>
<td>Cefixime</td>
<td>po</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>im</td>
<td>50-150</td>
<td>3-4</td>
</tr>
<tr>
<td></td>
<td>iv</td>
<td>100-200</td>
<td>3-4</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>im</td>
<td>50</td>
<td>1-2</td>
</tr>
<tr>
<td></td>
<td>iv</td>
<td>75-100</td>
<td>1-2</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>im / iv</td>
<td>50-150</td>
<td>3-4</td>
</tr>
<tr>
<td>Gentamycin</td>
<td>im / iv</td>
<td>3-5</td>
<td>1-3</td>
</tr>
<tr>
<td>Netilmicin</td>
<td>im / iv</td>
<td>7,5</td>
<td>1-3</td>
</tr>
<tr>
<td>Amikacin</td>
<td>im / iv</td>
<td>15</td>
<td>1-3</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>iv</td>
<td>40</td>
<td>1-3</td>
</tr>
<tr>
<td>Imipenem</td>
<td>im / iv</td>
<td>500 mg/jour</td>
<td>1-3</td>
</tr>
</tbody>
</table>
Having a targeted indication, they are often used in resistant bacteria cases. They should never be
used as first-line in a lower urinary tract infection. The second-line antibiotics are represented by
amoxicillin with clavulanic acid, aminoglycosides and cephalosporins as first, second and third
generation. Ceftazidime (C3G), vancomycin and imipenem have targeted indications. Quinolones
have no marketing authorization in children.

IV- THE DOSAGE AND CHOICE OF ANTIBIOTICS
The dosage and choice of antibiotics should take into account certain factors. (3)

A- Age and land
Age leads to certain restrictions, sulfonamides, nalidixic acid and nitrofurantoin being
contraindicated in neonates and infants aged less than 3 months.
Ceftriaxone should be used with caution in the newborn due to the displacement of bilirubin
albumin binding. In any case, in the newborn and even in other age groups, the severity of the
clinical picture, the existence of an uropathy requires the use of an appropriate antibiotic according
to the antibiogram.

B- Renal failure
The presence of renal failure requires dose adjustment based on the degree of glomerular filtration.
The interval between doses will be extended in proportion to the decrease in creatinine clearance
or when the unit dose will be reduced (3). The use of nitrofurantoin is prohibited while the use
of nalidixic acid is not recommended. In the newborn with renal failure, plasma dosages are
essential to adjust the dose, especially for aminoglycosides and vancomycin.

C- Sensitivity to germs
Antibiotic therapy prescription must take into account the level of bacteria resistance to the
envisaged antibiotics. Bacterial resistance varies according to each country and according to local
prescribing habits. This resistance concerns particularly Escherichia coli that remains the most
frequently encountered germ during urinary tract infection.

Knowledge of the germs bacteriological situation and their sensitivity to various antibiotics in
Africa is hampered by the lack of comprehensive surveys and the lack of a monitoring network of
bacteria resistance level to antibiotics. Some scattered studies can note that:

1. The most frequently found germ remains E. coli, to some variation.
2. E. coli sensitivity to different antibiotics is contrasted between the Maghreb and African countries.
   • In the Maghreb countries, E. coli resistance rate to aminopenicillins is high. In Morocco (4), it
     was about 69% in 2004 it ranged from 61 to 65% in Tunisia (5), during the years 1999 to 2003.
     In Algeria, the national network of resistance to bacteria surveillance, the rate was 78% in 2008
     (6). As for the E. coli resistance to other antibiotics, including amoxicilline clavulanic acid, the
     rate ranges across the Maghreb countries from 29 to 44%. Resistance to cotrimoxazole, which is
     increasing, is about 40 to 59%.
   • In other African countries, the rate of E. coli resistance to aminopenicillins is even higher. In a
     survey carried out in Mali (7) in 2006 concerning 1549 isolates, the resistance level was around
     81%. It was 72% in a cross-sectional survey done in Congo (8) during the 2010s and 80% in
     Senegal (9). A rate of 100% has been noted in a retrospective study of 133 infants in Abidjan, Ivory
Coast (10). E. Coli resistance to amoxicillin clavulanic acid ranges from 33 to 68% in different countries. Moreover, resistance to cotrimoxazole seems high. It is about 53% in Congo (8) 60% in Senegal (9), 60% in Madagascar (9) and 80% in Mali (7). The resistance level to 3rd generation cephalosporins is not always tested in these countries.

V- CONDUCT OF TREATMENT

A- Cystitis treatment

Cystitis treatment generally uses oral monotherapy. The choice of antibiotics, which varies from one country to another, is often guided by the level of germs resistance to these antibiotics. The products often used (11,13):
- Cotrimoxazole (6 –7 mg /Kg of TMP 30mg / kg SMZ)
- Nitrofurantoin (3 – 5mg /kg /d)
- Nalidixic acid (30- 60mg/kg /d)
- Nitroxoline (50mg/kg/d)
When these molecules cannot be prescribed, then other antibiotics may be used.
- Amoxicillin (50 -100mg/kg/d)
- Amox/Aclavulanic (40 mg/ kg /d)
- Cefalexin (20 mg/ kg /d)
The duration of the treatment remains questionable. It tends to be shortened as 3 meta-analyzes have shown (14,16) gathering 49 studies, more than 3,000 children, in which short treatments were compared - from 2 to 4 days-versus long treatment - from 7 to14 days, resulting in the following conclusions:
- The single-dose treatment is associated with an increased risk of failure
- Quite good results were observed by short treatment from 2 to 4 days. Thus, the recommended duration of treatment based on the findings of these three meta-analyzes ranged from 2 to 7 days, usually a period of 5 days is proposed.

B- Acute pyelonephritis treatment

Although several consensuses have been proposed, the treatment of acute pyelonephritis (APN) currently still arises some problems and several questions remain arisen:
- What is the first-line treatment?
- Should it be a single or double agent therapy?
- What is the route of administration?
- What is the optimal duration of treatment?
For most authors, the treatment approach is often based on the presentation type of pyelonephritis. The American Academy of Pediatrics (AAP) (17,18) identifies certain severity factors allowing individualizing two types of APN: uncomplicated APN and complicated APN.

1- Severity signs are
- Fever of 39 ° and more, a severe infectious picture
- Persistent vomiting
- Moderate or severe dehydration
- Non-compliance to treatment.

Note that some authors (19) have considered that less than 6 months of age and / or the existence of a known or discovered uropathy during ultrasound are two potential risk factors.

2- Which first-line antibiotic?
Surveys, comparing the different drugs used in the APN, have not demonstrated superiority of some compared to others (20, 21, 22). When prescribing (the high price of some cephalosporins limits their use in some countries), the cost of drugs is taken into account. Antibiotics recommended by the American Academy of Pediatrics in 2011 are oral or parenteral 3G cephalosporins, aminoglycosides, amoxicillin clavulanic acid and cotrimoxazole.

3- Single or double agent therapy?
Should we associate an aminoglycoside to initial treatment with beta-lactams? It is established that double-agent therapy with an aminoglycoside is more rapidly bactericidal in cases of bacteremia (1.3, 23). In addition, aminoglycosides are antibiotics that have the best intra-renal penetration. Although currently it is not yet established that the association of an aminoglycoside with a 3rd generation cephalosporin reduces the risk of renal scarring, double-agent therapy is usually recommended for the initial treatment of APN in young children, in any case, before three months and, for some, from 6 to 18 months. Aminoglycosides administration modalities in 2 or 3 doses or in a single daily dose, have been outlined in recent years (24) and in favor of a daily dose administration in a single injection.

4- Antibiotics: orally or parenterally?
The oral route seems interesting in the non-complicated ANP treatment. The results of a prospective randomized survey by Hoberman (25) have confirmed that oral treatment with cefixime for 14 days, on incidence of renal scarring observed 6 months after PNA, is as effective as treatment with intravenous cefotaxime. Although the effectiveness of the oral route has been highlighted, most authors draw the attention of pyelonephritis severity, especially in infants, and insist on parenteral treatment at least in the first 2 days.

5- Short or long parenteral treatment?
The short parenteral treatment of 3 to 4 days seems unanimous. Cochrane Library recent publications (2003) (23) through a meta-analysis compared the short treatment of 3 to 4 days for parenteral and oral treatment with a long parenteral treatment of 10 days, it did not note any differences between the two groups as to the persistence of bacteriuria at the end of treatment, recurrence of infection, as well as the incidence of renal scarring six months later. In addition, studies that compared the direct cost of the two strategies have clearly demonstrated that the long parenteral treatment is seven times more expensive than the short one (26). In Algeria, a prospective survey (27) on 180 children aged 3 months to 15 years hospitalized for a first pyelonephritis episode without obstructive malformation showed that a short treatment associating ceftriaxone with gentamicin for 4 days with oral relay cefixime for 6 days is equivalent to a 10-day treatment associating ceftriaxon with four days of gentamicin.

6- What is the optimal duration of treatment?
During an APN, the current trend is shortening the duration of treatment.
There are no studies comparing the period of 10 days versus 14 days. The literature review
conducted by the American Academy of Pediatrics states that the duration of treatment that is most often recommended is 7 to 14 days (1, 4, 23). There are several treatment protocols. The first adopted therapeutic diagrams by the infectious diseases society of French language in 1990 (28) recommend a double agent in therapy in neonates and infants under 18 months. The parenteral route is from 10 to 15 days.

In children over 18 months, a 3-day double-agent therapy is prescribed, followed by monotherapy parenterally or orally. Since 1997, after a French national randomized study (26), the therapeutic diagrams have been revised and refined, three situations were then individualized:

**a**- For infants less than 6 months, parenteral double-agent therapy (C3G + aminoglycosides), a treatment duration of 10 days

**b**- For 6 to 18 months infants
- With risk factors: double-agent therapy (C3G + aminoglycoside) relay by parenteral single-agent therapy.
- Without risk factors: a double-agent therapy for 2 days (C3G + aminoglycoside) short parenteral relay then oral monotherapy

**c**- Children over 18 months
If there are no risk factors, two days parenteral single-agent therapy followed by 8-day oral treatment.

The latest recommendations of the American Academy of Pediatrics 2011 AAP 2011 recommendations (28) applying more easily and are perfectly adapted to the terrain, three situations are planned.

**d**- If a child shows severity signs, a double-agent therapy for 24 to 48 hours (C3G + aminoglycoside) and an oral treatment for 7 to 14 days, provided that the clinical and bacteriological situation is controlled

**e**- If the child has no signs of severity, but has persistent vomiting, the same recommendations will be implemented

**f**- If the child shows no signs of severity or vomiting, the oral route will be recommended with such preference, cotrimoxazole.

**IV- CONCLUSION**

The treatment of urinary tract infection in Africa must be adapted to each country according to local bacterial flora and its resistance level to antibiotics. Treatment protocols should consider the therapeutic resources available in each country.

Codification and simplification of treatment is necessary to reduce the resistance level of bacteria to antibiotics and to also have health savings. The current global trend, being a therapeutic escalation, a simplification of treatment, in which all African must monitor the principles countries-is recommended.
Table: Dose adjustment of drugs in renal failure

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>Normal dose</th>
<th>30 &lt; FG &lt; 50</th>
<th>10 &lt; FG &lt; 30</th>
<th>FG &lt; 10</th>
<th>Extraction by dialysis</th>
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<tbody>
<tr>
<td><strong>Aminoglycosides</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Amikacin</td>
<td>15mg/kg/d</td>
<td>40</td>
<td>20</td>
<td>10</td>
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<tr>
<td>Gentamicin</td>
<td>3-5mg/kg/d</td>
<td>60</td>
<td>10</td>
<td>5</td>
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<td>Netilmicin</td>
<td>6mg/kg/d</td>
<td>60</td>
<td>15</td>
<td>10</td>
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<tr>
<td>Imipenem + cilastatin</td>
<td>60mg/kg/d</td>
<td>75</td>
<td>25</td>
<td>15</td>
<td>yes</td>
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<td><strong>Cephalosporins</strong></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Cefaclor</td>
<td>40mg/kg/d</td>
<td>DN</td>
<td>DN</td>
<td>DN</td>
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</tr>
<tr>
<td>Cefazolin</td>
<td>50-10mg/kg/d</td>
<td>75</td>
<td>30</td>
<td>10</td>
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</tr>
<tr>
<td>Cefixime</td>
<td>8mg/kg/d</td>
<td>DN</td>
<td>75</td>
<td>50</td>
<td>no</td>
</tr>
<tr>
<td>Cefotaxime</td>
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<tr>
<td>Cefazimide</td>
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<td>15</td>
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<tr>
<td>Ceftriaxone</td>
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<td>DN</td>
<td>DN</td>
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<tr>
<td>Cefuroxime axetil</td>
<td>25mg/kg/d</td>
<td>DN</td>
<td>33</td>
<td>25</td>
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<td><strong>Glycopeptides</strong></td>
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<tr>
<td>Teicoplanin</td>
<td>DC 20mg/kg DE 6-10mg/kg/d</td>
<td>40</td>
<td>10</td>
<td>DC puis dosages no</td>
<td></td>
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<tr>
<td>Amoxicillin</td>
<td>50mg/kg/d</td>
<td>DN</td>
<td>30</td>
<td>15</td>
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</tr>
<tr>
<td>Amoxicillin + acid clavulanic</td>
<td>40mg/kg/d PO</td>
<td>DN</td>
<td>25</td>
<td>15</td>
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</tr>
<tr>
<td>Ampicillin</td>
<td>100mg/kg/d</td>
<td>DN</td>
<td>25</td>
<td>15</td>
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<tr>
<td><strong>Macrolides and related</strong></td>
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<td></td>
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<tr>
<td>Clarithromycin</td>
<td>10-20mg/kg/d</td>
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<td>50</td>
<td>50</td>
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<tr>
<td>Erythromycin</td>
<td>30-50mg/kg/d</td>
<td>DN</td>
<td>DN</td>
<td>60</td>
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<tr>
<td>Clindamycin</td>
<td>20mg/kg/d PO</td>
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<td>DN</td>
<td>DN</td>
<td>no</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>30mg/kg/d</td>
<td>DN</td>
<td>DN</td>
<td>50</td>
<td>yes</td>
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<td><strong>Quinolones</strong></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Ciprofloxacin</td>
<td>15mg/kg/d PO</td>
<td>DN</td>
<td>50</td>
<td>25</td>
<td>no</td>
</tr>
<tr>
<td>Pefloxacine</td>
<td>10-20mg/kg/d</td>
<td>DN</td>
<td>DN</td>
<td>DN</td>
<td>no</td>
</tr>
<tr>
<td><strong>Cyclins</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doxycyclin</td>
<td>2-4mg/kg/d</td>
<td>DN</td>
<td>DN</td>
<td>75</td>
<td>yes</td>
</tr>
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<td>Sulfamides</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sulfamethoxazole</td>
<td>5mg/kg/d TMP</td>
<td>DN</td>
<td>50</td>
<td>50</td>
<td>yes</td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>3-5mg/kg/d</td>
<td>Cl</td>
<td>Cl</td>
<td>Cl</td>
<td>yes</td>
</tr>
</tbody>
</table>
References

CHAPTER 25

VOIDING DISORDERS

Mina Oumil, Casablanca - Morocco
HIGHLIGHTS

✓ The child’s voiding disorders are a common reason for consultation, particularly in early schooling.
✓ The intermittent daytime incontinence is recognized as an uncontrolled leakage of urine during the day for children over five years.
✓ There are two types of voiding disorders: isolated primary enuresis without daytime flight and occur only during sleep and dysfunctions of the urinary elimination grouping storage disorders (unstable bladder, bladder retentionist) and emptying disorders (detrusor-sphincter dyssynergia, lazy bladder).
✓ Voiding disorders of functional origin, require careful history to be well recognized and qualify for a specific treatment.

I- INTRODUCTION

Voiding disorders in children are a common reason for consultation, especially at the early schooling years. As their name implies, these are voiding disorders. For a better understanding, it is essential to know some epidemiological evidence regarding the acquisition of cleanliness as well as some definitions. The neurogenic bladder, urinary tract malformations and urinary tract infection are excluded from the voiding disorders.

II- DEFINITIONS

The International Children’s Continence Society published in 2006 new terminology for incontinence. Thus, intermittent diurnal incontinence is recognized as an uncontrolled leakage of urine during the day in children over five years. We no longer talk about diurnal enuresis, rather intermittent diurnal incontinence. Enuresis is defined as nocturnal incontinence with intermittent urine loss during sleep.

We can, therefore, distinguish between two types of voiding disorders:
- The isolated primary enuresis and therefore bedwetting without diurnal leakage occurring exclusively during sleep.
- The dysfunction of the urinary elimination including storage disorders (bladder instability, retentionist bladder) and emptying disorders (bladder sphincter dyssynergia, underactive bladder).

III- EPIDEMIOLOGY

The acquisition of cleanliness goes through several stages, first diurnal and then nocturnal. Placing on the child early pot does not accelerate the cleanliness of the latter, but may instead affect normal development. Girls are clean earlier than boys. At three years, 84% of girls and 53% of boys have a diurnal cleanliness. At six years old, it represents 96% of girls and 94% boys. The child over five years is on average 4 to 7 urinations per day. Cleanliness, which is dependent on the maturation of the central nervous system, goes through 3 steps:

• Automatic or infantile bladder where the bladder contraction is reflex and of a low volume.
• Bladder physiological immaturity with detrusor hyperactivity and lack of cortical inhibition.
• Mature stage with cortical control of bladder hyperactivity.
• Normal micturition cycle is under the control of the sympathetic and parasympathetic nervous system. The sympathetic system allows bladder filling at low pressure by inhibiting the detrusor activity and increasing the muscle activity of the bladder neck and proximal urethra. During bladder emptying, the parasympathetic system causes detrusor contraction and slackening of the bladder trigone and proximal urethra through sympathetic inhibition.

IV- ENVIRONMENT HINDERING THE ACQUISITION OF CLEANLINESS

The acquisition of cleanliness usually goes well at home, but may be subject to constraints both at home and at school. Cleanliness often determines admission to kindergarten. Kindergarten teachers, who impose on children to wait for the recreation to pee, do not allow them to leave the classroom to go to the bathroom and recreation schedules do not often coincide with the children needs time.

The condition of the toilet is also a factor that does not help with cleanliness acquisition and maintenance. The toilets do not always have doors and if they exist, they are not closed. The toilets are far at the bottom of the yard, so less reassuring (the problem is when it’s cold and it’s raining). Cleanliness is poor: the girls refuse to sit on the bowl and then urinate by contraction the pelvic muscles. The Turkish toilets are not adapted to the size of children, especially girls. Wearing tight jeans to leggings and tights, pushes girls away little knees to urinate, so they do incomplete endo-vaginal urination, a source of locoregional irritation later.

The lack of toilet paper, stench and other factors push children, particularly girls, to get used to urine retention. This is what causes voiding disorders, particularly bladder instability. In contrast, the boys have no difficulty in urinating in toilets or even behind a tree or in a corner at the back of the playground.

V- CLINICAL STUDY

A- Anamnesis

It is an essential step to identify the type of micturition disorder, must answer the following questions:
• Is incontinence diurnal, nocturnal or both?
• Incontinence, is it primary or secondary?

Anamnesis should look for:
• A history of uro-nephrological or neurological affection
  - Pollakiuria and urinary urgency
  - A urinary leakage, its frequency and importance
  - The pace of the urinary stream
  - A dysuria
  - Constipation, defecation disorders, or encopresis.
• Anamnesis will study the child’s psychosocial experience, parental behavior, punishment, and the child’s reactions...
B- Physical examination

It includes taking weight, height, blood pressure, evaluating the general condition, the external genital organs (possible defects research) and a complete neurological examination. Urinalysis with dipstick must complete the clinical stage to eliminate the presence of a possible urinary tract infection or diabetes mellitus. Para-clinical tests are rarely needed as a first line. Often a useful kidney and bladder ultrasound, will analyze the kidneys, ureters and bladder (bladder wall thickness, post-void residual research...). The urodynamic exploration is reserved for cases of suspected bladder-sphincter dysfunction.

Some useful parameters must be known:

Expected bladder capacity (age in years + 1) x 30 (in ml)
Diuresis: Polyuria if> 2 L / m² / 24h
Post-voiding residue bladder: Normal = 0 to 20 Ml.

Major Voiding Disorders

C- Intermittent diurnal incontinence

From the clinic stage, we must distinguish between the bladder storage disorders (hyperactive bladder, retentionist bladder) and impaired emptying (detrusor-sphincter dyssynergia, hypo-active bladder). These disorders can evolve towards one another. An hyperactive bladder can develop into a retentionist bladder then to detrusor-sphincter dyssynergia. Intermittent diurnal incontinence should not be confused with the following situations: urinary tract infection, neurogenic bladder, ectopic ureter, diabetes mellitus, diabetes insipidus and urethral obstructions.

Storage and emptying disorders are summarized in the tables below:

Table 1: Storage and emptying disorders

<table>
<thead>
<tr>
<th>Storage Disorders</th>
<th>Characteristics</th>
<th>Symptoms</th>
<th>Treatment</th>
</tr>
</thead>
</table>
| Hypermature or Immature Bladder | - Often secondary, in girls in the early school years  
- Hyperactive bladder with sphincter contraction to minimize leakage  
- Small- functional bladder capacity. | Emergencies(pathognomonic) with specific posture  
- Pollakiuria  
- Squatting to minimize leakage, crossing the legs (squeezing)  
- Leaks in small quantities  
- Constipation and / or encopresis. | Oxybutynin 0.3- 0.5 mg / kg / day in 2-3 grip / day  
- Constipation treatment  
- Pelvic muscles slackening during urination (for two sexes urination sitting feet on the ground on each side of the toilet, legs apart, leggings, tights completely lowered to the ankles). |
| Retentionist Bladder         | - Seen in children who prefer to play and delay urination  
- Sphincter contraction at the forefront  
- The bladder expands | - Incomplete and uncommon urination  
- Emergency leaks with large amounts  
- Sensation loss of repletion and the urge to urinate. | - Voiding rehabilitation |
Other rarer causes of intermittent diurnal incontinence must be distinguished:
- Stress incontinence: leakage of small urine amounts during exercise or when abdominal pressure increases
- Giggle incontinence complete urination during a laugh or a giggle
- Post-voiding leakage on vaginal reflux
- Benign transient pollakiuria.

**D- Nocturnal isolated incontinence or enuresis**

Enuresis, defined as intermittent urinary leakage during sleep (at night or during naps) can be primary or secondary. A genetic predisposition can be found if one and / or both parents are bedwetting.

Bedwetting is isolated and is not accompanied by any other voiding disorder. It should not be managed until the patient is over the age of 5 years. The treatment is based on either desmopressin or on alarm systems. The latters are more effective with a success rate of 70% and few relapses, provided they are used from 3 to 4 months. Management is summarized in the following diagram:

<table>
<thead>
<tr>
<th>Storage Disorders</th>
<th>Characteristics</th>
<th>Symptoms</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underactive Bladder</td>
<td>Wide distended bladder with detrusor becoming ineffective.</td>
<td>Uncommon voiding, Dysuria, Weak urinary stream, Abdominal contraction to trigger diuresis.</td>
<td>Voiding rehabilitation</td>
</tr>
<tr>
<td>Detrusor-sphincter Dyssynergia</td>
<td>Often the terminal stage of the above symptomatology, Loss of coordination between the bladder contraction and the striated sphincter slackening, Trabeculate battling bladder, Severe Form: Hinman Syndrome that behaves like a neurogenic bladder, but without neurological cause.</td>
<td>Dysuria in the foreground, Jerky urinary-Jet, Recurrent urinary infections, Vesicoureteral acquired reflux, Reflux nephropathy.</td>
<td>Voiding rehabilitation with biofeedback may be associated with an alpha antagonist, Self-catheterization.</td>
</tr>
</tbody>
</table>

**Management Diagram**

- Isolated Enuresis
- Behavioral Measures
  - Alarm Systems (3 to 4 months)
  - Desmopressin (ineffective in 2 weeks)
  - Desmopressin (double dosage)
VI- CONCLUSION

Voiding disorders, which are often of a functional origin, require a careful anamnesis to be well recognized. Thus, during intermittent diurnal incontinence, bladder-type immature associated with enuresis, we must first deal with daytime problems. If there is persistent enuresis, it should be treated thereafter specifically.

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CHAPTER 26

THE POSTERIOR URETHRAL VALVES

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HIGHLIGHTS

✓ The posterior urethral valves (PUV) cause urethral obstruction in which the consequences on the upper urinary tract are often severe.
✓ Increasingly discovered by prenatal ultrasound, they require endoscopic section from the first days after birth.
✓ In our developing country diagnosis and management is often carried out late, hence a need to induct a management adapted to our work environment.

I-INTRODUCTION

The posterior urethral valves (PUV), described in 1919 by Young, produce lower urinary tract obstruction associated with persistent mucosal fold usually located under the verru montanum (1). The injuries consist of congenital valves located in the posterior urethra, just below the Verru montanum.

The incidence varies according to country: 1/25,000 births in the United States, 1/8,000 births in France (2). The consequence of this urethral obstruction is an expansion of the bladder and upper urinary tract resounding on renal function sometimes dramatically with kidney failure more or less significant.

The etiology of PUV remains unknown, likely related to improper positioning of Wolff channel orifices joining forces in the urethra. In the light of a better understanding of their pathogenesis, PUV classification has been modified from Young classical description to the one, clinically most appropriate, of Congenital Obstructing Posterior Urethral Membrane (COPUM)(3).

The diagnosis is suspected on an antenatal ultrasound in case of a major expansion, more or less symmetrical, of both kidneys and both ureters with a large thickened bladder wall in a boy. The diagnosis is often performed in the postnatal stage in our developing countries (4)

This is a serious malformation because it can lead to renal failure through destruction of the renal parenchyma.

II- CLINICAL SIGNS

A- Prenatal diagnosis

The diagnosis is possible around the twentieth week with the presence of a bilateral dilatation of the upper urinary tract, the bladder constantly too visible, distended, thick-walled and incomplete
emptying. The associated oligohydramnios should draw attention. The diagnosis is made only during the third semester where the dilatation of posterior urethra will be also visible. An associated renal anomaly should be monitored and eventually fetal urine should be analysed.

**B- Post-natal Diagnosis**

The more the anomaly is obstructive, the earlier the diagnosis is carried out and the more severe the resounding is. Clinical findings associate miction disorders, infectious manifestations, and renal failure, but to different degrees depending on age.

**1- In the newborn**

This has to do with general manifestations: diarrhea, vomiting, dehydration, abdominal ballooning, and presence of a full bladder, eventually large palpable kidneys, the presence of ascites. The urine stream is weak or even absent. The clinical picture sometimes shows a sepsis or renal failure. Normal bladder of newborns is not palpable.

2/3 of newborns urinate within the first 12 hours

92% of newborns urinate within the first 24 hours / 8% of newborns urinate within the first 48 hours.

**2- In infants**

The table is mostly dominated by infectious manifestations (febrile, pyuria) associated with abdominal distension, the presence of a full bladder, large kidneys and finally underdevelopment.

**3- In the young boy**

The manifestations will be more urological: pyuria, dysuria, retention more or less complete, full bladder, large palpable kidneys, diurnal and nocturnal incontinence. We sometimes note HBP, digestive disorders or retarded growth.

