Acquired Drivers of Disease
C3 glomerulopathy
C3 nephritic factor and other autoantibodies

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Disclosure of Interests

- Alexion – Funding for pre-clinical studies
- Achillion – Consultancy
C3 nephritic factors

Autoantibodies that prolong the half-life of the alternative pathway C3 convertase (denoted C3NeF)$^1$

C3 nephritic factors

Autoantibodies that prolong the half-life of the alternative pathway C3 convertase (denoted C3NeF)

- Required Mg but not Ca
- Extremely stable
- was an IgG molecule\(^2-4\)
- shown to bind to C3bBb\(^1\)
- heavily glycosylated and removal of carbohydrate groups was associated with loss of activity\(^5\)
- acquired antibody – discordant occurrence in identical twins\(^6\)

C3 nephritic factors

Autoantibodies that prolong the half-life of the alternative pathway C3 convertase (denoted C3NeF)

Robust association with C3 glomerulopathy

e.g. Dense deposit disease 86%\(^1\); C3 glomerulonephritis 54%\(^1\)

Table 4 | Complement component assessment according to histological type

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>MPGN 1</th>
<th>DDD</th>
<th>GNC3</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>115</td>
<td>41</td>
<td>22</td>
<td>53</td>
</tr>
<tr>
<td>C3(^9) (660 to 1250 mg/l)</td>
<td>621.91 ± 339.5</td>
<td>583.1 ± 360.7</td>
<td>492.8 ± 337.7</td>
<td>705.4 ± 305.2</td>
</tr>
<tr>
<td>Low C3 (&lt;660 mg/l)</td>
<td>53 (46.1%)</td>
<td>19 (46.3%)</td>
<td>13 (59.1%)</td>
<td>21 (39.6%)</td>
</tr>
<tr>
<td>C4(^7) (93 to 380 mg/l)</td>
<td>227.9 ± 86.3</td>
<td>198.4 ± 65.7</td>
<td>204.8 ± 88.9</td>
<td>260.8 ± 89.3</td>
</tr>
<tr>
<td>Low C4 (&lt;93 mg/l)</td>
<td>2 (1.7%)</td>
<td>1 (2.4%)</td>
<td>1 (4.5%)</td>
<td>0</td>
</tr>
<tr>
<td>Factor B(^9) (90 to 320 mg/l)</td>
<td>116.4 ± 49.3</td>
<td>110.9 ± 42.2</td>
<td>112.6 ± 39.9</td>
<td>122.2 ± 57.7</td>
</tr>
<tr>
<td>Low factor B (&lt;90 mg/l)</td>
<td>34 (29.6%)</td>
<td>14 (34.1%)</td>
<td>6 (27.3%)</td>
<td>14 (26.4%)</td>
</tr>
<tr>
<td>Low factor H (&lt;338 mg/l)</td>
<td>8 (6.9%)</td>
<td>2 (4.9%)</td>
<td>4 (18.2%)</td>
<td>2 (3.8%)</td>
</tr>
<tr>
<td>Low factor I (&lt;42 mg/l)</td>
<td>3 (2.6%)</td>
<td>3 (7.3%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>C3NeF</td>
<td>65 (58.6%)</td>
<td>22 (53.6%)</td>
<td>19 (86.4%)</td>
<td>24 (45.3%)</td>
</tr>
<tr>
<td>Unexplained C3 &lt;660 mg/l</td>
<td>6 (5.2%)</td>
<td>1 (2.4%)</td>
<td>0</td>
<td>5 (9.4%)</td>
</tr>
</tbody>
</table>

Abbreviations: C3NeF, C3 nephritic factor; DDD, dense deposit disease; GNC3, glomerulonephritis with isolated C3 deposits; MPGN, membranoproliferative glomerulonephritis.
\(^1\)Normal values are indicated in brackets.
\(^2\)C3NeF determination was not available in four patients.
\(^3\)Patients under immunosuppressive therapy at the time of complement assessment were excluded from this analysis (N=19). Mean ± s.d., number (percentage).

