WELCOME TO

ESPN/ERKNet
Educational Webinars on Pediatric Nephrology & Rare Kidney Diseases

Date: 02 February 2021

Topic: C3 Glomerulopathies

Speaker: Christoph Licht

Moderator: Marina Vivarelli
Outline

• MPGN – the traditional classification

• From MPGN to C3G – the new classification

• Pathogenesis – lessons learned from mice and men

• Diagnosis, treatment and outcome

• Summary and perspectives
MPGN – the traditional classification
Historical background

- Volhard and Fahr (1914): Die Brightsche Nierenkrankheit
  “Camera lucida” drawing of lobular glomerulonephritis

- Habib and Hamburger (1960):
  At the first worldwide Renal Biopsy Meeting, MPGN is first defined via a variety of findings made in patients with Bright's disease; MPGN becomes a formally named sub-type of glomerulonephritis ("a disease").

- Clinical phenotype (1960's):
  - Mean age 10 (range 2-17)
  - Nephrotic syndrome (70%)
  - Hematuria (90%)
  - Renal function “low” (33%)

- Clark West (1965):
  - Describes hypocomplementemia in MPGN
  - Complement defects (classical pathway) suspected
Bright's disease

Volhard and Fahr (1914). Die Brightsche Nierenkrankheit
Membranoproliferative pattern

Membranoproliferative pattern

C3 and IgG
Membranoproliferative pattern
Membranoproliferative pattern (1970's-1980's)

• **MPGN Type I:**
  Subendothelial deposits
  West et al, J Pediatr 1965

• **MPGN Type II / DDD:**
  Deposits in lamina densa of glomerular basement membrane

• **MPGN Type III:**
  Subendothelial and subepithelial deposits
  Burkholder et al, Am J Pathol 1969
  Anders et al, Virchows Arch A Pathol Anat Histol 1997
  Strife et al, Clin Nephrol 1984
Histological findings in MPGN include ... ?

A. Electron dense deposits in various glomerular localizations

B. C3

C. IgG

D. All of the above
Which is not a cause of secondary MPGN?

A. HIV
B. Hepatitis B / C
C. Leukemia / lymphoma
D. Cystic fibrosis
## Secondary MPGN (80%)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infections</strong> (bacterial / viral / protozoal)</td>
<td>Hepatitis B / C</td>
</tr>
<tr>
<td></td>
<td>EBV</td>
</tr>
<tr>
<td></td>
<td>HIV</td>
</tr>
<tr>
<td></td>
<td>Malaria</td>
</tr>
<tr>
<td></td>
<td>Mycoplasma</td>
</tr>
<tr>
<td></td>
<td>Tuberculosis</td>
</tr>
<tr>
<td><strong>Systemic immune disease</strong></td>
<td>Cryoglobulinemia</td>
</tr>
<tr>
<td></td>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td></td>
<td>Sjögren’s syndrome</td>
</tr>
<tr>
<td></td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td><strong>Neoplasmas / dysproteinemias</strong></td>
<td>Plasma cell dyscrasia</td>
</tr>
<tr>
<td></td>
<td>Light / heavy chain disease</td>
</tr>
<tr>
<td></td>
<td>Leukemia / lymphoma / other malignancies</td>
</tr>
<tr>
<td></td>
<td>Waldenstrom macroglobulinemia</td>
</tr>
<tr>
<td><strong>Chronic liver disease</strong></td>
<td>Hepatitis / cirrhosis</td>
</tr>
<tr>
<td></td>
<td>Alpha-1-antitrypsin deficiency</td>
</tr>
<tr>
<td><strong>Miscellaneous (null C3 + null IgG)</strong></td>
<td>TMA (aHUS / TTP)</td>
</tr>
<tr>
<td></td>
<td>Radiation nephropathy</td>
</tr>
<tr>
<td></td>
<td>Antithrombophilipid syndrome</td>
</tr>
<tr>
<td></td>
<td>Sickle cell disease</td>
</tr>
<tr>
<td></td>
<td>Transplant glomerulopathy</td>
</tr>
</tbody>
</table>
From MPGN to C3G – the new classification
New concept of a complement disease spectrum:
- aHUS and C3G share common genetic risk factors
- Constitutional or acquired risk factors are associated with disease spectrum ranging from aHUS to C3G
- aHUS is caused by local (EC) complement dysregulation
- C3G is caused by systemic complement dysregulation
Historical vs. current classification of MPGN