**4- In adolescents**

The table is dominated by voiding disorders: dysuria, full, diurnal or nocturnal incontinence, and infectious manifestations: prostatitis, burning urination, pollakiuria, pyuria, high fever.

The recognition of these clinical features should lead to the prescription of paraclinical examinations in search of PUV.

**III- EXPLORATIONS**

**A- Ultrasound**

It highlights a bladder in which the wall is considerably thickened and dilated posterior urethra. The ureters are visible and at the kidney level there is urinary tract dilation, thinning of the parenchyma is often hyperechoic with loss of cortico-medullary differentiation and sometimes the presence of cysts.

**B- Urethrocystography**

It will be carried out where appropriate through retrograde or subpubic ways but always include voiding clichés:

Posterior and floppy urethra, there is a diameter rupture between the posterior and anterior urethra that is filiform.
For type 1 valves: discontinuation is cupuliform,
In type 3 valves, the discontinuation is rectilinear and located a little lower. Bladder shows signs of struggle with cells, diverticula, and residue. The neck is often prominent and there is finally a unilateral or bilateral reflux (Fig. 1).

**Figure 1: Suprapubic cystography. Typical aspect of posterior urethral valve**

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**C- Intravenous urography or CT urography (if renal function permits).**
This urography may be normal in 15 to 20% of cases, but most often reveals a bilateral ureter hydronephrosis, sometimes asymmetrical or even unilateral.

**D- Biology**
The creatininemia at birth reflects in fact the mother's it reaches its real infantile level in 96 hours.
The biological assessment is mainly based on the study of renal function.
The cytobacteriological examination is required to search for a urinary tract infection and it's monitoring.

**IV- DIFFERENTIAL DIAGNOSIS OF POSTERIOR URETHRA VALVES**
- Non-obstructive urethral folds
- Prolapsed ureterocele
- Polyp of the posterior urethra
- Anterior urethral valve
- Diverticulum of the anterior urethra
- Meatal stenosis (hypospadias)
- Post-traumatic urethral stenosis
  - Iatrogenic
- Urethral lithiasis
- Sarcoma of the genital urogenital sinus
- Bladder sphincter dyssynergia
V- MANAGEMENT

On the therapeutic level, the goal is to remove the urethral obstruction, prevent urinary tract
infections and preserve bladder and renal function, which are closely interrelated (5). The PUV
require endoscopic section (6) in the early days after birth. This act is not easy and requires a
pediatric environment (anesthesia, neonatology), special endoscopic equipment and a habit of
pediatric urinary tract endoscopy. These pediatric endoscopic means are lacking in the technical
platform of our developing countries where they often resort to two stages management
First, the creation of a vesicostomy (The bladder being the main functional obstruction of urine
flow, we usually opt for non continent-surgical vesicostomy) Secondly, the removal of valves. The
top appliance must then be decompressed by urinary diversion. The destruction of valves must
often be followed by a longnephro-urological monitoring of ureterovesical and renal sequelae of
the initial obstruction.

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PART VIII

CHRONIC KIDNEY DISEASE

CHAPTER 27

I- CHRONIC KIDNEY DISEASE

Deirdre Hahn, Johannesburg - South Africa
HIGHLIGHTS
✓ More than 50% of kidney which conduit with chronic renal failure are hereditary or congenital.
✓ A break of growth abnormalities in food intake or polyuria syndrome in a child should evoke a CKD, with a major challenges of growth, nutrition and renal osteodystrophy.
✓ Support for complex, multidisciplinary and individualized care that must be explained to the child and his family.
✓ Taking psychological and social support is an integral part of treatment.
✓ Peritoneal dialysis is the preferred renal replacement technique in children under two years with an increased risk of peritonitis.
✓ The treatment of choice for ESRD is technically feasible from 10 kg kidney transplantation.

I- INTRODUCTION
The childhood dilemmas of malnutrition, diarrhoeal disease and infectious diseases are still a major challenge that healthcare workers are faced with in developing countries. However, in many countries with improvement of public health services, there have been decreases in mortality rates due to these conditions and a shift in causes of mortality to chronic diseases.

The number of patients, more specifically adults with ESRD, and CKD, has increased alarmingly and is becoming a global public health problem. Children less than 20 years of age account for about 2% of the ESRD population in the USA. To achieve optimal outcomes in children requires greater resources, specialized care and time. Chronic renal failure is usually a progressive and inexorable loss of kidney function, and in children often results from heterogeneous causes.

II- DEFINITION AND CLASSIFICATION
One can best define CKD as a spectrum ranging from renal damage with a normal GFR to CRF necessitating dialysis. The NKF-K/DOQI has characterised CKD through 5 stages:

<table>
<thead>
<tr>
<th>Stages of CRF</th>
<th>GFR ml/min/1.73m²</th>
</tr>
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<tbody>
<tr>
<td>1. Kidney damage with normal or increased GFR</td>
<td>&gt; 90</td>
</tr>
<tr>
<td>2. Kidney damage and mildly decreased GFR</td>
<td>60-89</td>
</tr>
<tr>
<td>3. Moderate decrease in GFR</td>
<td>30-59</td>
</tr>
<tr>
<td>4. Severe decrease in GFR</td>
<td>15-29</td>
</tr>
<tr>
<td>5. Kidney failure</td>
<td>&lt;15 (nécessité de dialyse)</td>
</tr>
</tbody>
</table>

In establishing a common classification, staging is easier for patients and healthcare workers when discussing CKD. Stages 1+2 would be better defined with associated abnormalities such as proteinuria and haematuria. A further problem, more so for children, is that the normal GFR varies with age, body size and gender, approaching mean adult values at approximately 2 years of age. For this reason K/DOQI guidelines are only applied to children above 2 years of age. The GFR is the best measurement of overall renal function. This has usually been done using the Schwartz formula, which is convenient but, with deteriorating renal function, tends to overestimate function. A more recent formula is the CKiD formula.
III- EPIDEMIOLOGY

A- Generality

Information related to epidemiology and incidence of CKD in children is limited, particularly in the less advanced stages of renal impairment. In these early stages CKD is often asymptomatic, and hence underreported and under diagnosed. Present data, relating to the epidemiology in children relates to the more severe and late stages of CKD. There are many well-designed registries but are restricted to specific information and only small reference populations.

To compare prevalence and incidence data of different geographical settings is impossible, as characteristics of CKD are different as are the disease classification.

In developed countries registries such as NAPRTCS, EDTA and Ital. Kid provide valuable data. In developing countries in Asia and Africa, where approximately half of the world’s childhood population resides, and epidemiological information is very limited and grossly based on tertiary centre referrals.

B- Incidence and prevalence

Incidence and prevalence figures of CKD in Africa are largely unknown as there are no national registries to collect and collate vital data. In Southern Africa, Kwa-Zulu Natal, an incidence of CRF of 1-2 per million of age related population is reported. Of the total number of children screened (653), 8.8% had CKD stages 2-5.

Data from Johannesburg and Cape Town show that 589 renal transplants were performed on children between 1968 to 2009. Of these 405 were done in Johannesburg. The mean age of the children was 11.25 years. The South African population in 2010, is just under 50 million, with approximately 11.19 million residing in Gauteng and in Kwa-Zulu Natal 10.6 million. Thirty one per cent of the population is below 15 years of age. The incidence of chronic renal failure in children under 15 years is 10 per million per year, indicating 30 new patients with chronic renal failure in Gauteng alone. The lower incidence in Kwa-Zulu Natal may be due to patients self-referring to centres such as Cape Town and Johannesburg, and patients dying undiagnosed.

A review, over 15 years of admissions at a teaching hospital, in Nigeria, estimated the median annual incidence of severe CKD (CrCl < 30 ml/min/1.73 m^2) to be 3 per MARP, with a prevalence of 15 patients per million children.

IV- ETIOLOGY

Adequate data on the etiology of CKD from less developed countries again is limited, due to inadequate data collection. Many of these countries continue to suffer with the burden of infectious diseases, TB, malaria, and infectious related GN. Various glomerulopathies, were reported as the cause for half of the causes of CKD in a Nigerian report. HIV associated nephropathy is underreported and is likely to increase with the increasing incidence of HIV. It is important to note that the causes for CKD in children are significantly different to those seen in adults.

Hypertension and diabetic nephropathy predominates in adults but are uncommon causes in children. Particularly in younger children, structural abnormalities, congenital and urologic abnormalities predominate. With increasing age the glomerular diseases increase and urologic abnormalities decrease as an etiology. Most data also demonstrates that CKD affects more males than females. This would reflect the higher incidence of congenital disorders such as posterior urethral valves in boys versus girls.
In KZN, the commonest cause of CKD in all ages was nephrotic syndrome. There was a preponderance of black patients. FSGS was the predominant histological form.

The second most common cause of CKD was obstructive uropathy, 16.4% in children < 5 years. HUS due to Shigella dysenteriae Type 1, 5, 4% in children less than 5 years and 7% in children > 5 years. Similarly, when assessing the main causes for ESRD, in the population in Johannesburg, FSGS, glomerulonephritis and congenital nephrotic syndrome were the dominant causes in black patients. Reflux nephropathy, autosomal recessive polycystic kidney disease and dysplasia were dominant causes in the white patients. During this time period, patients from KZN, with HUS, were dialysed and subsequently transplanted. Areas where consanguinity is common, hereditary causes are common. One third of Jordanian children have hereditary renal disorders such as congenital nephrotic syndrome and ARPKD. Similarly clusters of Congenital Nephrotic Syndrome are seen in the black population in Southern Africa and ARPKD is noted the Afrikaner population.

V- PROGRESSION AND PATHOPHYSIOLOGY OF CKD

Two morphological processes are involved: Obliteration of the glomerular capillaries due to mesangial expansion and destruction of the extraglomerular interstitium. This involves a number of growth factors, cytokines and hormones. Regardless of the initial insult CKD progresses and the final histological appearance is similar. The natural history of the earlier stages of CKD however is unpredictable.

Most data show a slower progression in patients with congenital renal disorders compared to patients with glomerular diseases. CKD progression is also influenced by non-modifiable mediators such as race, genetics and gender. Puberty regardless of the initial stage of CKD seems to be critical in patients with renal impairment, as there is often then a precipitous decline in function. The kidneys play an important role in homeostasis and endocrine functions.

A- Calcium and phosphorus metabolism

With advancing CKD, secondary hyperparathyroidism develops. With decreasing renal function there is decreased phosphorus excretion and phosphorus retention occurs. Increasing phosphorus suppresses calcitriol production. Decreased calcitriol production causes decreased calcium absorption from the gut and resulting hypocalcemia. Phosphorus retention increases PTH secretion indirectly by lowering ionized calcium levels and reducing renal synthesis of 1,25(OH)2D3, through inhibition of 1α-hydroxylase in the proximal tubules. Increasing PTH stimulates increased bone turnover.

B- Growth failure

Is one of the major obstacles in management of children with CKD, and is long recognised as one of the most profound clinical features in infants and children with the condition. Factors related to growth retardation include, malnutrition form protein and energy deprivation, metabolic acidosis and age at onset and type of primary renal disease.

C- Anemia

Develops frequently during the course of CKD. It is often a predictor of morbidity and mortality, particularly in association with cardiovascular disease. Impaired cognitive dysfunction has been associated with anemia in adults with renal insufficiency.
D- Nutrition
Cachexia, characterised by a loss of lean body mass and high metabolic rate despite an inadequate dietary intake is a common feature. Insulin resistance, metabolic acidosis and increased cytokine expression stimulate muscle protein loss are contributory factors. An inadequate dietary intake has been shown to occur in the majority of children with CKD. This is hampered by the fact that with deteriorating renal function, energy intake declines further.
Energy intake is a vital predictor of growth during infancy, and hence poor nutrition is an important determinant of growth impairment in children with chronic disorders. An energy intake below 80% of the RDA correlates with growth failure in these children.

E- Metabolic acidosis
Overt metabolic acidosis is common in patients with a GFR < 30 ml/min/m². This may result from a number of abnormalities
• Reduction in ammonia synthesis
• Decreased excretion of titratable acid
• Reabsorption of filtered bicarbonate
• Decreased acidification of tubular luminal fluid by distal nephron.
With chronic metabolic acidosis the tubular synthesis of 1,25(OH)2D3 decreases, impacting on calcium, PTH and bone metabolism

F- Clinical manifestations
There are few symptoms and signs of CKD in children. Often the diagnosis is only made in an emergency room due to a complication, such as gastritis, encephalopathy or pericarditis. As a result of the paucity of symptoms many children in developing countries only present in ESRD. Failure to thrive or short stature are important signs in infants and young children.
New onset of enuresis or polyuria, due to ineffective concentration of urine should be investigated. These are often associated with tubulointerstitial disorders or obstructive uropathy.

VI- MANAGING THE CHILD WITH CHRONIC KIDNEY DISEASE
The care of children with chronic kidney disease is complex, and has an increasing emotional, financial burden on the family as the disease progresses.
It is vital for a team approach involving as many disciplines as possible, including nurses, nephrologists, surgeons, social workers, therapists and teachers.
In a developing country this is not always a possibility, and increasingly the majority of care is left to the medical and nursing staff, who tend to most of the patients needs.
The aims in management however are:
- Monitoring GFR and clinical assessment
- Prevention of progression of renal dysfunction
- Management of sequelae, allow for optimal growth and quality of life
- Renal replacement therapy
The patient and family need to be counselled and prepared psychologically for ESRD, dialysis and transplantation. Attitudes and religious beliefs need discussion and are to be respected. With a patient presenting in fulminant ESRD, this is challenging and repeated counselling sessions are required. With increasing education and counselling our parents in our black community are volunteering to donate an organ for a living related transplant.

A- Nutrition
This is one of the major challenges in children with CKD, particularly in a developing country, with patients admitted in malnourished states. Patients with obstructive uropathy require sodium supplements due to ongoing urinary sodium losses. With declining renal function, and oliguria, potassium restriction becomes vital.

Infants struggling with anorexia and nausea, may be aided with a feeding gastrostomy or nasogastric feeds. This requires major education to the caregivers, but has proven to be beneficial where this has been achieved. To ensure continuity of growth and prevent a decline in growth rate or development of a child, children < 6 years should receive 100% of RDA and children > 6 years should receive 80% of RDA.

Minerals such as zinc and iron and water-soluble vitamins should also be given. Avoid hypervitaminosis A, which is a risk in CKD patients, as there is decreased clearance in renal dysfunction. Dietary phosphorus requires restriction, and phosphate binders should be added at meals for phosphate binding.

B- Anemia
The aim in anemia management is to prevent repeated blood transfusions, which will pre-sensitise the patient, and obviously to correct the anemia. Underlying disorders such as folate or iron deficiency require correction. Hyperparathyroidism aggravates the anemia.

Treatment with human recombinant erythropoietin (rHuEPO) is used to correct anemia.

Recommended daily allowance of calories and protein

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>Energy (WHO) kcal/kg/day</th>
<th>Protein (NRC RDA) g/kg/day</th>
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</thead>
<tbody>
<tr>
<td>Infants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.0-0.5</td>
<td>108</td>
<td>1.8</td>
</tr>
<tr>
<td>0.5-1.0</td>
<td>98</td>
<td>1.6</td>
</tr>
<tr>
<td>Children</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-3</td>
<td>102</td>
<td>1.2</td>
</tr>
<tr>
<td>4-6</td>
<td>90</td>
<td>1.1</td>
</tr>
<tr>
<td>7-10</td>
<td>70</td>
<td>1.0</td>
</tr>
<tr>
<td>Males</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11-14</td>
<td>45</td>
<td>1.0</td>
</tr>
<tr>
<td>15-18</td>
<td>55</td>
<td>0.9</td>
</tr>
<tr>
<td>Females</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11-14</td>
<td>47</td>
<td>1.0</td>
</tr>
<tr>
<td>15-18</td>
<td>40</td>
<td>0.9</td>
</tr>
</tbody>
</table>
It may be given subcutaneously, intravenously or intraperitoneally. The half-life is longer if given subcutaneously, and hence a lower dose is required. With administration of rHuEPO, the patient's hemoglobin increases, appetite improves, body iron stores decrease, cognition and quality of life improves. Patients show variability in dosing and response, this may be related to residual renal function, iron stores or ongoing blood losses. Recommended dosage is 50-100u/kg/dose one to three times per week. Dosage is altered upon response. Young children often require a higher dose per kg. Newer erythropoietin preparations with a longer half-life are available, but safety in children has not been assessed yet. A non-response in hemoglobin may be due to several factors:

- Iron deficiency
- Hyperparathyroidism
- Infection/inflammation
- Inappropriately low dose of rHuEPO

Iron deficiency requires correction, and maintenance iron should be continued to maintain adequate hematopoeiesis. If not tolerated orally, iron may be given intravenously.

The target hemoglobin as recommended by KDOQI is 11g/dl and hematocrit 33-36%. In patients with an intercurrent infection the dosage should be increased by 25%. Complications of rHuEPO include hypertension and hyperkalemia.

### C- Renal osteodystrophy

The aim is to achieve normal bone growth and mineralisation, and avoiding hyperphosphatemia, hypocalcemia and hyperparathyroidism. Treatment includes phosphate restriction, phosphate binders, calcium supplements and vitamin D analogues. The first step in managing hyperphosphatemia is in limiting dietary phosphate. Oral binding agents such as calcium carbonate or acetate are given at mealtimes to bind intestinal phosphate: 200-500mg elemental calcium/meal.

It is important for hyperphosphatemia to be corrected before a vitamin D analogue is added, to avoid an increased calcium phosphate product.

### D- Growth retardation

Linear growth should be assessed regularly, with the aim of achieving the patient's genetic potential.

- Acid-base disturbances require correction.
- Patients serum bicarbonate level should be maintained over 22mmol/l to decrease excess protein catabolism and prevent bone disease.
- Oral alkali salts, containing citrate may be beneficial.
- Careful attention to managing bone disease is required.

In the developed world human growth hormone is given, but in our setting and in most developing countries this is not an option.

### E- Minimising further renal injury

Interventions, commenced in earlier stages of CKD, to prevent renal nephron loss and deterioration in renal function have shown some effect in the adult population. These include ACE inhibitor therapy to decrease intraglomerular pressure and so minimise proteinuria and regulate hypertension. Control of infections, such as managing UTI's and dysfunctional voiding is part of...
ongoing care. It is also imperative to avoid further nephrotoxic injury with over the counter and
prescribed medication.
Dosages should be altered accordingly, for level of renal dysfunction and parents should be warned
against NSAID. Similarly, it is prudent to warn parents to stop ACE inhibitors, should their children
develop any diarrhoea or vomiting.

VII- PLANNING FOR DIALYSIS AND TRANSPLANTATION
This is a difficult and emotional issue for the parents and the patient, and discussions should be
commenced early, indicating this is the endpoint. Renal replacement therapy is commenced when
the GFR is <15ml/min/m2. An earlier start of renal replacement therapy may be warranted if there
is severe growth impairment, or developmental delay.
The modality of dialysis should be tailored to the needs of the patient, but this may not always be
available or practical. It depends what is available locally or what one is experienced with. Where
possible a pre-emptive transplant may be planned, if a parent or relative is a suitable match and
healthy donor.
Where resources for RRT are not available, careful counselling is required, and conservative
management and palliative care is given.

VIII- CONCLUSION
The management of children with CKD, through all the various stages is complex, frustrating
challenging but extremely rewarding. Children, particularly adolescents require vigilant care, due
to their marked changes in development and maturation occurring at the time.
With meticulous care and dedication it can be done, despite not having infrastructure available
in the first world. As paediatricians in a developing world we should endeavour to cope with the
challenges of CKD.
Even-though, we may not be equipped to deliver renal replacement therapy, it is important to start
recognising the patients with CKD, in all stages. It is only once this is done, that the true impact of
this disease and its challenges can be identified globally.

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CHAPTER 28

II- ISSUES AND CHALLENGES OF THE MANAGEMENT OF CHRONIC KIDNEY DISEASE IN AFRICA

Amal Bourquia, Casablanca - Morocco
I- INTRODUCTION
African countries are developing or poor countries with many important socio-economic problems associated with such limited financial resources, a high illiteracy rate, a health coverage problem and the difficulties in accessing information. This lack of resources pushes families to resort to alternative solutions and discouraging for regular monitoring.

The main health problems in Africa are still represented by infectious diseases such as: AIDS, tuberculosis, malaria, gastroenteritis, as she faces the most chronic diseases emerging as Chronic Kidney Disease (CKD).

A situation that leads to many medical problems. A situation that leads to many medical problems. Because of its medical, social and economic consequences, the treatment of chronic renal failure is a medical problem more acute in Africa as the rise of alternative therapies in renal function remains closely links socioeconomic conditions and health strategies of each country. As what is happening in the world, the management of CKD in Africa could not remain limited to periodic hemodialysis. The development of kidney transplant has therefore emerged as an obvious complementary solution initiates in some countries such as South Africa, Tunisia, Morocco and Algeria.

II- EPIDEMIOLOGICAL DATA
A- Incidence
There is no data on the true incidence and prevalence of CKD in African children. There is a lack of information about valid epidemiology, although children with CKD represent a minority of the total child population. However it can be argued that in these countries:

- The prevalence of CKD is underestimated and should be higher than in developed countries,
- A low prevalence of children with CKD is treated in these countries so that about 90% of dialysis patients from developed countries who can afford the cost of renal replacement therapy (RRT).

B- What are the causes of CKD in Africa?
The lack of national registers does not give accurate statistics, as we advance some estimates based on single center studies with large regional disparities.

Chronic glomerulonephritis (CNG) is the leading cause of CKD (30-60%) in different countries, it is more common in Africa and appears more severe than in the West. Moreover, the kidney problem represents 2-3% of medical admissions in tropical countries, the majority being of GN. The format is the nephrotic syndrome, which appears to the age of 5 to 8 years. But often the etiology of IR remains undetermined.

III- STATE SUPPORT OF THE CKD
A- What is the status of support for the CKD?
Huge disparities exist and continue to exist between patients according to their socio-economic level and the profit or not for a health coverage. However, the majority of supported rest incomplete and does not satisfied the quality required by dialysis: insufficient number of sessions, no support for drugs or balance sheets and especially the non-inclusion of kidney transplant the register of care. Many problems limit access to transplantation, including inadequate funds allocated. A
national reflection of each country, with the involvement of all stakeholders is needed to optimize spending and draw a strategy for the future where kidney transplant would see as a necessary alternative.

The results of the treatment of children with CKD are dependent on the economy and the availability of health care resources. Give a TRR is difficult in developing countries and access to this therapy is blocked by financial problems and limited resources. This is inherent:
- At national income insufficient to cover basic needs: low GDP and low health expenditure.
- Health officials little or no awareness of this problem and the existence of two-tier health care system with care abroad for those who can afford it.
- Is not a priority for the planners of health care.
- Some African countries are making efforts to establish programs.
- specialized infrastructure deficits, in facilities and human resources. There are few hospitals dedicated to children, and little or no unit for the treatment of kidney disease in children. With a shortage of pediatricians and greater NP.
- Children who live far from big cities do not have access to a nephrology care.

**B- Prognosis IRC**

This situation makes the IRC poor prognosis generated by
- delayed diagnosis inherent to the ignorance, the poverty and the remoteness.
- The lack of use of conservative measures. Adjuvant treatment often unavailable and expensive.
- The reference of patients at later stages: 25-65% in the terminal stage of IR with many complications.
- The support or lack retardation generates medical problems and facts in this context, 75-85% of children with ESRD are denied their right to TRR.

When hemodialysis is possible it prolongs life in poor conditions:
- Frequency of infections, malnutrition, iron deficiency, vitamin D.
- Inadequate Support (anemia, short stature, bone involvement).
- Frequent hospitalization causing increased expenses.
- School failure, depression, major handicap.
- Poor compliance sometimes leading to discontinuation of treatment.
- Mortality is high and the survival rate is low.

It runs very difficult for the child and family, often ends in death and generates negative affective psychological effects.

**C- What to do?**

There is an urgent action with responsibility.

IRC is a medical problem, devastating economic and social for patients and their families. High cost of alternative means of renal function: a huge burden on health budgets. Importance of a comprehensive vision, organized and pragmatic IRC by acting on several fronts:
- Strengthening and extension of the offer in dialysis.
• Development of transplant activity.
• Prevention and Screening.

Importance of developing NP units that have the essential role:

1- Optimizing the quality of care
• It allows early identification of the CKD before the complications that result in additional costs to ensure proper monitoring and help families.
• Ensure effective HD to all patients: 3 sessions / week, support for paraclinical explorations and accessibility to essential drugs on dialysis.
• Adapt to our therapeutic context and Work to reduce the cost of dialysis: cancel taxes on equipment, consumables, dialysis medications.

2- Development of the TR from living donor
Over the years, renal transplantation has emerged as the most effective treatment in case of irreversible deterioration of renal function. It not only saves and prolongs life, but it also improves the quality of the latter. TR is the treatment of choice for children with CKD in countries where the treatment of ESRD is available. It is therefore essential to convince officials that the TR is much cheaper that prolonged dialysis, in addition to the huge advantage in terms of quality of life. The rise of kidney transplant has raised many ethical issues making it appear complex and ambivalent in its philosophical basis, social, legal and medical practice.

IV- KIDNEY TRANSPLANTATION

A- transplantation a social issue
The organ transplantation is surrounded by a set of cultural representations around the perception of the body, giving and death. Also, is it necessary that citizens are not excluded from the debate, which should not be confiscated by experts. In an attempt to assess the perception of the donation and transplantation of organs by the Moroccan population, we conducted an opinion poll. The main results of this survey show an overall positive attitude vis-à-vis the donation and organ transplantation, despite the lack of knowledge of the subject. The survey reveals the lack of information on the practice of kidney transplantation in Morocco, ignorance of the techniques used and the types of donors, the absence of any information on legislation, the first of the rare topic in the discussions, erroneous beliefs as well as vis-à-vis fears of possible insecurity of the art.

Diffusion in a simple and accessible information, as well as the involvement of the Moroccan population in general and the medical community in particular is becoming a pressing need.

Religious confessions, are now agreed not to oppose the donation and the removal of organs and the renal transplant has made tremendous progress in recent years. In Africa, we have to engage in dialogue between religious, medical professionals, managers and all social actors to jointly explore attitudes to adopt.

B- Ethics and gift
The answers to the different ethical issues raised by the kidney transplant, which may vary depending on the companies involved to take account of a given society, its rules and its feelings. Several ethical aspects to consider.
1- Living Donor

- Informed consent and freedom to give
Consent must be expressed freely and without influence or pressure. The practitioner must be vigilant about possible constraints and entourage pressures. Consent is informed when the subject has received all the necessary information to understand the issues of the gift. Free and informed consent is an ethical principle which implies a duty of information to the donor can decide with full knowledge of the facts.

- Right to dispose of her body
Legal measures governing the transplant from living donor considerably limit the freedom to dispose of her body, since, under the law, the gift may be granted only for the benefit of specific individuals. The donor can freely dispose of his body. These laws are made to counter the financial benefits. Thus, the kidney donation, justified by family solidarity, initially private matter becomes public action protected by law against any commercial transaction.

- Psychological Lived in renal transplant
The donation from a living related donor can cause real psychological and relational changes. The donor can live a great anxiety before surgery because of the risks involved and declare a depression with the feeling of losing a part of yourself. It is important not to forget the disadvantage of the scar, especially among women in our societies.

Living donor, a social choice
The use of living donors has great disparity between countries. The results with the grafts from living donors are higher than those of the original cadaveric grafts, both for patient survival than those plugins. The living donor can become the choice of our company and all of our people should support.

2- Brain-dead donor
Regarding the brain-dead donor, it is important to consider the beliefs and the cultural and social diversity of individuals. Respect for the remains is a feeling deep in every culture. The apprehension of what is brain death is a social problem that can delay or even prevent the development of transplantation from deceased subjects in our countries. This decision is even more difficult to take that maintaining artificial organ function does not encourage the acceptance of death.

- The provisions of the law
In all societies, the legislator has always tried to establish a protective framework for the human person and avoid slippage. The dissemination of information to the wider public registry must allow any citizen to vote for or against the gift in his lifetime, and so make it easier for relatives and sampling teams.

3- Deny business of kidney
The human body is priceless and cannot be subject to financial transactions. A free trade in human body parts would be degrading and morally indefensible. The WHO recommends that the human body and its parts do not at any time the subject of commercial transactions. The delay in the development of this therapy is that our fellow citizens renal impairment trying to look for solutions elsewhere, even in the organ trade. This activity puts doctors before an ethical problem.
V- PREVENTIVE MEASURES

It is important to work urgently to reduce this burden:

- Screening in primary health care to reduce the incidence of CKD: early treatment of infectious diseases and fight against tropical diseases and healers.
- Development of simple preventive measures: use of the test strip, BP measurement.
- Treatment of escalators IRC: hypertension, proteinuria, other factors (anemia, hypoalbuminemia.)

A- Awareness and practitioners training

- Ongoing training of pediatricians and general practitioners NP and include them in these actions (early diagnosis of UTI, screening for malformations uropathies ...). Training meetings: Identify specific problems
- and initiate appropriate strategies.
- Develop cooperation between different specialists involved in the care of the CKD.
- Initiate epidemiological research projects in NP for strategies adapted to African countries and to encourage international cooperation .

B- Awareness of public authorities

- Departments to address the socio-economic problems and appropriate strategies.
- Collaboration with existing associations, media ...
- Assess the distribution of resources between regions and between the different modalities of treatment.
- Monitor the development of CKD treated and forecast needs.
- Adequate information of the population to improve the problems associated with delayed diagnosis, compliance, distance and cultural habits.
- Ethically: unequal access depending on the social level.

For reflection!

This affection raises problems for both humans and professionals:

- The difficulties faced by parents of children with CKD to heal, confer on this problem a powerful emotional charge.
- Health policies are in a dilemma, and often in opposition to our moral and cultural references.
- Kidney transplantation challenges the society in all its components.
- In human terms: children affected by renal disease exist independently of NP services. These children with kidney disease represent a minority in our society which its value is directly related to the way on how to treat its minorities.

References


Many children with kidney disease do not receive adequate medical care. There is a critical shortage of pediatric nephrologists (NP) and resources in several African countries. In Egypt, there is a NP for 500,000 children in Nigeria, a NP 4.5 million children in Morocco when we have no pediatric nephrologists in many countries. Due to limited resources in these areas, most hospitals are not equipped with dialysis equipment. For better quality of care for African children with kidney disease, it is essential to promote pediatric nephrology (NP) in Africa. Which implies the creation of a NP unit managed by competent doctors in their field. Thus, it would allow children with kidney disease to have support provided by specialists in NP instead of general pediatricians or treating nephrologists usually adult patients.

South Africa
Most universities in South Africa have very active NP service. These services include consultation activities and therapies for dialysis and renal transplant (RT), and sometimes a clinical research program (Cape town, Johannesburg and Durban). Despite efforts, chronic kidney disease (CKD) is not a priority for health officials in South Africa, and this is especially true for children. Infectious diseases such as HIV and TB have a much more important status as a major cause of morbidity and mortality. The reality is that very few children with End-stage kidney disease (ESRD) have access to dialysis or kidney transplantation. As in most of our countries, so it is imperative that all health care professionals should be vigilant in identifying children with underlying kidney disease and institute preventive treatment to slow the progression of the disease to ESRD. The number of pediatric nephrologists is insufficient in light of the high infant population.

Algeria
It is always difficult to report with clarity the situation of pediatric nephrology in Algeria without having reliable and comprehensive statistics. Which is, unfortunately, the case. As a hospital practitioner, I can only talk about nephrology witnessed in the hospital. It is clear now that the pediatric specialties are well advanced. Nephrology is among them. Advances: pediatricians get gradually interested, since each service is identified in a reference. Patients are increasingly diagnosed, treated and monitored in specialized consultation. There is collaboration between pediatricians and adult nephrologists. ESRD patients are dialyzed (hemodialysis or peritoneal dialysis) in adult nephrology and then transferred to a pediatric monitoring. Collaboration with surgeons is provided (case discussion and interventions programming ...). Training courses are still run even though they are still insufficient. Nuclear medicine services are available in 3 university hospital centers. What is still lacking: the management of children with kidney diseases problems is still carried out for most cases in general pediatrics services. Peritoneal dialysis is the privilege of adults. Although in a center in Oran, it is made in pediatrics. Hemodialysis is exclusively made in adult nephrology, which obviously poses many constraints for children. Renal biopsy is also done in adults. Reading remains problematic. In Algiers, there is one person who does the immunofluorescence survey. The uropathies are still diagnosed after a urinary tract infection. Their management is performed but with some delay. Prenatal diagnosis is ensured only by some centers. It is not yet effective.
Benin

NP in Benin, as in many countries in Sub-Saharan Africa is still in its infancy. It is characterized by tiny human resources: two pediatric nephrologists to ten million inhabitants, a third about to install. There is a lack of infrastructure and services are drowned in the general pediatric services. In addition to a lack of material resources and care equipment there are no HD and the beginning of DP for two years. Renal biopsy is theoretically possible but pathological examination is very difficult. There is no support for program of Chronic renal failure (CRF). The outlook is the training of human resources, research funding for equipment and services the organization of services for optimal care.

Burkina Faso

The NP is almost non-existent as a full specialty. Kidney diseases in children are supported in the general pediatric services with the assistance of adult nephrologists in some cases. These adult nephrologists are only two at the moment for the country, one holds an DIU diploma of NP but the workload is such that it is difficult to care for children. NP training pediatrician with the ambition to be able to implement a medium-term NP unit at University Hospital Pediatric Charles-De-Gaulle Ouagadougou, which will be a center of reference and management of kidney diseases of children in Burkina Faso.

Cameroon

Cameroon is a vast country of over 20 millions people with 40.5% of children aged from 0 to 14 years. Pediatric Nephrology began to emerge in 2005 with the creation of a pediatric nephrology unit at Mère et Enfant Centre (CME) of the Chantal Biya Foundation. From 2006 to 2008, every Tuesday afternoon, I monitored some adult nephrology consultations at General de Yaounde Hospital. It is in 2010, after Marrakech IPNA congress, that I saw the big difference between the adult nephrology and pediatric nephrology. In 2011, I had training in pediatric nephrology for a year in Lyon, sanctioned of an DIU diploma in pediatric nephrology. Currently, three pediatricians are trained in pediatric nephrology, one is still in France and the other is at the end of training in Pediatrics in Cameroon. The Department of Nephrology CME increasingly receives cases either from private consultations or other hospitals. In 2011, an educational talk with parents, friends and kidney patients took place in the CME hospital training. In 2013, the kidney week lasted 3 days. The first day was devoted to the kidney disease screening by dipstick and to taking children’s blood pressure. The second day focused on an educational talk with parents, friends and kidney patient. The third day was purely pediatric devoted solely to pediatric nephrology with four themes outlined as follows: Children’s urinary infection, malarial hemoglobinuria, children’s blood pressure and finally acute kidney failure in children. Nowadays, nephrology is rapidly emerging; however, we should lay out an appropriate room with tiled floors and walls with storage closet and adjacent bathroom. Pediatric surgeons as well as medical and nursing staff should be trained on the placement of peritoneal dialysis catheters and on peritoneal dialysis.
Central African Republic
There is no adult as well as pediatric dialysis business, and no support for children with kidney disease. The material difficulties and the political situation worsen considerably the situation of these children, who die from lack of care. The country faces huge challenges at various levels.

Demographic Republic of Congo
Towards the 80s there has been the creation of the unit NP Cliniques Universitaires de Kinshasa (CUK) by Professor Prosper BINDA first NP in black Africa, formed in KUL Belgium. Reactivation in 2001, the Unit’s activities with a new team overseen by an NP formed in Paris. The unit of NP CUK, is the only service organized in DR Congo, which supports kidney disease of children from different cities across the country. It has eight hospital beds. The activities are consultations about 80 per month, hospitalizations with an average monthly occupation of 85% of the beds in the RFP and acute renal biopsy in collaboration with the adult nephrology pathology and anatomy of Service of CUK. Research areas include: kidney and sickle cell anemia, kidney and HIV infection, kidney and heart disease and kidney and malaria. The future we hope to develop a great activity dialysis (PD and HD) and create a large national network of care for kidney disease with the formation of at least three experts in each field of research.

Ivory cost
The first hemodialysis center, established in 1988 in Ivory Coast, has allowed to manage chronic renal failure in adults, but due to lack of adequate equipment and trained staff, the children did not benefit from this structure’s care. Indeed, until the opening of the pediatric nephrology unit in December 2008 (ten years later), children under 5 years with renal insufficiency (RI) and responding poorly to the proposed medical treatment, evolved inexorably towards death, if they were not quickly transferred to specialized centers in the West, South Africa or North Africa, for renal replacement. Pediatric Nephrology unfortunately did not exist in West Africa, or even in Black Africa. Some older children have benefited from hemodialysis, but because of inadequate management, statistics have shown that survival after two years was not possible.

For these reasons, it was imperative to create a pediatric nephrology unit to screen early and treat appropriately all kidney diseases of children, especially those that can be induced by common infections such as malaria, sickle cell anemia or simple diarrhea. Pediatric Nephrology unit is the only specialized center treating kidney disease in children in the country. Pediatric services can provide support for common renal diseases such as nephrotic syndrome or glomerulonephritis, but in case of complications or renal replacement therapy, patients are referred to the pediatric nephrology unit of Yopougon University Hospital which has existed for 5 years so far.
Egypt

Egypt undoubtedly has the largest number of pediatric nephrologists in the Arab world, and the number of members of the Egyptian Society of Pediatric Nephrology and Transplantation (ESPNT) has exceeded 100 this year (112). The ESPNT meets regularly every April for its annual meeting and in 2010 the eleventh annual meeting was held during the last week of April 2010, and was attended by most of the members of the society as well as by many general pediatricians. Due to the revolution, this year’s meeting was postponed to a later date. The ESPNT publishes two issues of its Journal, GEGET, per year, which contains original articles by Egyptian pediatric nephrologists (editor: Dr. Hesham Safouh). There are at least four smaller scientific meetings held by ESPNT in different cities every year in addition to the major annual meeting every April, targeting a specific issue in pediatric nephrology. There are several difficulties with pediatric nephrology services in Egypt such as the lack of disease registries, lack of long term PD and cadaveric transplantation in Egypt, limited support by the government for procedures like LRD renal transplantation and the very high cost of drugs required for such a service, dependence on donations from individuals and NGOs to provide for such financial needs, some resistance by families to LRD transplantation. A large percent of ESRD patients present late with unknown causes for their disease, concern about environmental pollution as a contributing factor, excessive use of nephrotoxic antibiotics / drugs by GPs, high cost of labs needed to reach a precise diagnosis in many renal diseases, and inability of the patients to afford the cost of such lab tests.

Ethiopia

Ethiopia is one of the Horn of African Countries with a population of 85 million people. The second populous country in Africa. The Ethiopian people are young. 43% of the population is under fifteen years of age and about 49% are under 25 years of age. Though population based studies are not conducted many cases of acute and chronic kidney diseases are expected. Studies in our teaching hospital show that the commonest cause of acute kidney injury is hemolytic uremic syndrome and the commonest causes of chronic kidney disease are congenital urogenital anomalies. Tikur Anbassa Hospital which is known as Black Lion Hospital is a tertiary university hospital which is responsible to take care of all referred cases from all over Ethiopia. We have a follow up clinic in our referral hospital to take care of all referred patients from all over the country. There is adult hemodialysis center in this hospital but pediatric hemodialysis is on the process of development. Peritoneal dialysis is done only is this hospital for pediatric patients. There are many adult hemodialysis centers in the private health institutions but do not give service to pediatric patients. There is only one pediatric nephrologists in the public sector in the country who is only me. General pediatricians handle pediatric patients with nephrology problems in other public and private institutions in the country. We are trying to twin our institution with other developed renal centers to upgrade our renal unit.

Gabon

There is an HD adult center while NP is still nonexistent. Children with kidney disease are supported by general practitioners or pediatricians GPs. Efforts are needed to help these children.
Guinea Bissau / Equatorial Guinea / Guinea Conakry

The NP is still non-existent in Guinea and as is the case in many sub-Saharan countries in particular, children with kidney disease are supported by general practitioners or pediatricians GPs. These may seek advice from the nephrologist adults are also very rare and only the CHU. Efforts are needed to help these children. There are not yet even dialysis for adults in Guinea Bissau and limited supply in HD in other Guineas.

Libya

Libya is an African country in the Maghreb region of North Africa. It is the fourth largest country in Africa by area, and the 17th largest in the world. The largest city, Tripoli (the capital of Libya), is home to 1.7 million of Libya’s 6.4 million people. There are three pediatric nephrology centers in Libya (Tripoli Children Hospital, Tripoli medical center and Benghazi children hospital). Nearly 12 nephrologists distributed in these units to cover all the country. In my unit in Tripoli we have 10 beds and 6 Hemodialysis machines, with good experience on peritoneal dialysis. The most common causes of CKD in Libya are obstructive nephropathy more than 50% of them due to Posterior urethral valve (study done on Libyan children on 2010). Renal stones and hyperoxaluria also common in Montanans places which may be due increase consangius marriage in these places.

Mali

The hospital prevalence of kidney disease in children is not well known in the country as elsewhere in sub-Saharan Africa. Renal failure remains a major public health problem. Only nephrology and hemodialysis service of G Point provides support for kidney disease in both adults and children. Replacement therapy technique of the renal function that is used is hemodialysis with 60 offices available across the country and only in adults. G Point in UHC has thirty offices. Hemodialysis is realized only in Bamako, the capital of the country. ESRD management in children remains a major challenge that we intend to face within the shortest time, by opening a pediatric nephrology unit at the G point in UHC with a peritoneal dialysis center (PD). This replacement therapy technique called the ‘PD’ will allow us to extend ESRD management in other areas, both in children and adults in the coming years. The establishment of this center will require significant human and financial equipment investment. The actors involved in the organization and realization of this PD center, as a gateway to the pediatric dialysis, are the Ministry of Health, G Point hospital administration, the technical and financial partners of the Ministry of Health and G Point in UHC. For the moment, Mali pediatric nephrology is at the planning stage, in which the implementation will depend on the willingness of different actors involved.
Morrocco

Morocco has nearly 32 million inhabitants, with a percentage of young people under 15 years of 30% (2003), about 10 million. In our country, the pediatric nephrology is not among health priorities. There are still no national statistics in clinical nephrology. However, many indicators, gathered from the personal exercise of this specialty for over 30 years, allow to argue that the incidence of renal disease in the Moroccan child is at least equal, if not higher than the one found in Western countries and this is due to many reasons:

- The frequency of cutaneous and nasopharyngeal infections can be complicated by glomerulonephritis (GN), although their number has decreased;
- The possibility of prenatal diagnosis limited by the small percentage of pregnancies follow-up, especially in the countryside, causing a delayed treatment of these pathologies (frequency of severe and complicated forms);
- The frequency of urinary tract infections often neglected, and specific diseases such as gallstones;
- The frequency of hereditary kidney disease favored by consanguineous marriages, in which the diagnosis is often difficult to determine due to access to certain explorations.
- Screening and genetic counseling is blocked by the lack of information and a priori social;
- Problems related to the use of toxic chemicals, particularly in the context of traditional medicine-“Takaout, Harmel, Addad” and many other plants and decoctions.

The causes of acute uremia in the Moroccan children are dominated by acute glomerulo-nephritis (50%), infectious diseases, followed by hemolytic uremic syndrome (15%) and renal hypoperfusion (10%), while in over 10% of cases, no etiology is found. The delay in diagnosis and remote health centers make these children arrive in critical conditions requiring urgent care, but many of them cannot be treated. Some educational measures can avoid the occurrence of some cases but it is essential to develop the PD in all cities, a simple and effective method to avoid the ARF stage. The causes of chronic renal failure are dominated by chronic glomerulonephritis followed by complex uropathy malformations, diagnosed and managed late.

Mauritania

The first nephrology and hemodialysis service was established in 1996 in Nouakchott Hospital Center. At that time, it used to be the only dialysis center in Mauritania, a hospital service with 8 beds with initially 10 machines in the center. In 2006, this capacity increased to 20 machines. Since then, several hemodialysis centers were set up in our country, two hemodialysis private clinics, several dialysis centers in Nouakchott hospitals (Military Hospital, Sheikh Zaed Hospital, l’Amiétié Hospital) and since 2010 within the country (Nema Ayun, Nouadhibou, Kiffa). Unfortunately, we have so far a few nephrologists (4 nephrologists, 2 internists with nephrology option), outside UHCN, all other centers are managed by GPs dialyzers. We have recently made an extension and renovation of nephrology and hemodialysis service with a capacity of 16 beds and the center with a capacity of 25 machines. Dialysis in Mauritania is supported by the state to 100% for indigent patients and those with health insurance. Renal biopsy has started for just 4 months due to an anatomical pathologist problem; we send biopsies to Casablanca waiting to send a pathologist trained in kidney. We also take care of the monitoring and the management of Mauritanians
transplant patients. The first Mauritanian Society of Nephrology has been set up for no less than a year (SOMANEPH). With our new medicine faculty dating from 7 years and the government involvement beginning to regard the CRD as a public health problem, we hope to develop this specialty in our country very soon.

Niger
Hospital prevalence of kidney diseases in children remains unclear as Sub-Saharan Africa and the Chronic renal failure (CRF) remains a major public health problem. Adult nephrology with dialysis is available with few resources and does not cover all needs. The management of children with renal disease remains highly problematic. Training and project initiation NP are discussed.

Nigeria
Nigeria is a large country with a large child population and less than 20 pediatric nephrologists to support these children. These practitioners are facing significant demand compounded by the delay in diagnosis, illiteracy and lacked resources. About 7.5 children per million children per year reach the end-stage renal disease (ESRD). There dialysis centers adult and no pediatric dialysis. The RFP is available only for children in acute situations, not in the country. Many difficulties impede the treatment of chronic DP. Patients with parents who have the means to treat their child traveling in the West.

Republic of the Congo
The NP is still nonexistent in Congo. Nephropathy children are supported by general pediatricians. These may seek advice from the adult nephrologist who is also the only one in the university hospitals and throughout the republic currently pending the receipt of other doctors who are in the process of specializing in nephrology abroad. However, a glimmer of hope since there remains an under construction dialysis center at the University Hospital of Brazzaville; which may partly solve some problems. Furthermore two young pediatricians will leave form in NP.

Senegal
General pediatrics is developed in Senegal. At least, we have three level 3 pediatrics services in Dakar. Pediatricians, who are university professors, are at least 14 in number including nutritionists, neonatologists, pulmonologists, cardiology, hematologists, oncologists, endocrinologists, pediatric surgeons, and a pediatric nephrologist with a pediatric oncology trend. For over a decade, the pediatric nephrology has been muzzled (no thesis, no published articles.) Before, some theses and monographs had been published tackling nephrosis, acute glomerulonephritis, urinary tract infection, hemolytic uremic syndrome, enuresis and renal biopsy. Many prevention policies, aiming at reducing morbidity and mortality in children, are developed by the Ministry of Health but they do not specifically relate to kidney disease in children. This may be explained by the lack of epidemiological data on children renal disease that can guide the ministry’s actions. Compared to the adult nephrology, pediatric nephrology is delayed of about twenty years. Hemodialysis has existed since the 80s and peritoneal dialysis for more than ten years. Many prevention and
management policies of Chronic kidney failure, Hypertension, Diabetes and ARF particularly those of perfume post are functional in Senegal. For this purpose, hemodialysis centers are open in three rural areas. Children kidney disease is frequent 1.2% (85 case/6994) hospitalizations (2010 thesis). It should be noted that since 2009, the renal biopsy and the reading by the optical microscope and immunofluorescence have been available on site. Infectious glomerular and nephrosis seem to be the most identified causes. Renal failure prevalence is not well known. There is no peritoneal dialysis unit (PD) for children. We had two DP children cases where peritoneal catheters were placed by urologists. Fortunately, adult nephrology provides assistance to children from time to time especially for acute hemodialysis and sometimes chronic hemodialysis. Currently, the kidney transplantation project is well underway awaiting vote by the law parliamentarians allowing organ donation in Senegal. We are currently house physicians who are interested in pediatric nephrology. There are no pediatric dialysis technicians. The setting up of a pediatric nephrology unit could be an early solution to the management of kidney disease in children. This could foster epidemiological studies, the training of students, kidney disease management and finally the full participation in renal transplantation in children.

**Togo & Tchad**

Two countries that each have an adult hemodialysis center with many difficulties to support all adult patients. No structure of NP and no doctors trained in this area.
CHAPTER 30

PROPOSAL TO CONTRIBUTE IN THE DEVELOPMENT OF PEDIATRIC NEPHROLOGY IN AFRICA PARTICULARLY IN FRENCH SPEAKING COUNTRIES

Amal Bourquia, Casablanca - Morocco
I- INTRODUCTION
The recent years have witnessed a growing demand for specialized care for kidney disease and this has been noticed even in African countries with limited resources. However, Africa is a special continent whose functioning is almost split into the French and English speaking countries, which greatly complicates the cooperation between us. Among the 54 African states, 31 are French-speaking with 21 countries having French as their first language, that is more half of the African population. On the other hand, the sub-Saharan countries have very low income, very few resources and often with lack of health insurance system.

The various meetings and discussions highlight common challenges in PN:
- Big problem of access to medicines, unreliable sources of manufacture, trafficking
- An increase of antibiotic resistance as a result of uncontrolled use;
- No access to some important drugs, including PN.
- Technical and logistical problems such as limited access to renal biopsy, often no needles and no pathologist.

In the majority of countries most children are first processed by traditional means (herbs, decoctions, scarification). The majority of children with kidney disease do not receive adequate medical care. Secondary care is provided by general practitioners and pediatricians sometimes when it exists. Resources are more limited for tertiary care. There is also a critical shortage of pediatric nephrologists and resources in several African countries. PN generally has no place and there is 0-5 nephrologists pediatricians country. Most hospitals are not equipped with facilities for dialysis due to limited resources in these regions.

To improve the quality of care for African children with kidney disease, it is essential to promote pediatric nephrology (NP) on our continent. Thus, it would allow small patients to benefit from care provided by specialists in NP instead of general pediatricians or treating nephrologists usually adult patients.

II- THE POLITICAL WILL AS ESSENTIAL PRIORITY
The first step is to approach policy makers to raise awareness. In African countries, decisions are usually taken by previously sensitized officials, convinced and interested. The development of pediatrics in any country whatsoever, requiring specialized units managed by competent doctors in their field, involves the creation of a PN unit. The head of the unit -or a personality recognized throughout the country- needs to communicate with policy makers and convince them of the value to bring to the pediatric nephrology. Among the ways to stimulate this interest include the drafting of a report –which can be coordinated with IPNA- that highlights the importance of creating at least one PN unit. The introduction of the pediatric specialized structure in a university hospital, in addition it enables provide effective care to many sick children, is an area where medical students will be trained at all levels related to kidney disease, the same time as an opportunity to launch research programs relating thereto.
III- CONTRIBUTION OF PN

A- Role of PN units
NP structure allows to handle severe kidney problems such as:
• All children’s kidney damage before the stage of renal failure: glomerular disease (nephrotic and nephritic syndrome), vascular and tubulointerstitial;
• Some common diseases, such as different types of urinary tract infections and other urinary tract symptoms, provided that this discipline also ensures medical care for stones and several kinds of abnormalities of the urinary tract;
• high blood pressure management, the main cause in children is nephrology character;
• The acute renal failure (ARF) and its many etiologies;
• Chronic renal failure with the introduction of a dialysis program and purely pediatric transplantation;
• Several kidney disease, genetic, requiring the intervention of the PN for their diagnosis and treatment.

B- Transverse Activities of PN
Pediatricians nephrologists can work with other specialists to help improve the care of children. For example:
• The management of uropathy, in collaboration with pediatricians and urologists;
• Their involvement in hematology-oncology, knowing that several drugs used in this specialty can cause toxicity in the kidneys;
• Intensive care, many patients being hospitalized for kidney failure, electrolyte disturbances and problems related to blood pressure;
• Several infectious diseases (common in Africa) and other conditions causing renal complications, pediatricians nephrologists also involved in the general pediatric services, emergencies and neonatology;
• The uropathy malformations diagnosed before birth by providing care before and after birth.

IV- PROPOSALS TO DEVELOP PN IN AFRICA
In African countries, the situation of the PN can probably be improved. This is based on some specific directions more or less dependent on the socio-economic development of the country. We have to work to improve the treatment of kidney disease in African children and adapt advanced therapies to our context and our means. Similarly, the development of any treatment program must take account of local circumstances.

A- ARF Management
Managing ARF has never been regarded as a major priority in Africa as it should be treated like any other therapeutic emergency. An unacceptable situation, and the development of peritoneal dialysis (PD) and its accessibility to a large part of the African pediatric population contribute to solve this problem. It must be our main goal. Thus, international cooperation are in the process of being born, including several partners including SKCF, which has already started its cooperation in Benin, the IPNA, ISN ... A broader program including other countries should be implemented as of
2014. It is obvious that instability in some countries severely limits this cooperation.

Some solutions adapted to each state should be proposed. The most important is to work for PD development. Thus, with regard to countries that have the PD, efforts should focus on:

- Enhancing in-house training of pediatric nephrologists, surgeons, pediatricians, intensive care practitioners and nursing staff.
- Facilitating access to all PD material: pouches, cycler, catheters (proper storage), and adaptation to local infrastructure.
- Developing exchange practices regarding local facilities and adjusting technical problems.
- Developing better connections with health authorities.

2- With regard to countries that have not yet launched PD,

- Fostering the international aid program, and benefiting from the experience of those who are familiar with the PD.

For countries that have not yet started PD, it’s necessary to promote international aid program, and benefit from the experience of those who are familiar with the PD. Our challenge is to provide acute PD for all African children in need and save lives threatened by the IRA.