C3 nephritic factors

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Partial Lipodystrophy, Idiopathic MPGN1, Post-streptococcal glomerulonephritis\(^2\), membranous glomerulopathy\(^3\) (rare); Systemic lupus erythematosus (rare), healthy (rare)

C3 nephritic factors

Autoantibodies that prolong the half-life of the alternative pathway C3 convertase (denoted C3NeF)

Heterogeneous...

C3NeF of the amplification loop

C3 low, normal C5
‘MPGN2’, Partial lipodystrophy

C3NeF of the terminal pathway

C3 and C5 activation
Properdin-dependent (low properdin levels)
‘MPGN3’, ‘MPGN1’ (some)

C3 nephritic factors

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Properdin-\textit{independent} C3NeF have no effect on C5 activation; increase convertase half-life >50-fold\(^4\)

Properdin-\textit{dependent} C3NeF enhance C5 activation and terminal pathway activation; increase convertase half-life 10-20-fold\(^4\)

C3 nephritic factors

Autoantibodies that prolong the half-life of the alternative pathway C3 convertase (denoted C3NeF)

Relationship to renal disease:

- Systemic hypocomplementaemia that is associated with C3NeF predisposes to nephritis
- C3NeF acts locally to cause tissue injury
- Abnormal immune complex clearance due to both hypocomplementaemia and molecular interactions of C3NeF with regulators
C3 nephritic factors

Autoantibodies that prolong the half-life of the alternative pathway C3 convertase (denoted C3NeF)

Relationship to renal disease:

Conflicting associations between:

- serum C3 and C3NeF levels
- presence of C3NeF and rate of progression of nephritis
- C3Nef and recurrence of disease in allograft
C3 nephritic factors

Several assays that utilise convertase binding and stabilisation\textsuperscript{1-3}

Techniques include:

- Fluid-phase C3 activation
- C3 convertase stabilisation
- C3 convertase stabilisation with properdin
- C3Nef IgG-binding to pre-formed convertase on cells\textsuperscript{3} or ELISA\textsuperscript{4} plates
- Hemolytic assay

\textsuperscript{1} Fremeaux-Bacchi et al Nephrol. Dial. Transplantation 1994; \textsuperscript{2} Paixao-Cavalcante et al Kidney International 2012; \textsuperscript{3} Zhang et al CJASN 2014; \textsuperscript{4} Enzyme-linked immunosorbent assay
C3 nephritic factors

Several assays that utilise convertase binding and stabilisation\(^1-^3\)

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Other autoantibodies:

- Anti-factor B autoantibodies\(^5\), anti-factor H antibodies\(^6\)
- Combined anti-C3 and anti-factor B autoantibodies\(^7\)

Breakout group - Questions

3. How should C3 nephritic factors be measured in the clinical laboratory? (Discussion needs to include relevance of quality controls, reliable quantitation, standardization of tests)

5. At what time and at which frequency should acquired factors be screened?
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Other autoantibodies:

- Anti-factor B autoantibodies\(^5\)
- Combined C3Nef and anti-factor B autoantibodies\(^6\)

1. What are the clinically important acquired factors that should be screened for in patients with C3 glomerulopathy?
2. What are the clinically important acquired factors that should be screened for in patients with aHUS?
4. How should anti-factor H autoantibodies be measured and quantified? (Discussion needs to include relevance of quality controls, reliable quantitation, standardization of tests)
5. At what time and at which frequency should acquired factors be screened?
6. Should we include the screening of other biomarkers or genetic predisposition for acquired disease?
7. Can acquired drivers of disease be used to define subtypes of C3G?
C3 nephritic factors

Several assays that utilise convertase binding and stabilisation

Example¹:

C3 nephritic factors

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Relationship to renal disease: