Henoch Schonlein Purpura and IgA Nephropathy

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Systemic leukocytoclastic small-vessel vasculitis with predominant IgA deposits
Henoch Schonlein Purpura: Diagnosis

**Palpable Purpura**

+ 3 of 4 criteria:

- Diffuse abdominal pain
- Arthritis or arthralgia
- Kidney involvement (hematuria and/or proteinuria)
- Bioptic demonstration of predominant IgA deposits

Ozen et al. EULAR/PRES endorsed Consensus Guidelines... Ann Rheum Dis 2005
Most common vasculitis in childhood
90% of cases occur in 3rd to 10th year of life

Clustering in winter season

Two thirds of cases associated with upper respiratory tract infections

Major ethnic differences in incidence
HSP: Triggering Factors

Viral pathogens:
Parvo B19, Coxsackie, Adeno, HBV, HCV, HIV

Bacterial pathogens:
Streptococci, S.aureus, Mycoplasma
Salmonella, Shigella

Drugs:
Antibiotics
ACEI
NSAIDs

Toxins:
Vaccinations, Insect stings, nutritional allergens
<table>
<thead>
<tr>
<th>Country</th>
<th>Incidence (Cases/million children/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>217</td>
</tr>
<tr>
<td>Denmark</td>
<td>180</td>
</tr>
<tr>
<td>Northern Ireland</td>
<td>135</td>
</tr>
<tr>
<td>Spain</td>
<td>105</td>
</tr>
<tr>
<td>England</td>
<td></td>
</tr>
<tr>
<td>Asians</td>
<td>240</td>
</tr>
<tr>
<td>Caucasians</td>
<td>178</td>
</tr>
<tr>
<td>Africans</td>
<td>62</td>
</tr>
<tr>
<td>Jordan</td>
<td>85</td>
</tr>
<tr>
<td>Kuwait</td>
<td>67</td>
</tr>
</tbody>
</table>
HSP: Gastrointestinal Symptoms

GI involvement in 2/3 of HSP cases

GI involvement precedes purpura in 25% of cases

Colic pain (bowel angina), hemorrhagic colitis

In 5% severe
(mainly invagination, rarely infarction, perforation, pancreatitis, perforation, protein losing enteropathy)
HSP: Joint Involvement

Joint involvement present in 2/3 of HSP cases

Typical: Arthralgia + periarticular swelling

Predilection: Knee, ankle, elbows, wrist

No synovial effusion!
HSP: Rare Manifestations

Cerebral vasculitis
  seizures, cortical blindness, psychiatric disorders

Testicular ischemia, scrotal swelling
  differential diagnosis: testicular tortion

Ureteral ischemia/hemorrhage
  can cause obstruction

Hemorrhagic cystitis
**IgA Isotypes**

**IgA1:**
Main constituent of *serum* IgA
90% monomeric
Source: Bone marrow plasma cells
   Hinge region with 5 O-linked oligosaccharide side chains
   (N-acetyl-galactosamine, galactose ± Sialinyl residue)

**IgA2:**
Main constituent of *secreted* IgA
Multimeric
Source: Mucosal epithelia
HSP: Pathophysiology

- Increased IgA synthesis following mucosal antigen presentation
- Deficient O-galactosylation and/or sialisation of IgA1
- Diminished IgA1 clearance via asialo-glycoprotein receptor
- Accumulation of circulating IgA1
- Aggregation to macromolecular IgA complexes
- Increased matrix adhesion of hypoglycosylated IgA1
- IgA deposition in mesangium, endothelia
HSP Nephritis: Pathophysiology

Mesangial deposition of IgA complexes

Interaction with mesangial Fcα- and/or IgA1-Rec.

Alternative **Complement** pathway ↑ (C3, Properdin) -> C5b-9 Membrane Attack Complex

**iNOS** ↑ -> Radical formation, apoptosis, sclerosis

**Cytokines** ↑: IL-6, PDGF, IL-1, TNFa, TGFβ

**Vasoactive Factors** ↑:
Prostaglandins, Leukotrienes, Thromboxan, Endothelin

**Chemokines** ↑: MCP-1, IL-8, MIP-1, RANTES
HSP Nephritis: ISKDC Classification

10%  Class I: Minimal glomerular lesions

15%  Class II: Endocapillary proliferation (no crescents)
      IIa  Mesangial proliferation
      IIb  Focal-segmental endocapillary proliferation
      IIc  Diffuse endocapillary proliferation

50%  Class III: Extracapillary proliferation with <50% crescents
      IIIa with focal-segmental endocapillary proliferation
      IIIb with diffuse endocapillary proliferation

15%  Class IV: Extracapillary proliferation with 50-75% crescents
      IVa with focal-segmental endocapillary proliferation
      IVb with diffuse endocapillary proliferation