**B- Developing prevention and awareness**

It is very difficult to implement support programs of CRF in our country, as it is interesting to work upstream. Measurements of screening and prevention are to implement as soon as possible to try to reduce the number of preventable cases kidney failure. Our nephrologists African pediatricians are also called to be closer to the people to help raise awareness for the large number of illiterates in our country and the many shortcomings of health systems. This involvement in civil society has allowed some NP units to develop. These preventive measures include:

- the treatment of infectious diseases such as angina, which could help reduce the number of infectious glomerulonephritis post.
- The simple preventive measures: use of the test strip, measuring blood pressure, early treatment of infections, as well as curative measures simply managing urinary tract infections, acute nephritic syndrome and some forms of preventable CRF.
- Adequate public information to improve the problems associated with delayed diagnosis, compliance, distance and cultural habits.
- Antenatal diagnosis is still very limited by the quality of the monitoring of pregnancies and the cultural or religious denial of medical termination of pregnancy.
- The basic rules for genetic counseling, knowing that hereditary kidney disease have a special place favored by cultural habits.
- Involvement with associations of sick parents.
- Access to health care remains limited and the problem of cessation or lack of treatment for the poorest.

**C- Improve training for pediatricians**

An awareness and training program for general practitioners and pediatricians to help improve the care of children with kidney disease seems necessary, as well as specialist training in this area to meet the request without continually growing on PN. The cooperation can help to implement projects that offer the African Child advanced therapeutic adapting to our environment and our
resources. The connections with the PN in developed countries are necessary: Discussion files by email, by twinning cooperation, exchange of equipment, training assistance juniors. The support for this support is based on the work of non-governmental organizations (NGOs), but also on the learned societies like what has been done in Marrakech. In this context the follow IPNA program is of significant help.

**D- facilitate exchanges and access to scientific literature**

An active and accessible website is necessary, consider creating a speaking part at the African Association site, which was also sponsored by IPNA. This site should allow the development of discussion and sharing of training and information materials forums. It can also help to bibliography exchange and sharing of local and regional jobs. Other means of encouragement are also discussed in the future: a free subscription to the magazine PN per unit, supply a copy of the book of IPNA PN country...

**E- Initiate African cooperative projects**

The project of a book: Pediatric Nephrology African Guide is a repeat initiative. The main objectives of this work are to work African experts on a common issue, allow them to explain the specific data of the continent, with the international community to share their experiences and difficulties. This book is also a fundamental tool for young physicians in their daily worries. It also constitutes a key step in the African PN cooperation.

**F- A greater involvement in the IPNA**

It is through the efforts of the IPNA, especially in recent years, these activities have been realized and our hope is still great in its support. Our continent must also be involved in this international institution and many actions can be developed:

- A larger membership each, it would demonstrate our interest and the role of the office is essential. Especially that effort has been made in the contributions to our country.

- Regular and representative participation of Africa in the Congress of the IPNA which is only held every 4 years which could allow us to meet other colleagues around the world. Exchanges that are likely to help us and show our interest and support for the body that requires encouragement and involvement from us.
I- WHAT IS THE SITUATION OF THE PN IN FRENCH SPEAKING AFRICA

It is disastrous for its development is not considered a priority by governments. The socio-economic climate of these countries is the main cause behind this, since most French-speaking African countries are situated in sub-Saharan Africa known for poverty of a large part of the population, limited financial resources and huge medical problems. It requires, therefore, an efficient strategy to come up with the most effective means of cooperation and collaboration between African countries and IPNA.

For example, pediatric dialysis unit exists only in North Africa: Morocco, Tunisia, Algeria while we find peritoneal dialysis units in Ivory Coast and Benin. These structures are found only in university hospitals and the number of pediatric nephrologists remains very insufficient (one pediatric nephrologist for two million children in Morocco). Children with kidney disease are then cared in the general pediatrics structures. When a renal replacement therapy is required, a small proportion is supported (including adolescents) in adult nephrology structures knowing that the majority of these countries are equipped with few dialysis units. We are reporting an overview of the situation that is experienced by the pioneers of this specialty in their country.

II- NETWORKING TO FACILITATE COOPERATION

A network of pediatric nephrologists in African French-speaking countries is interesting, and the meeting of representatives in Casablanca was the foundation of this network. The objectives of this group would be the exchange of information, discussion of issues particular by mails (conference and group discussion), easy and it doesn’t cost much, although many problems related to Internet access has limited its use in some countries. This cooperation could also include financial support, facilitating the patients’ movement, the implementation of collaborative work, training courses...

Our network has been set up in the pediatric nephrology meeting of French-speaking Africa organized in Casablanca in February 2013 and the second meeting will be held in Abidjan in September 2013.

III- INTRODUCTION OF THE FRENCH LANGUAGE COURSE IN IPNA

Particularly «IPNA Course» held in French with the collaboration of the local unit. The first experience took place in Casablanca in 2008 resorting, in the beginning, to the two languages, followed by that of Marrakech in 2010 where the course was entirely conducted in French, and in parallel with the congresses of the PN French-speaking society. This meeting was an opportunity to bring together pediatricians so as to benefit from training sessions in PN consolidating, thus, the pediatric nephrologist group. This training project is a good example of North-South collaboration.
waiting to develop a South-South one. The practical and interactive aspects as well as developed workshops during these courses should be maintained and enhanced. Facilitating training sessions in French should not hinder participation that must be greatly oriented towards English language training, and involvement in the actions of English-speaking countries in an attempt to unify the efforts of these two parts enabling, therefore, to boost this discipline in our continent.

**IV- ASPIRATIONS OF THE NETWORK**

The objectives of this group are the exchange of information, training and discussion of issues, including by mail (lecture and group discussion), although many problems with Internet access limit its implementation in some countries. This cooperation could also include the establishment of cooperative work and the organization of training sessions. It appears as a real opportunity to promote exchange for those speaking specialists. Our network is primarily a motivation for the group and a space dedicated to research.

It helps promote the skills of members, facilitate exchange, forge, consolidate gains and make a real contribution in the African association, mainly oriented towards English speaking countries. To better understand our needs, we must have epidemiological research with the establishment of registers that are essential to assess the health burden of disease. It is in this context that we initiated regional research projects, especially for specific diseases in the region. We worked on the identification of medical and logistical problems in these countries and came up with proposals for local and regional collaboration.

Similarly, it seemed important to shed light on diseases prevalent in sub-Saharan countries, such as renal disease in kidney damage in HIV infection and its management difficulties. Sickle cell disease is one of the most common genetic diseases in Africa with frequent kidney damage. Similarly, malaria is one of the most important causes of ARF, characterized by a late treatment because the family was first used in traditional medicine. However, late diagnosis of the disease leads to major complications, and limited access to conservative measures worsens the position of the CRF. Moreover, the situation of the ARF management remains unacceptable. The development of peritoneal dialysis and its accessibility to a large part of the African pediatric population will help to solve this problem. We also stressed the need to provide additional technical assistance to IPNA fellows after their return to their countries to support them morally and financially. We will need to develop a common approach regarding the specific common diseases in this area, conduct local inquiries resistance patterns of UTI in order to better adapt the first-line antibiotics and raise awareness about the benefits of recognition early PN. It would also help to provide information on the risk of Nephrology and adequate monitoring of these diseases.

Furthermore, aware of the importance of financial difficulties facing most African colleagues, and with the support of Isidro Saluski (Secretary General of the IPNA in this time) and Pierre Cochot (Secretary General of the IPNA) we were able to get help from the IPNA to cover the travel expenses of African colleagues, a move that allowed them to participate in this course and actively work to build this network and strengthen thereafter.

The rise of PN in this region depends on the establishment of a good strategy to find the most effective ways to encourage cooperation. This must be developed both between African countries and abroad, notably IPNA.
PART X

APPENDIX

NORMS IN PEDIATRIC NEPHROLOGY

Georgette Guemkam, Yaoundé Bastos - Cameroun
HIGHLIGHTS
✓ Norms can be defined as a state conforming to a majority of cases.
✓ Many biologic parameters change with age and or sex, the measurement method also and should be validated by the laboratory according to the technical use and the population.
✓ Glomerular filtration rate increases with age and in African countries, it should be estimated from serum creatinine by using 2009 Schwartz formula. In developed countries, it can be measured by using many methods (creatinine clearance, inulin clearance, cystatine C clearance, iohexol clearance...)

I- GLOMERULAR FUNCTION
Chronic renal disease is defined as a renal disease for more than three months or a glomerular filtration rate less than <60 ml/mn/1.73 m2. We have 5 stages of chronic renal disease: stage 1, stages 2 to 4 that represent chronic renal failure while stage 5 is the end stage kidney failure.

Table 1: Chronic renal failure stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Glomerular filtration rate (ml/min/1.73m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Renal injury with normal or increased glomerular filtration rate (GFR)</td>
<td>&gt;90</td>
</tr>
<tr>
<td>2</td>
<td>Renal injury with low GFR</td>
<td>60 - 89</td>
</tr>
<tr>
<td>3</td>
<td>Moderate reduction of GFR</td>
<td>30 – 59</td>
</tr>
<tr>
<td>4</td>
<td>Severe reduction of GFR</td>
<td>15 – 29</td>
</tr>
<tr>
<td>5</td>
<td>End stage of kidney failure</td>
<td>&lt; 15</td>
</tr>
</tbody>
</table>

Table 2: Glomerular filtration rate

<table>
<thead>
<tr>
<th>Age</th>
<th>Glomerular filtration rate in ml/mn/1.73m² (mean± 2SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature baby</td>
<td></td>
</tr>
<tr>
<td>1st week after delivery</td>
<td>15 ± 6</td>
</tr>
<tr>
<td>2 – 8 weeks</td>
<td>29 ± 14</td>
</tr>
<tr>
<td>2 months – 2 years</td>
<td>51 ± 20</td>
</tr>
<tr>
<td>New born</td>
<td></td>
</tr>
<tr>
<td>1 week</td>
<td>41 ± 15</td>
</tr>
<tr>
<td>2 – 8 weeks</td>
<td>66 ± 25</td>
</tr>
<tr>
<td>2 months – 2 years</td>
<td>96 ± 22</td>
</tr>
<tr>
<td>2 -12 years</td>
<td>133 ± 27</td>
</tr>
<tr>
<td>13 – 21 years (boy)</td>
<td>140 ± 30</td>
</tr>
<tr>
<td>13 – 21 years (girl)</td>
<td>126 ± 22</td>
</tr>
</tbody>
</table>
### Table 3: Normal values of serum creatinine according to Jaffe modified method

<table>
<thead>
<tr>
<th>Age</th>
<th>µmol/L</th>
<th>mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature Newborn (J3)</td>
<td>25 – 95</td>
<td>0,29 – 1,04</td>
</tr>
<tr>
<td>New born (J3)</td>
<td>21 - 75</td>
<td>0,24 – 0,85</td>
</tr>
<tr>
<td>2 – 12 months</td>
<td>15 – 37</td>
<td>0,17 – 0,42</td>
</tr>
<tr>
<td>1 – 3 years</td>
<td>21 – 36</td>
<td>0,24 – 0,41</td>
</tr>
<tr>
<td>3 – 5 years</td>
<td>27 – 42</td>
<td>0,31 – 0,47</td>
</tr>
<tr>
<td>5 – 7 years</td>
<td>28 – 52</td>
<td>0,32 – 0,59</td>
</tr>
<tr>
<td>7 – 9 years</td>
<td>35 – 53</td>
<td>0,40 – 0,60</td>
</tr>
<tr>
<td>9 – 11 years</td>
<td>34 – 65</td>
<td>0,39 – 0,75</td>
</tr>
<tr>
<td>11 – 13 years</td>
<td>46 – 70</td>
<td>0,53 – 0,79</td>
</tr>
<tr>
<td>13 -15 years</td>
<td>50 – 77</td>
<td>0,57 – 0,87</td>
</tr>
<tr>
<td>Men</td>
<td>62 – 106</td>
<td>0,70 – 1,20</td>
</tr>
<tr>
<td>Women</td>
<td>44 – 80</td>
<td>0,50 – 0,90</td>
</tr>
</tbody>
</table>

**NB:** Serum creatinine at delivery is the mother creatinine  
*Serum creatinine in mg/dL × 88,5 = serum creatinine in µmol/L*  
**Schwartz 2009 formula** to estimate the glomerular filtration rate is: k × height in centimeter/serum creatinine inµmol/L  
The K constant is equal to 36,5 at any age

### Table 4: Proteinuria and albuminuria on spot urine

<table>
<thead>
<tr>
<th>Normal ranges</th>
<th>Proteinuria (mg/m2/h)</th>
<th>Proteinuria/creatininuria mg/mg (mg/mmol)</th>
<th>Albuminuria/creatininuria mg/mg (mg/mmol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6– 24 months</td>
<td>&lt; 4</td>
<td>&lt; 0,5 (&lt; 50)</td>
<td></td>
</tr>
<tr>
<td>&gt;24 months</td>
<td>&lt; 4</td>
<td>&lt; 0,2 (&lt; 20)</td>
<td>&lt; 30 (&lt; 3)</td>
</tr>
<tr>
<td>Nephrotic proteinuria</td>
<td>&gt;40</td>
<td>&gt; 2 (&gt; 200)</td>
<td></td>
</tr>
</tbody>
</table>

**NB:** proteinuriashould be measured on a 24 hour urine collection or by doing the proteinuria/creatininuria ratio on spot urine.
II- TUBULAR FUNCTIONS
The proximal tubule is responsible for the reabsorption of electrolytes, glucose, and amino acids. Studies to determine proximal tubular function compare urine and blood levels of specific compounds arriving at a percent tubular reabsorption (Tx).
A urine acidification defect (distal renal tubular acidosis) should be suspected when random urine pH values are > 6 in the presence of moderate systemic metabolic acidosis. Acidification defects should be confirmed by simultaneous venous or arterial pH, plasma bicarbonate concentration, and pH meter determination of the pH of fresh urine.