Historical classification
- MPGN type I: Mesangial and subendothelial deposits
- MPGN type II: Highly electron-dense mesangial and intramembranous deposits ± Bowman’s capsule deposits
- MPGN type III: Mesangial, subendothelial, subepithelial, and/or intramembranous deposits

Electron microscopy
- C3 with IgG and/or IgM and/or C1q
- C3 alone
- C3 alone
- C3 alone
- C3 with IgG and/or IgM and/or C1q

Immunofluorescence
- C3GN
- DDD
- C3GN

Modern categories
- Immunoglobulin-mediated MPGN type I
- C3 glomerulopathies
- Immunoglobulin-mediated MPGN type III

Consider autoimmunity, infection and monoclonal gammopathy

Cook and Pickering, Nat Rev Nephrol 2015
Dominant C3 staining: C3 staining 2 magnitudes stronger than IgM, IgA, IgG, C1q staining  

C3 Glomerulopathy Consensus 

First biopsy: IC-MPGN

IgG

IgM

C3

C1q

Courtesy of Francesca Diomedi, Pathology, Bambino Gesu Pediatric Hospital, Rome, Italy
Second biopsy (+10 months): C3GN

Courtesy of Francesca Diomedi, Pathology, Bambino Gesu Pediatric Hospital, Rome, Italy
First biopsy: IC-MPNG

Courtesy of Patrick Walker, Arkana Laboratories, Little Rock, AR
Second biopsy (+6 months): C3GN

Courtesy of Patrick Walker, Arkana Laboratories, Little Rock, AR
Pathogenesis
Lessons learned from mice and men
Which complement pathway is mainly involved in the pathogenesis of MPGN?

A. Classical pathway

B. Lectin pathway

C. Alternative pathway

D. Terminal pathway
Cfh−/− pigs

Thickened GBM with intramembraneous dense deposits

Intramembraneous dense deposits contain C3

Intramembranous dense deposits contain C5b-9

WT

CFH I1166R

Cfh-/- mice

Cfh-/-

C3

C9

Cfh-/-Cfb+/-  Pickering et al, Nat Genet 2002

Cfh-/-Cfb-/-
Alternative pathway activation and regulation

Decay acceleration:
- CFH
- DAF
- CR1

Terminal pathway activation:
- CFH
- CFI
- MCP

C3 activation:
- CFB
- CFD
- CFP

C3 inactivation:
- CFH
- CFI
- MCP
- CR1
- THBD

Adapted from Riedl / Licht, Pediatr Nephrol 2017
Alternative pathway dysregulation

*aHUS vs. C3G*

**aHUS**
- EC activation
- EC injury

**C3**

**C3b**

**C5**

**C5b-9**

**iC3b**

**C3d, C3e, C3f, C3g**

**C3G**

- Glomerular deposits

Adapted from Riedl / Licht, Pediatr Nephrol 2017
Role of C3 in complement-mediated glomerular disease: *Cfh-/- Cfi-/-* mice

Rose et al, J Clin Invest 2008
Complement alternative pathway defects in C3G

**Summary**

- **Autoantibodies**
  - C3bBb components
    - C3NeF etc.
    - FB
    - C3b
  - C3bBb regulators
    - FH

- **Mutations**
  - C3bBb components
    - C3
    - FB
  - C3bBb regulators
    - FH
    - FI
    - MCP/CD46
    - THBD/CD141

![Diagram showing the complement system and C3Bb components](image_url)
### Glomerular Complement Profile in C3G

#### Table:

<table>
<thead>
<tr>
<th>Protein Description</th>
<th>Patient 01</th>
<th>Patient 02</th>
<th>Patient 03</th>
<th>Patient 04</th>
<th>Patient 05</th>
<th>Patient 06</th>
<th>Patient 07</th>
<th>Patient 08</th>
<th>Patient 09</th>
<th>Patient 10</th>
<th>Patient 11</th>
<th>Patient 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complement C3</td>
<td>71</td>
<td>44</td>
<td>79</td>
<td>10</td>
<td>15</td>
<td>21</td>
<td>75</td>
<td>24</td>
<td>8</td>
<td>7</td>
<td>25</td>
<td>22</td>
</tr>
<tr>
<td>Complement factor H-related protein 1</td>
<td>22</td>
<td>5</td>
<td>16</td>
<td>3</td>
<td>2</td>
<td>7</td>
<td>19</td>
<td>11</td>
<td>4</td>
<td>3</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Complement component C9</td>
<td>21</td>
<td>15</td>
<td>17</td>
<td>3</td>
<td>4</td>
<td>4</td>
<td>14</td>
<td>6</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Complement component C5</td>
<td>16</td>
<td>7</td>
<td>13</td>
<td>4</td>
<td>4</td>
<td>6</td>
<td>16</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Complement factor H-related protein 5</td>
<td>11</td>
<td>7</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Complement component C8 alpha chain</td>
<td>5</td>
<td>2</td>
<td>9</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>6</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Complement component C6</td>
<td>5</td>
<td>4</td>
<td>5</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Complement component C8 beta chain</td>
<td>6</td>
<td>3</td>
<td>5</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Complement component C7</td>
<td>6</td>
<td>2</td>
<td>5</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Complement component C8 gamma chain</td>
<td>3</td>
<td>2</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Complement C4-A</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Complement factor H-related protein 2</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Complement factor H</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Complement factor I</td>
<td>7</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

#### Notes:

- **Probability Legend:**
  - Over 95%
  - 80% to 94%
  - 50% to 79%
  - 20% to 49%
  - 0% to 19%

- **Data Source:**
  - Sethi et al, Kidney Int 2009
  - Sethi et al, Nephrol Dial Transplant 2017
### Autoimmune causes for C3G

**Autoantibodies**

<table>
<thead>
<tr>
<th>Autoantibody</th>
<th>Incidence</th>
<th>Co-existing with C3Nef?</th>
<th>Effect on complement</th>
<th>Routine testing?</th>
</tr>
</thead>
<tbody>
<tr>
<td>C3NeF</td>
<td>Common</td>
<td>-</td>
<td>Stabilizes AP C3 convertase</td>
<td>Yes</td>
</tr>
<tr>
<td>C4NeF</td>
<td>Rare</td>
<td>Yes</td>
<td>Stabilizes CP C3 &amp; C5 convertases</td>
<td>No</td>
</tr>
<tr>
<td>C5NeF</td>
<td>Rare</td>
<td>Yes</td>
<td>Stabilizes AP C5 convertase</td>
<td>No</td>
</tr>
<tr>
<td>Anti-FB Ab</td>
<td>Rare</td>
<td>No</td>
<td>Stabilizes AP C3 convertase</td>
<td>No</td>
</tr>
<tr>
<td>Anti-C3b Ab</td>
<td>Rare</td>
<td>No</td>
<td>Stabilizes AP C3 convertase</td>
<td>No</td>
</tr>
<tr>
<td>Anti-FH Ab</td>
<td>Rare</td>
<td>Yes</td>
<td>Fluid phase regulation</td>
<td>Yes</td>
</tr>
</tbody>
</table>
# Genetic causes for C3G

<table>
<thead>
<tr>
<th>Gene/Protein</th>
<th>Mutation/SNP</th>
<th>Function</th>
<th>Phenotype</th>
</tr>
</thead>
</table>
| FH           | Homo-/compound heterozygous SCRs 1–4 (regulatory domain) | Intact surface binding  
Reduced C3b binding  
Loss of FH cofactor and decay-accelerating activity | C3G IC-MPGN |
| FI           | Homozygous  
Heterozygous | Decreased FI mediated C3b degradation | C3G IC-MPGN |
| C3           | Heterozygous | C3mut – resistant to cleavage by C3bBb  
C3mut convertase – resistant to FH inactivation  
C3 binding with FI or FH | C3GN IC-MPGN |
| FB           | Heterozygous/homozygous | Alters C3-FB interaction | C3G IC-MPGN |
| THBD         | Homozygous   | Not tested | DDD |
| DGKE         | Homozygous  
Heterozygous – unclear impact | Not complement mediated | MPGN |
Cohort: 140 patients with idiopathic Ig-MPGN (52%) and C3G (DDD 33%; C3GN 66%)

Biochemical analysis:
- Ig-MPGN vs C3G No difference in C3, C4, SC5b-9 and C3NeF
- Ig-MPGN vs DDD/C3GN C3NeF higher in DDD than in Ig-MPGN / C3GN
  C3 levels lower in DDD than in Ig-MPGN / C3GN
- Mutation ± C3NeF Associated with lower C3 and higher sC5b-9 levels

Genetic analysis:
- Mutations Detected in Ig-MPGN and C3G
  Affect complement alternative pathway (C3bBb: C3, CFB)
- Susceptibility variants CD46 366A in Ig-MPGN; CFH V62 and A473 in C3G
- Disease manifestation Only combination of mutation and susceptibility variant increases risk of disease manifestation

Clinical implications:
- Outcome No difference between Ig-MPGN and C3G (DDD; C3GN)
- Absence of mutation ± C3NeF predicts worse outcome

Genetic causes for C3G
Susceptibility variants

The role of FHRs in C3G

- 11 y/o male
- Macroscopic hematuria, nephrotic range proteinuria 3 days post chicken pox immunization
- **Kidney biopsy:** DDD
- Treatment with prednisone and MMF
- Nevertheless, progression to ESKD within 3 months (PD)
- Kidney transplant (deceased donor) after 4 years
- Proteinuria recurs immediately post TX
- **Complement system:**
  - Low C3; normal C4
  - C3NeF positive
  - No mutations in FH, FHR5, F1, MCP/CD46, THBD/CD141, FB, C3
Serial biopsies of renal graft

Post-TX day 6

Post-TX day 17

Post-TX day 180
Three copies of FHR1 - 150% plasma FHR1
Localization of renal FH and CFHR1

6 mths post RTX

Graft NX

6 mths post RTX

FHR1

Graft NX

Graft NX
Competition between FHR1 and FH

- FHR1 competes with FH for surface and C3b binding
- FHR1 lacks intrinsic cofactor activity
- FHR1 surplus impairs complement regulatory activity of FH on surfaces
FHRs 1, 2, 5 are prone to form dimers / oligomers