10%  Class V: Extracapillary proliferation with >75% crescents
      Va with focal-segmental endocapillary proliferation
      Vb with diffuse endocapillary proliferation

1%   Class VI: Pseudo-membranoproliferative GN
HSP Nephritis: Clinical Presentation

- Hematuria
- Small proteinuria

Frequently persistent or recurrent (associated with infections) -> IgA nephropathy

- Nephritic syndrome
- Nephrotic syndrome

- Renal insufficiency

- Rapidly progressive GN
Demographics of HSP Nephritis

Narchi, Arch Dis Child 2005

HSP: 1133 cases

746 (66%) normal urinary findings

387 (34%) urine abnormalities

305 (79%)
Isolated hematuria ± proteinuria

82 (21%)
Nephritic or nephrotic syndrome

HSP Nephritis:

approx. 7% of 150 HSP cases/million children per yr:
200 pediatric cases per year in Germany
Adults approx. 10% of all HSP cases: 20 cases per year
Long-Term Renal Risk
Meta-analysis 12 studies, unselected HSP

HSP: 1133 cases

746 (66%) Normal urinary findings

387 (34%) Urine abnormalities

305 (79%) Isolated hematuria ± proteinuria

82 (21%) Nephritic or nephrotic syndrome

Long-term renal disorder (nephrotic syndrome, GN, CKD, hypertension)

Narchi, Arch Dis Child 2005; 90:916
HSP Nephritis: Long-Term Prognosis in Tertiary Centers of Care
HSP Nephritis: Predictors of Late Outcome

Multivariable analysis:
Predictors of active nephropathy at last observation (after median 4.6 (1-23) years)

- Initial renal failure $p=0.004$
- Initial nephrotic syndrome $p=0.04$
- Degree of biopsy $p=0.05$

Not predictive:
- Age at disease onset
- Duration of follow-up
- Gender
- Initial hypertension
- Recurrent purpura

Schärer et al. Pediatr Nephrol 1999
Predictive Value of Extracapillary Proliferation