Table 5: Urine concentration

<table>
<thead>
<tr>
<th>Age</th>
<th>maximal urine concentration after dDAVP (mOsm/kg) (mean± 2 SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature new born</td>
<td>500 ± 100</td>
</tr>
<tr>
<td>&lt;3 months</td>
<td>750 ± 300</td>
</tr>
<tr>
<td>3 – 12 months</td>
<td>1000 ± 300</td>
</tr>
<tr>
<td>&gt;2 years</td>
<td>1050 ± 250</td>
</tr>
</tbody>
</table>

Table 6: Urinary excretion fraction of ion

<table>
<thead>
<tr>
<th>Ion</th>
<th>d3 premature</th>
<th>d8 premature</th>
<th>d3 neonates</th>
<th>d8 neonates</th>
<th>infant / adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>1 - 5</td>
<td>&lt;2</td>
<td>5</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Potassium</td>
<td>4</td>
<td>4</td>
<td>9</td>
<td>9</td>
<td>9 - 23</td>
</tr>
<tr>
<td>Chloride</td>
<td></td>
<td></td>
<td>1,2 - 1,8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bicarbonate</td>
<td></td>
<td></td>
<td>&lt;5 (2mmol/l)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose</td>
<td></td>
<td></td>
<td>&lt;1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phosphorus</td>
<td></td>
<td></td>
<td>15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Magnesium</td>
<td></td>
<td></td>
<td>1,5 - 3,5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uric acid</td>
<td>70</td>
<td>70</td>
<td>38</td>
<td>38</td>
<td></td>
</tr>
</tbody>
</table>

d: day
Excretion fraction of ion (Fei): Ui × Pcr/Pi × Ucr
Ui: concentration of ion in urine
Ucr: concentration of creatinine in urine
Pi: concentration of ion in plasma
Pcr: concentration of creatinine in plasma
Tubular reabsorption rate (TRi) = 1 – Fei x 100%
# III- FLUIDS AND ELECTROLYTES

## Table 7: Water volume in children

<table>
<thead>
<tr>
<th>Age</th>
<th>0-1 month</th>
<th>1-12 month</th>
<th>1-10 years</th>
<th>10-16 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total water (% of body weight)</td>
<td>75</td>
<td>64</td>
<td>62</td>
<td>62</td>
</tr>
<tr>
<td>Extracellular volume (% of body weight)</td>
<td>33</td>
<td>25 – 30</td>
<td>19</td>
<td>16</td>
</tr>
<tr>
<td>Serum volume (ml/kg)</td>
<td>50</td>
<td>50</td>
<td>48</td>
<td>47</td>
</tr>
</tbody>
</table>

## Table 8: Diuresis in children

<table>
<thead>
<tr>
<th>Age</th>
<th>Volume of diuresis (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st and 2nd days</td>
<td>30 – 60</td>
</tr>
<tr>
<td>3 - 10 days</td>
<td>100 – 300</td>
</tr>
<tr>
<td>10 days - 2 months</td>
<td>250 – 450</td>
</tr>
<tr>
<td>2 months - 1 year</td>
<td>400 – 500</td>
</tr>
<tr>
<td>1 - 3 year</td>
<td>500 – 600</td>
</tr>
<tr>
<td>3 - 5 year</td>
<td>600 – 700</td>
</tr>
<tr>
<td>5 - 8 year</td>
<td>650 – 1000</td>
</tr>
<tr>
<td>8 - 14 year</td>
<td>800 – 1400</td>
</tr>
</tbody>
</table>

## IV- METABOLIC EVALUATION OF RENAL CALCULI

## Table 9: Urinary lithiasis is rare in children

<table>
<thead>
<tr>
<th>Urinary parameters</th>
<th>Normal ranges</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH (morning urine)</td>
<td>&lt; 6 months 7 - 12 months 1 - 2 months 3 - 5 months &gt;5 months 5,5 - 6,2</td>
</tr>
<tr>
<td>Trou anionique (Na+,K+, Cl-)</td>
<td>30 - 40 mmol/L</td>
</tr>
<tr>
<td>Calcium</td>
<td>&lt; 0,15 mmol/kg/24 h</td>
</tr>
<tr>
<td>Calcium/creatinine (mmol/mmol)</td>
<td>&lt; 2,4  &lt; 1,7  &lt;1,1  &lt; 1,1  &lt; 0,7</td>
</tr>
<tr>
<td>Citrate/creatinine</td>
<td>0,3 - 0,7 mmol/mmol</td>
</tr>
<tr>
<td>Magnesium</td>
<td>&gt;4 mmol/1,73 m2/24 h</td>
</tr>
<tr>
<td>Oxalate</td>
<td>&lt; 0,5 mmol/1,73 m2/24 h</td>
</tr>
<tr>
<td>Oxalate/creatinine (mmol/mmol)</td>
<td>&lt; 0,36  &lt; 0,23  &lt; 0,18  &lt; 0,10  &lt; 0,08</td>
</tr>
<tr>
<td>Uric acid</td>
<td>&lt; 4 mmol/1,73m2/24 h</td>
</tr>
<tr>
<td>Cystine</td>
<td>&lt; 0,13 mmol/1,73 m2/24 h</td>
</tr>
<tr>
<td>Cystine/creatinine</td>
<td>30 µmol/mmol</td>
</tr>
</tbody>
</table>
V- PHOSPHOCALCIUM METABOLISM
It comprises calcium, phosphorus, parathormone and vitamins D (native and active forms).

Table 10: Normal values according to the age in serum are

<table>
<thead>
<tr>
<th>Age</th>
<th>Phosphorus (mmol/L)</th>
<th>Ionisedcalcium (mmol/L)</th>
<th>Total calcium (mmol/L)</th>
<th>PTH (ng/L)</th>
<th>25 OH-vitamin D (ng/mL)</th>
<th>1,25-OH2 vitamin D (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D0 – D7</td>
<td>1,15 - 2,50</td>
<td>1,22 - 1,40</td>
<td>1,80 - 2,75</td>
<td>10 - 46</td>
<td>30 - 80</td>
<td>10 - 110</td>
</tr>
<tr>
<td>0 - 3 months</td>
<td>1,55 - 2,39</td>
<td>1,22 - 1,40</td>
<td>2,20 - 2,83</td>
<td>10 - 46</td>
<td>30 - 80</td>
<td>10 - 110</td>
</tr>
<tr>
<td>1 - 5 years</td>
<td>1,45 - 2,10</td>
<td>1,22 - 1,32</td>
<td>2,35 - 2,70</td>
<td>10 - 46</td>
<td>30 - 80</td>
<td>10 - 110</td>
</tr>
<tr>
<td>6 - 12 years</td>
<td>1,16 - 1,87</td>
<td>1,15 - 1,32</td>
<td>2,35 - 2,57</td>
<td>10 - 46</td>
<td>30 - 80</td>
<td>10 - 110</td>
</tr>
<tr>
<td>13 - 20 years</td>
<td>0,74 - 1,45</td>
<td>1,12 - 1,30</td>
<td>2,20 - 2,55</td>
<td>10 - 46</td>
<td>30 - 80</td>
<td>10 - 110</td>
</tr>
<tr>
<td>Adulte</td>
<td>0,85 - 1,50</td>
<td>1,20 - 1,34</td>
<td>2,25 - 2,60</td>
<td>10 - 46</td>
<td>30 - 80</td>
<td>10 - 110</td>
</tr>
</tbody>
</table>

VI- FOETAL BIOCHEMISTRIES

<table>
<thead>
<tr>
<th>Biochemical parameters</th>
<th>Values link with an abnormal renal function at 2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary sodium</td>
<td>&gt;50 mmol/L</td>
</tr>
<tr>
<td>Urinary beta 2 microglobulin</td>
<td>&gt;2 mg/L</td>
</tr>
<tr>
<td>Serum beta 2 microglobulin</td>
<td>&gt;5 mg/L</td>
</tr>
</tbody>
</table>

VII- UROLOGY

<table>
<thead>
<tr>
<th>Normal values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonates</td>
</tr>
<tr>
<td>Bladder capacity</td>
</tr>
<tr>
<td>Maximal urinary flow</td>
</tr>
<tr>
<td>Mean urinary flow</td>
</tr>
<tr>
<td>Pression of filling the uretral sphincter</td>
</tr>
<tr>
<td>Permictional pression of detrusor (boy)</td>
</tr>
<tr>
<td>Permictional pression of detrusor (girl)</td>
</tr>
<tr>
<td>Duration of voiding</td>
</tr>
<tr>
<td>Post mictional residue</td>
</tr>
</tbody>
</table>
### A- Plasma Immunoglobulins

There are Ig G, IgA, Ig M and are important to study the humoral function. Their rate has to be interpreted by taking the age in the consideration.

### Table: Plasma Immunoglobulins

<table>
<thead>
<tr>
<th>Age</th>
<th>Total (g/L)</th>
<th>Ig G (5g/L)</th>
<th>IgA (g/L)</th>
<th>IgM (g/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cord blood</td>
<td>12.8 (8.1 - 16.1)</td>
<td>8.5 (4.0 - 16.5)</td>
<td>&lt;0.04 (0.0 - 0.15)</td>
<td>0.12 (0.0 - 0.23)</td>
</tr>
<tr>
<td>1 - 6 months</td>
<td>6.3 (2.4 - 10.5)</td>
<td>4.0 (2.3 - 9.5)</td>
<td>0.2 (0.04 - 0.6)</td>
<td>0.3 (0.1 - 0.9)</td>
</tr>
<tr>
<td>1 years</td>
<td>8.4 (3.2 - 11.8)</td>
<td>7.2 (2.8 - 12.8)</td>
<td>0.5 (0.2 - 1.7)</td>
<td>0.7 (0.4 - 17.6)</td>
</tr>
<tr>
<td>2 - 3 years</td>
<td>10.8 (7.3 - 14.6)</td>
<td>7.0 (4.9 - 15.6)</td>
<td>0.9 (21 - 250)</td>
<td>1.0 (0.4 - 2.3)</td>
</tr>
<tr>
<td>4 - 7 years</td>
<td>12.2 (5.4 - 19.5)</td>
<td>8.5 (3.5 - 17.6)</td>
<td>1.2 (3.0 - 3.3)</td>
<td>1.2 (0.3 - 3.2)</td>
</tr>
<tr>
<td>8 - 9 years</td>
<td>13.8 (7.0 - 20.3)</td>
<td>9.0 (5.0 - 17.2)</td>
<td>2.0 (5.0 - 6.5)</td>
<td>1.3 (0.3 - 2.8)</td>
</tr>
<tr>
<td>10 - 16 years</td>
<td>13.8 (7.0 - 20.3)</td>
<td>12.2 (6.0 - 17.2)</td>
<td>2.0 (4.4 - 6.7)</td>
<td>1.3 (0.3 - 2.0)</td>
</tr>
<tr>
<td>Adult</td>
<td>12.8 (6.5 - 17.5)</td>
<td>9.9 (6.2 - 17.0)</td>
<td>2.0 (4.5 - 6.5)</td>
<td>1.9 (0.7 - 3.8)</td>
</tr>
</tbody>
</table>
B- Renine – angiotensin – aldosteronesystem (RAAS)
This system is describe as a renal hypertension system, and present in all the organism. His normal values vary with age and the position of the patient.

<table>
<thead>
<tr>
<th>Age</th>
<th>Renine (pg/mL)</th>
<th>Renine (pmol/L)</th>
<th>Age</th>
<th>Aldosterone (ng/dL)</th>
<th>Aldosterone (nmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>birth</td>
<td></td>
<td></td>
<td>d15 – 3 months</td>
<td>15 - 105</td>
<td>0,4 – 2,9</td>
</tr>
<tr>
<td>&lt;6 months</td>
<td>18 - 120</td>
<td>0,4 – 2,8</td>
<td>3 months - 1 years</td>
<td>6 - 90</td>
<td>0,2 – 2,5</td>
</tr>
<tr>
<td>6 months – 5 years</td>
<td>7 - 115</td>
<td>0,2 – 2,7</td>
<td>1 an – 3 years</td>
<td>10 - 80</td>
<td>0,3 – 2,2</td>
</tr>
<tr>
<td>6 years – 15 years</td>
<td>6,5 - 80</td>
<td>0,15 – 1,9</td>
<td>&gt;3 years</td>
<td>4 - 40</td>
<td>0,1 – 1,1</td>
</tr>
<tr>
<td>&gt;15 years lay</td>
<td>10 - 20</td>
<td>0,2 – 0,5</td>
<td>&gt;15 years stand</td>
<td>3 - 14</td>
<td>0,08 – 0,4</td>
</tr>
<tr>
<td>&gt;15 years stand</td>
<td>10 - 40</td>
<td>0,2 - 1</td>
<td>&gt;15 years stand</td>
<td>200 - 1000</td>
<td>5,5 - 28</td>
</tr>
</tbody>
</table>

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Yassir El Habbi
All the contributors
The pediatric nephrology has made tremendous progress. However, it is still at an embryonic stage, or even absent in most African countries. This specialty, characterized by a vast field of action and multiple interconnections with other disciplines, has imposed itself in recent years in the treatment of children with renal disease.

The management of renal diseases is costly, especially when the disease reaches advanced stages. This financial burden is one of the first obstacles hampering the development of pediatric nephrology in Africa. Its development must also take into account the customs and cultures that are still extremely anchored in our continent. The development of this discipline also involves strengthening domestic, regional and international cooperation.

The chapters of this Book, to which and for the first time, have contributed several African pediatric nephrologists, were written by some doctors with particular expertise in field experiments- often consolidated by international data- with an aim to deliver a basic reference tool providing information that is often crucial to all African practitioners.