## Genetic causes for C3G – *FH* deregulation

<table>
<thead>
<tr>
<th>Protein name</th>
<th>Protein structure</th>
<th>Phenotype</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Normal proteins</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FHR1</td>
<td><img src="image" alt="FHR1 structure" /></td>
<td>NA</td>
<td>Homodimerizes and heterodimerizes with FHR2; competitive antagonist of factor H; C5 convertase inhibitor and terminal complement cascade blocker</td>
</tr>
<tr>
<td>FHR2</td>
<td><img src="image" alt="FHR2 structure" /></td>
<td>NA</td>
<td>Homodimerizes and heterodimerizes with FHR1; competitive antagonist of factor H; C3 convertase inhibitor</td>
</tr>
<tr>
<td>FHR3</td>
<td><img src="image" alt="FHR3 structure" /></td>
<td>NA</td>
<td>Exact function unknown</td>
</tr>
<tr>
<td>FHR5</td>
<td><img src="image" alt="FHR5 structure" /></td>
<td>NA</td>
<td>Homodimerizes; competitive antagonist of factor H; binds to extracellular matrix; complement amplifier and surface anchor for properdin</td>
</tr>
<tr>
<td><strong>Fusion proteins</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FHR2_{1-2}–FHR5_{1-9}</td>
<td><img src="image" alt="FHR2_{1-2}–FHR5_{1-9} structure" /></td>
<td>DDD</td>
<td>Normal gene copies present in variant allele: <em>CFHR3</em>, <em>CFHR1</em> and <em>CFHR4</em></td>
</tr>
<tr>
<td>FHR5_{1-2}–FHR5_{1-9}</td>
<td><img src="image" alt="FHR5_{1-2}–FHR5_{1-9} structure" /></td>
<td>C3GN</td>
<td>Normal gene copies present in variant allele: <em>CFHR3</em>, <em>CFHR1</em>, <em>CFHR4</em>, <em>CFHR2</em> and <em>CFHR5</em></td>
</tr>
<tr>
<td>FHR3_{1-2}–FHR1_{1-5}</td>
<td><img src="image" alt="FHR3_{1-2}–FHR1_{1-5} structure" /></td>
<td>C3GN</td>
<td>Normal gene copies present in variant allele: <em>CFHR3</em>, <em>CFHR1</em>, <em>CFHR4</em>, <em>CFHR2</em> and <em>CFHR5</em></td>
</tr>
<tr>
<td>FHR1_{1-2}–FHR5_{1-9}</td>
<td><img src="image" alt="FHR1_{1-2}–FHR5_{1-9} structure" /></td>
<td>C3GN and/or DDD</td>
<td>Normal gene copies present in variant allele: <em>CFHR3</em> and <em>CFHR5</em></td>
</tr>
<tr>
<td>FHR1_{1-4}–FHR1_{1-5}</td>
<td><img src="image" alt="FHR1_{1-4}–FHR1_{1-5} structure" /></td>
<td>C3GN</td>
<td>Normal gene copies present in variant allele: <em>CFHR3</em>, <em>CFHR4</em>, <em>CFHR2</em> and <em>CFHR5</em></td>
</tr>
<tr>
<td>FHR5_{1-2}–FHR2_{1-4}</td>
<td><img src="image" alt="FHR5_{1-2}–FHR2_{1-4} structure" /></td>
<td>C3GN</td>
<td>Normal gene copies present in variant allele: <em>CFHR3</em>, <em>CFHR1</em>, <em>CFHR4</em>, <em>CFHR2</em> and <em>CFHR5</em></td>
</tr>
</tbody>
</table>

Smith et al, Nat Rev Nephrol 2019
FH deregulation in C3G via FHR multimers

Diagnosis, treatment and outcome
### Diagnostic workup for C3G patients

<table>
<thead>
<tr>
<th>Category</th>
<th>Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global complement function</td>
<td>CH50, APH50</td>
</tr>
<tr>
<td>Complement activation</td>
<td>C3, C4, C3d</td>
</tr>
<tr>
<td>Terminal pathway activation</td>
<td>SC5b-9</td>
</tr>
<tr>
<td>Complement protein levels</td>
<td>CFH, CFI, CFB</td>
</tr>
<tr>
<td>Autoimmune forms</td>
<td>C3 Nephritic factor (C3NeF), CFH/CFB/C3b autoantibodies</td>
</tr>
<tr>
<td>Genetic forms</td>
<td>Mutations/CNVs in CFH, CFI, CFB, MCP/CD46, C3 CFHR–5 (MLPA)</td>
</tr>
</tbody>
</table>

**Other Nephritic factors**

**Genetic variants in FHR locus**
How to treat C3G patients?

A. There is no treatment for C3G.

B. Transplant is a definitive treatment for C3G.

C. Current treatment recommendations for C3G mainly rely on case reports / small case series.

D. Current treatment recommendations for C3G builds on RTCs.
Treatment

Immunosuppression

Steroids:
- Benefit of long-term (6-12 months) low-dose steroids in patients with MPGN and C3G with respect to proteinuria and renal function.

