Infection related Glomerulonephritis

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Overview

• Epidemiology
• Definitions
  • Post-infectious (PIGN) vs. Infection related (IRGN)
  • Post-infectious (PIGN) vs. Post-streptococcal GN (PSGN)
• Other IRGN
• PSGN
  • Pathology, Pathogenesis, Clinical manifestations, Outcome
• Comparison with other GN
• Atypical PIGN/C3GN
Global incidence

Est annual incidence ~ 9.3/100,000 (Carapetis et al)

X 4 Low resource setting in adults

Highest: Indigenous Australians 239/100,000

Caveats
- Definition
- Under-reporting
- Sporadic vs. epidemic
- Paediatric vs. adult
Changing epidemiology

Proposed definitions

Infection related GN (IRGN)
- Non-renal infection
- GN
- Immunological

Post infectious GN (PIGN)
- Infection resolved
- Latency

Post streptococcal GN (PSGN)

GN of active infection
- Staph A. related nephritis (SARN)
- Viral GN
- Other

Immunosuppression in refractory disease?

Eradication of infection

Staph A related GN

• In elderly and diabetics
• Concurrent infection
• MRSA
• IgA dominant IC GN
• Triggered by super-antigens
  • Enterotoxin A , C
  • Toxic shock syndrome toxin-1
Viral associated GN

### Hep B Virus
- **Chronic HBV Carrier**
  - HBeAg - IgG
  - HBsAg - IgG
  - Type III MC
  - Direct Tissue Infection
  - MN
  - Type I MPGN
  - PAN
  - IgA, FSGS

### Hep C Virus
- **Chronic HCV Carrier**
  - Type II MC
  - Type I MPGN
  - PAN
  - HCV Ag - IgG
  - Direct Tissue Infection
  - MN
  - IgA
  - FSGS

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Infection & Autoimmunity

PSGN
Pathogenesis

- Group A Strep. (GAS) [Strep. Pyogenes]
- No animal model, GAS human pathogen
- In-situ sub-epithelial Immune complex (IC) deposition
  - No correlation to circulating IC
  - Preformed IC – largely sub-endothelial
- Alternative complement (AP) pathway activation
- Cellular immunity

Reproduced from Heptinstall’s pathology of the kidney 7th edition
Pathogenesis: mechanisms

- Nephritogenic strains
  - URTI (M types 1, 2, 4, 12, 18, 25)
  - Skin (M types 49, 55, 57, 60)
- Nephritogenic antigens
  - M proteins, streptokinase are unlikely
- Autoimmunity
  - Anti-IgG
  - Epiphenomenon?
- Molecular mimicry
  - M protein in Rheumatic caditis

Pathogenesis: Penetrating the GBM

Pathogenesis: Nephritogenicity

- SpeB/zSpeB 28 kDa
- GAPDH (NAPlr) 43 kDa

- Serological: Specific Antibody response
- Histological: Co-localization
- Plasmin binding receptor protein
  Activates collagenase & MPP
- Immune complex GN

Clinical features

- **Latency**:
  - Pharyngitis: 2 weeks
  - Skin: >2 weeks

- **GAS infection**

- **Haematuria**: (~100%)
  - Microscopic 2/3

- **Oliguria**: (~60%)
  - Oedema: (~70%)
  - Hypertension: (~80%)
  - CCF
  - Intra-glomerular blood flow
  - ↓ FeNa → Na/water retention
  - ↓ Renin state

- **Proteinuria**: (~70%)
  - Sub-nephrotic

- **Acute Nephritic syndrome**

- **Recovery**

- **Serology**
  - ASOT: URTI > skin
  - Anti DNaseB: skin > URTI
  - Anti-hyaluronidase: skin > URTI
  - Autoantibodies (RF, AntiDNA, ANCA)

- **Complements**
  - Predominantly AP (C3)

- **Culture**: (~25%)
Histology

Nasr et al. 1995-2005 (N=86) : NY, USA
- Diffuse prolif. GN: 72%
- Focal prolif. GN: 13%
- Mesangial prolif. GN: 8%
- Membrano prolif. GN: 2%
- Crescentic GN: 5%

Ramanathan et al. 2004-2014 (N=43) : NT Aus
- Diffuse prolif. GN: 72%
- Focal prolif. GN: 9%
- Membrano prolif. GN: 5%
- Crescentic GN: 9%

Histology: LM: Glomeruli

- Diffuse, monomorphic
- Hypercellularity
- Lobular expansion
- Crescents are rare

Reproduced from Heptinstall's pathology of the kidney 7th edition
Histology : LM : Glomeruli

- GBM is not thickened
- Hypercellularity
  - External (predominant, early)
    - PMN
    - Monocytes
    - Lymphocytes, eosinophils unusual
  - Internal (late stage)
    - Mesangial
    - Epithelial
    - Endothelial