% crescents in initial biopsy

RECOVERED  PERSISTENT ABNORMALITIES  ESRD

### Therapeutic Studies in HSP Nephritis

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>No. of patients</th>
<th>Age group</th>
<th>Therapy</th>
<th>Mean follow-up (years)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allen</td>
<td>1960</td>
<td>Not stated</td>
<td>Children</td>
<td>P</td>
<td>4.3</td>
<td>Concluded steroids not beneficial</td>
</tr>
<tr>
<td>Meadow</td>
<td>1972</td>
<td>30</td>
<td>Children</td>
<td>P, A, Cy</td>
<td>&gt; 2</td>
<td>Concluded treatment of no benefit</td>
</tr>
<tr>
<td>Couhanan</td>
<td>1977</td>
<td>30</td>
<td>Children</td>
<td>P, A, Cy</td>
<td>9.9</td>
<td>Longer follow-up of patients in study 2; same conclusion</td>
</tr>
<tr>
<td>Michael</td>
<td>1967</td>
<td>2</td>
<td>Children</td>
<td>P, A</td>
<td>0.75</td>
<td>GFR returned to normal</td>
</tr>
<tr>
<td>Hurley</td>
<td>1972</td>
<td>6</td>
<td>Children</td>
<td>P, A</td>
<td>3.2</td>
<td>All improved</td>
</tr>
<tr>
<td>Kalowsky</td>
<td>1973</td>
<td>17</td>
<td>Adults</td>
<td>P, A, Cy, Co, D</td>
<td>3.7</td>
<td>Renal function improved in patients</td>
</tr>
<tr>
<td>Levy</td>
<td>1976</td>
<td>34</td>
<td>Children</td>
<td>P, Ch, I, M, H, Co, Cy, D</td>
<td>&gt; 1</td>
<td>Treated 10 patients; outcome: 6/10 patients with GFR &gt; 100 mL/min; 4/10 patients with GFR &lt; 100 mL/min; 10/10 patients with complete recovery</td>
</tr>
<tr>
<td>Brown</td>
<td>1974</td>
<td>2</td>
<td>Children</td>
<td>P, A, H, Co, D</td>
<td>2.8</td>
<td>Creatinine declined from 5.4 to 1.9 mg/dL</td>
</tr>
<tr>
<td>Sinniah</td>
<td>1978</td>
<td>2</td>
<td>Adults</td>
<td>Ig</td>
<td>1.1</td>
<td>Proteinuria reduced; decreased in halted progression of disease (GFR) stopped</td>
</tr>
<tr>
<td>Rose</td>
<td>1982</td>
<td>2</td>
<td>Adults</td>
<td>Ig</td>
<td>1.1</td>
<td>Proteinuria reduced; improved histologic activity index</td>
</tr>
<tr>
<td>Niaudet</td>
<td>1983</td>
<td>14</td>
<td>Children</td>
<td>Ig</td>
<td>1.1</td>
<td>Proteinuria reduced; improved histologic activity index</td>
</tr>
<tr>
<td>Roth</td>
<td>1984</td>
<td>14</td>
<td>Children</td>
<td>Ig</td>
<td>1.1</td>
<td>Proteinuria reduced; improved histologic activity index</td>
</tr>
<tr>
<td>Jardin</td>
<td>1985</td>
<td>12</td>
<td>Children</td>
<td>Ig</td>
<td>1.1</td>
<td>Proteinuria reduced; improved histologic activity index</td>
</tr>
<tr>
<td>Rostoker</td>
<td>1995</td>
<td>3</td>
<td>Adults</td>
<td>Ig</td>
<td>&lt; 1</td>
<td>Proteinuria reduced; improved histologic activity index</td>
</tr>
<tr>
<td>Oner</td>
<td>1995</td>
<td>12</td>
<td>Children</td>
<td>MP, P, Cy, D</td>
<td>0.5</td>
<td>GFR rose from mean of 37 to 86 mL/min/1.73 m²</td>
</tr>
<tr>
<td>Niaudet</td>
<td>1993</td>
<td>34</td>
<td>Children</td>
<td>MP, P, Cy</td>
<td>1–9</td>
<td>22 patients showed improvement</td>
</tr>
<tr>
<td>Gianviti</td>
<td>1996</td>
<td>14</td>
<td>Children</td>
<td>P, Cy, A, PE</td>
<td>3.3</td>
<td>Five patients developed ESRD; the remainder had mean creatinine 0.65 mg/dL</td>
</tr>
<tr>
<td>Faedda</td>
<td>1996</td>
<td>8</td>
<td>Adults</td>
<td>MP, P, Cy</td>
<td>4.8</td>
<td>Seven patients entered complete remission</td>
</tr>
<tr>
<td>Bergstein</td>
<td>1998</td>
<td>21</td>
<td>Children</td>
<td>MP, P, A</td>
<td>1.2</td>
<td>16 patients entered complete remission</td>
</tr>
<tr>
<td>Niaudet</td>
<td>1998</td>
<td>38</td>
<td>Children</td>
<td>MP, P</td>
<td>8</td>
<td>16 patients entered complete remission</td>
</tr>
<tr>
<td>Iijima</td>
<td>1998</td>
<td>14</td>
<td>Children</td>
<td>P, Cy, H, Co, D</td>
<td>7.5</td>
<td>27 patients recovered clinically, three had minimal urinary abnormalities, four had persistent nephropathy, and four progressed to ESRD</td>
</tr>
<tr>
<td>Schärer</td>
<td>1999</td>
<td>64</td>
<td>Children</td>
<td>P, Cy, PE</td>
<td>11.5</td>
<td>Nine patients showed normal U/A and GFR, four had minor U/A abnormalities, and one had heavy proteinuria</td>
</tr>
<tr>
<td>Hattori</td>
<td>1999</td>
<td>9</td>
<td>Children</td>
<td>PE</td>
<td>9.6</td>
<td>Overall renal survival 10 years after onset was 73%</td>
</tr>
<tr>
<td>Foster</td>
<td>2000</td>
<td>20</td>
<td>Children</td>
<td>P, A</td>
<td>5.4</td>
<td>Four patients entered complete remission, two had only microscopic hematuria, one had proteinuria, and two progressed to ESRD</td>
</tr>
<tr>
<td>Flynn</td>
<td>2001</td>
<td>12</td>
<td>Children</td>
<td>MP, P, Cy</td>
<td>3</td>
<td>Chronicity score and renal outcome improved with treatment</td>
</tr>
</tbody>
</table>

P: oral prednisone, Cy: Cyclophosphamide, PE: Plasma exchange, Co: coumadine, D: dipyridamole, Ig: Immunoglobulin, I: Indomethacin

Fervenza Int J Dermatol 2003; 42: 170
Therapeutic Approaches in Severe HSP Nephritis

Niaudet & Habib, 1998: 38 children
3 MPR pulses, followed by 3 months oral prednisone
Outcome (8 yrs): 70% compl. remission, 10% CKD, 10% ESRD

Kawasaki et al. 2003: 56 children
3 MPR pulses, 7 urokinase pulses, then oral prednisone, dipyridamol und coumarine for 6 months
Outcome: Proteinuria initially 3.5, 6mo 0.8, 2yr 0.3 g/m²/d
10yr: 1/56 CKD