Mycophenolate mofetil (MMF):
- Benefit of use alone or in combination with steroids in patients with primary MPGN with respect to proteinuria and renal function.
- 5/9 children with MPGN treated with steroids + MMF for 40 months had CR/PR (of note, all patients with low C3 failed).
- 42/97 C3G patients (81 C3GN; 16 DDD) treated with steroids + MMF had remission of proteinuria and prevention of renal failure compared to other immunosuppression and eculizumab regardless of presence of complement mutations and/or autoantibodies.
- 22/30 C3G patients treated with steroids + MMF and f/u of 22 months had CR/PR. 50% of patients with MMF taper relapsed.

KDIGO expert opinion:
- MMF is beneficial in patients with IC-MPGN and C3G.
- Following steroid taper over 6-12 months, MMF monotherapy is continued for 12-18 months.

Goodship et al, Kidney Int 2017
<table>
<thead>
<tr>
<th>Reference</th>
<th>Diagnosis</th>
<th>Patients</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
</table>
| Pérez-Sáez et al, Transplant Proc 2011 | MPGN I    | 1 adult  | Rituximab + PE | Partial response  
Deterioration of renal function  
Proteinuria |
| Kmar et al, Clin Nephrol 2011  | DDD       | 1 adolescent | Steroids + Cyclo + PE | Complete remission  
Normal kidney function  
Normal AP activity |
| Haeffner et al, Pediatr Nephrol 2015 | C3G  
(Mut. neg., C3Nef pos.) | 4 children | PE +  
Steroids + MMF  
Eculizumab | Partial response  
Proteinuria improved (4/4) / normalized (2/4)  
eGFR normalized (4/4)  
C3 improved (2/4)  
TCC improved (2/4) (2 were always normal)  
C3Nef negative (4/4) |
| McGinley et al, Nephron 1985   | MPGN I / III DDD | 4 adults | PE | MPGN: Improved proteinuria  
Stabilization of kidney function  
DDD: Improved kidney function in 1 patient |
| Oberkircher et al, Transplant Proc 1988 | DDD (TX) | 1 child  | PE | Partial response  
Improved renal outcome |
| Kurtz and Schlueter, J Clin Apher 2002 | DDD (TX) | 1 adolescent | PE | Stabilized kidney function  
Treatment discontinued – graft loss |
## Treatment

### Eculizumab

<table>
<thead>
<tr>
<th>Patients</th>
<th>Complete response</th>
<th>Partial response</th>
<th>No response</th>
<th>Treatment response correlated with</th>
</tr>
</thead>
</table>
| **Vivarelli, 2014**<br>13 patients<br>C3G / DDD<br>Native / TX kidneys<br>C3Nef / genetic | 10 (77%) | 1 (8%) | 2 (15%) | - Elevated sC5b-9  
- Shorter disease duration |
| **LeQuintrec, 2018**<br>26 patients<br>13/26 pediatric<br>14 months | 6 (23%) | 6 (23%) | 14 (54%) | - Rapidly progressive disease & intense extracapillary proliferation  
- Complement AP mutations / autoantibodies made no difference |
| **Ruggenenti, 2019**<br>(EAGLE study:<br>2 x 48 weeks ecu with 12 weeks washout; aiming at improvement in proteinuria @ 24 / 48 weeks) | 0 | 3 (30%) | 7 (70%) – improvement during first period, but benefit lost during washout | |

Eculizumab in IC-MPGN/C3G currently recommended as rescue therapy, only. Best response in patients with recent onset of disease, intense inflammation, and high C5b-9 levels.
## Outcome