Reproduced from Heptinstall's pathology of the kidney 7th edition
Histology: LM: Tubules, interstitium, blood vessels

- Not directly affected
- Proteinuria -> hyaline droplets
- Casts
- ATN
- IF/TA in extensive crescentic
- Arteritis rare
Histology : IF

• Sorger et al:
  • Starry sky: early cases
  • Garland: assoc heavy proteinuria, more dense subepithelial
  • Mesangial: resolving

• No evidence that different aetiological factors are responsible

• Likely related to host and stage of the disease
Histology: IF

• Anti-C3
  • More intense than anti-IgG, sometimes only anti-C3
• IgM in 50%
• IgA in staph
• C1q-C4 absent; suggestive of alternate pathway
Histology : EM

- Sub-epithelial electron-dense deposits ("Humps")
- Sub-endothelial early in disease
- Not pathognomonic
- Mostly in the mesangial notch near GBM reflection over mesangium
- Abundant in the first few weeks and then decline, usually disappear in 6 weeks

Reproduced from Heptinstall’s pathology of the kidney 7th edition
Pathology: temporal profile

<table>
<thead>
<tr>
<th>TABLE 1. Poststrepococcal GN: The Interval Between the Onset of Renal Symptoms and Renal Biopsy Determines the Histologic Features</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Early Biopsy (&lt; 2 wk)</strong></td>
</tr>
<tr>
<td>Clinical features</td>
</tr>
<tr>
<td>Light microscopy</td>
</tr>
<tr>
<td>Immunofluorescence microscopy</td>
</tr>
<tr>
<td>Electron microscopy</td>
</tr>
</tbody>
</table>

*Garland pattern with confluent subendothelial deposits in patients with nephrotic syndrome. GN indicates glomerulonephritis; Ig, immunoglobulin.
PSGN vs. Primary MGN: sub-epithelial deposits

- PSGN
  - Variable sized sub-epithelial
  - Sub-endothelial and mesangial deposits

- Membranous

Reproduced from Heptinstall’s pathology of the kidney 7th edition
PSGN vs. MPGN type 1:

- **PSGN**
  - Predominant sub-epithelial
  - Sub-endothelial and mesangial deposits

- **MPGN type 1**
  - Predominant sub-endothelial
  - Occasional ‘humps’

*Reproduced from Heptinstall’s pathology of the kidney 7th edition*
Comparison of C3 dominant GN

- **PSGN**
  - IF: IgG
  - EM: Sub-epithelial
  - AP activation

- **C3GN**
  - IF: C3 deposition
  - EM: Sub-epithelial
  - AP activation

- **MPGN I**
  - IF: IgG
  - EM: Sub-endothelial
  - CP activation
Proposed GN classification based on Pathogenesis

Table 1. Classification of GN

<table>
<thead>
<tr>
<th>Pathogenic Type</th>
<th>Specific Disease Entity</th>
<th>Pattern of Injury: Focal or Diffuse</th>
<th>Scores or Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune-complex GN</td>
<td>IgA nephropathy, IgA vasculitis, lupus nephritis, infection-related GN, fibrillary GN with polyclonal Ig deposits</td>
<td>Mesangial, endocapillary, exudative, membranoproliferative, necrotizing, crescentic, sclerosing, or multiple</td>
<td>Oxford/MEST scores for IgA nephropathy</td>
</tr>
<tr>
<td>Pauci-immune GN</td>
<td>MPO-ANCA GN, proteinase 3-ANCA GN, ANCA-negative GN</td>
<td>Necrotizing, crescentic, sclerosing, or multiple</td>
<td>ISN/RPS class for lupus nephritis</td>
</tr>
<tr>
<td>Anti-GBM GN</td>
<td>Anti-GBM GN</td>
<td>Necrotizing, crescentic, sclerosing, or mixed</td>
<td>Focal, crescentic, mixed, or sclerosing class (Berden/EUVAS class)</td>
</tr>
<tr>
<td>Monoclonal Ig GN</td>
<td>Monoclonal Ig deposition disease, proliferative GN with monoclonal Ig deposits, immunotactoid glomerulopathy, fibrillary GN with monoclonal Ig deposits</td>
<td>Mesangial, endocapillary, exudative, membranoproliferative, necrotizing, crescentic, sclerosing, or multiple</td>
<td></td>
</tr>
<tr>
<td>C3 glomerulopathy</td>
<td>C3 GN, dense deposit disease</td>
<td>Mesangial, endocapillary, exudative, membranoproliferative, necrotizing, crescentic, sclerosing, or multiple</td>
<td></td>
</tr>
</tbody>
</table>

Atypical PIGN

- Rarely, persisting disease activity
- Role of C5i

Outcome

Table 7 Summary of characteristics and outcomes from previous studies of APIGN compared with our study

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Year</th>
<th>Case</th>
<th>Biopsy incidence</th>
<th>Mean/median age</th>
<th>Diabetes</th>
<th>Main organism</th>
<th>Site of infection</th>
<th>ESRF risk</th>
<th>Mortality risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Richmond et al. 21</td>
<td>New Zealand</td>
<td>1970–1987</td>
<td>41</td>
<td>N/A</td>
<td>36</td>
<td>N/A</td>
<td>Non-Streptococcal</td>
<td>URTI</td>
<td>34%</td>
<td>36%</td>
</tr>
<tr>
<td>2 Keller et al. 19</td>
<td>Germany</td>
<td>1984–1993</td>
<td>30</td>
<td>4.5%</td>
<td>49</td>
<td>N/A</td>
<td>Streptococcal</td>
<td>Teeth</td>
<td>13%</td>
<td>3%</td>
</tr>
<tr>
<td>3 Montseny et al. 22</td>
<td>France</td>
<td>1976–1993</td>
<td>76</td>
<td>4.5%</td>
<td>48</td>
<td>8%</td>
<td>Staphylococcus</td>
<td>URTI</td>
<td>8%</td>
<td>11%</td>
</tr>
<tr>
<td>4 Moroni et al. 23</td>
<td>Italy</td>
<td>1979–1999</td>
<td>50</td>
<td>N/A</td>
<td>54</td>
<td>10%</td>
<td>Streptococcus</td>
<td>URTI</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>5 Srivastava et al. 24</td>
<td>Thailand</td>
<td>1999–2005</td>
<td>36</td>
<td>3.6%</td>
<td>47</td>
<td>12%</td>
<td>Non-streptococcal</td>
<td>N/A</td>
<td>14%</td>
<td>0%</td>
</tr>
<tr>
<td>6 Nasr et al. 25</td>
<td>USA</td>
<td>1995–2005</td>
<td>86</td>
<td>0.6%</td>
<td>56</td>
<td>21%</td>
<td>Streptococcus</td>
<td>URTI</td>
<td>17%</td>
<td>8%</td>
</tr>
<tr>
<td>7 Wen et al. 26</td>
<td>Taiwan</td>
<td>2000–2008</td>
<td>20</td>
<td>N/A</td>
<td>61</td>
<td>25%</td>
<td>Staphylococcus</td>
<td>Skin</td>
<td>25%</td>
<td>30%</td>
</tr>
<tr>
<td>8 Nasr et al. 13</td>
<td>USA</td>
<td>2000–2010</td>
<td>109</td>
<td>0.9%</td>
<td>&gt;65</td>
<td>49%</td>
<td>Staphylococcus</td>
<td>Skin</td>
<td>11%</td>
<td>13%</td>
</tr>
<tr>
<td>9 Luo et al. 14</td>
<td>China</td>
<td>2000–2009</td>
<td>64</td>
<td>N/A</td>
<td>29</td>
<td>2%</td>
<td>Streptococcus</td>
<td>URTI</td>
<td>4%</td>
<td>0%</td>
</tr>
<tr>
<td>10 Helal et al. 27</td>
<td>Tunisia</td>
<td>1976–2004</td>
<td>148</td>
<td>N/A</td>
<td>36</td>
<td>4%</td>
<td>Streptococcus</td>
<td>URTI</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>11 Hamouda et al. 28</td>
<td>Tunisia</td>
<td>1991–2007</td>
<td>50</td>
<td>N/A</td>
<td>37</td>
<td>10%</td>
<td>Streptococcus</td>
<td>URTI</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>12 Natarajen et al. 18</td>
<td>India</td>
<td>2009–2011</td>
<td>102</td>
<td>N/A</td>
<td>33</td>
<td>3%</td>
<td>Streptococcus</td>
<td>URTI</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>13 Our study</td>
<td>Australia</td>
<td>2004–2014</td>
<td>43</td>
<td>11.4%</td>
<td>44</td>
<td>61%</td>
<td>Streptococcus</td>
<td>Skin</td>
<td>50%</td>
<td>14%</td>
</tr>
</tbody>
</table>

Modified from Luo et al. 14 with permission. We would like to thank the authors and Dustri-Verlag for permission to use their table. N/A, not applicable; URTI, upper respiratory tract infection.

Treatment

• PSGN
  • Supportive care
  • Steroids in crescentic GN ? Weak evidence
  • Emerging role of C5i in Atypical forms

• IRGN
  • Supportive care
  • Prevention of infection ; vaccination
  • Eradication of infection
Conclusion

• Classical PSGN is becoming rarer. Non-PSGN/IRGN increasingly recognized.
• Immune complex based pathology
• PSGN associated with Nephritogenic antigens (SpeB / NAPLR)
• Complement defects lead to Atypical/C3GN
• Outcome is dependent on co-morbidities.