Bergstein et al. 1988: 21 children
3 MPR pulses + azathioprin + oral prednisone
vs. azathioprin + oral prednisone
Outcome: 2/21 (9%) ESRD, no advantage of iv steroids
Iljima et al. 1998: 14 children
Oral prednisone daily, then alternating
+ Cyclophosphamide + Coumarin
Outcome (7 yrs): 9 complete remission, 1 nephrotic

Foster et al. 2000: 17 children
Oral prednisone + azathioprine
Outcome (5 yrs): 15/17 complete remission

Tarshish et al. 2004: Randomized, 28 vs. 28 children
6 weeks oral cyclophosphamide vs. „supportive care“
Outcome (8 yrs): 50% complete remission in both groups
Schärer et al. 1999
Scr, proteinuria ↓ in 8/8
Outcome:
7/8 progression to CKD/ESRD

Hattori et al. 1999
Outcome:
4/9 normal renal function,
2/9 ESRD
HSP Nephritis: Relapse after Transplant

Relapse after transplantation
50% histologically
20% clinically
12% deterioration of graft function
  9% renal allograft loss

Relapse risk
1 yr  24 %
2 yr  29 %
5 yr  35 %

Meulders et al. Transplantation 1994; 58: 1179
IgA Nephropathy

Clinical presentation:

- 40-50% recurrent macrohematuria 1-3 days after URT infection

- 30-40% microhematuria and mild proteinuria

- 10% isolated nephrotic syndrome

- 10% acute GN with edema, hypertension, renal failure
IgA Nephropathy

Demographics:
Most common glomerulonephritis in adults and children
Incidence highest in Asians, lowest in Africans
North-South gradient in Europe

Kyriluk et al. PLOS Genet 2012
**IgA Nephropathy: Prognosis**

Isolated hematuria, recurrent gross hematuria:
Good prognosis

Proteinuria and or hypertension:
Slowly progressive CKD

15% of patients develop ESRD within 10 y, 25 % within 20 y

Relapse of IgA nephropathy in transplant kidney:
Histological evidence in 50-80%
Allograft loss in 10%
HSP Nephritis ↔ IgA Nephropathy

**Age predilection:**

- HSP nephritis: 3-10 yrs
- IgA nephropathy: 10-40 yrs

**Occasional transition of phenotypes:**

- Isolated intermittent hematuria after HSP-associated hematuria
- Extrarenal symptoms in IgAN patients
- HSP after URL-related intermittent hematuria
- Post-transplant IgAN following HSP nephritis
HSP Nephritis ↔ IgA Nephropathy

**Genetics**
- Identical regional and ethnic incidence distribution
- Intrafamilial clustering of HSP and IgAN
- Twin case reports: 1 PSH, 1 IgAN

**Histopathology**
- Identical (renal and extrarenal IgA deposits)

**Biochemistry**
- Identical (serum IgA ↑, abnormal IgA1 glycosylation)
IgA Nephropathy: Genetic Epidemiology

Kyriluk et al. Nature 2014:

GWAS in 20,612 individuals:
6 novel, 9 confirmed genome-wide significant associations

Most loci associated with
- risk of inflammatory bowel disease
- maintenance of intestinal epithelial barrier
- response to mucosal pathogens

Genetic risk strongly correlated with variation in local pathogens, particularly helminth diversity, suggesting possible role for host-intestinal pathogen interactions
IgA Nephropathy: Risk Factors for Progressive Disease

Clinical data not associated with final outcome

Most important risk factor: **Time-averaged proteinuria during follow up**

Critical thresholds:
- Pre-treatment: 0.5 g/1.73m\(^2\)/day
- Post treatment: 0.2 g/1.73m\(^2\)/day

Kamei et al. cJASN 2011
IgA Nephropathy: Treatment Recommendations

For all children with IgAN

- Blood pressure control <90th percentile (RAS inhibition)
- Tonsillectomy if recurrent tonsillitis (>3/year)

For all children with IgAN and

- Mild disease
- Normal e-GFR
- Up/Ucr <0.5
- Normal blood pressure
- MEST = 0

- Watchful waiting
- RAS inhibition if Up/Ucr >0.5

For children with IgAN and

- Moderate/severe IgAN
- Up/Ucr >0.5
- Any MEST = 1
- No severe irreversible sclerotic changes

- RAS inhibition
- Glucocorticoids (pulses or >6 months)
  Cyclophosphamide when >30% crescents/rapidly progressive course

For children with IgAN and minimal changes lesions

- Glucocorticoids as for idiopathic nephrotic syndrome

M Mesangial hypercellularity, E endocapillary hypercellularity, S segmental sclerosis, T tubular atrophy/interstitial fibrosis