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Patients</th>
<th>Follow Up</th>
<th>Outcome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPGN</td>
<td>50 children</td>
<td>11 years (median)</td>
<td>50% ESKD in 10-15 years</td>
<td><em>Schwartz et al, Pediatr Allergy Immunol 2001</em></td>
</tr>
<tr>
<td>C3GN</td>
<td>12</td>
<td>26.4 months</td>
<td>Stable kidney function</td>
<td><em>Sethi et al, Kidney Int 2012</em></td>
</tr>
<tr>
<td>DDD vs C3GN</td>
<td>80</td>
<td>28 months</td>
<td>47% DDD and 23% C3GN progress to ESKD</td>
<td><em>Medjeral-Thomas et al, Clin J Am Soc Nephrol 2014</em></td>
</tr>
<tr>
<td>MPGN / C3GN</td>
<td>134</td>
<td>10 years</td>
<td>63.5% renal survival (MPGN, DDD, C3GN show no difference)</td>
<td><em>Servais et al, Kidney Int 2012</em></td>
</tr>
<tr>
<td>IC-MPGN / C3G</td>
<td>165</td>
<td>4 years</td>
<td>100% show preserved kidney function</td>
<td><em>Kirpalani et al, Kidney Int Reports 2020</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 years</td>
<td>80% do not meet composite outcome (eGFR &lt;30; 50% eGFR reduction; initiation of RRT)</td>
<td></td>
</tr>
</tbody>
</table>

**Negative outcome predictors:**
- Age at presentation
- eGFR
- Proteinuria
- Hypertension
- Kidney biopsy: glomerular crescents
Outcome
Renal transplant

- 32.4% risk of graft loss from recurrence at 5 years post TX in children with MPGN. (Van Stralen et al, Nephrol Dial Transplant 2013 – ESPN/ERA-EDTA registry)


- 66.7% risk of graft loss from recurrence in C3G patients with median time to graft failure of 6.4 years. (Zand et al, J Am Soc Nephrol 2014)

- Cohort of n=35 C3G patients:
  Recurrence risk of 43% in MPGN, 55% in DDD, and 60% in C3GN patients. (Servais et al, Kidney Int 2012 – French cohort)

- Cohort of n=13 C3G patients (6 DDD; 7 C3GN):
  - 69% overall graft survival at 5 years.
  - All 6 DDD recurred, and 3 (50%) failed due to recurrence.
  - 4/7 (57%) C3GN recurred, and 3/4 (75%) failed due to recurrence. (Medjeral-Thomas et al, J Am Soc Nephrol 2014 – English cohort)

High risk of disease recurrence and graft failure due to recurrence in patients with MPGN < DDD < C3GN.
Summary and perspectives
Kidney biopsy → Proliferative GN with intense C3 (IF)
Exclusion of secondary causes

IF: C3 and IgG positive → IC-MPGN

IF: C3 dominant → C3G
EM: Based on location of deposits → C3GN or DDD

AP complement workup
Including biochemistry, autoantibodies and genetics

Supportive therapy
Including RAAS blockade; low-salt diet; lipid control

Proteinuria >500 mg/24hr or moderate inflammation on renal biopsy

Immunosuppression
Prednisone ± MMF

Proteinuria >2,000 mg/24hr or severe inflammation and/or eGFR <90ml/min/m²

Immunosuppression
Prednisone + MMF
Consider methylprednisolone pulses

Reassess after 6-9 months: complete remission?

Yes
Taper prednisone, continue with MMF for 18-24 months

No
Consider rescue therapy with complement blockers
Next Webinars

**ERKNet/ERA-EDTA Advanced Webinars on Rare Kidney Disorders**
Date: 16 Feb 2021
Speaker: Frank Bridoux
Topic: Paraprotein associated disease

**ESPN/ERKNet & ERA-EDTA Webinars on Rare Kidney Disorders**
Date: 02 March 2021
Speaker: Hans Joachim Anders & Steven Marks
Topic: Lupus nephritis in children & adults

**ERKNet/ERA-EDTA Advanced Webinars on Rare Kidney Disorders**
Date: 16 March 2021
Speaker: Olivier Devuyst
Topic: Uric acid disorders

Subscribe the ERKNet and IPNA Newsletter and don’t miss Webinars!
Atypical PIGN - a role for complement defects?

<table>
<thead>
<tr>
<th></th>
<th>Postinfectious glomerulonephritis (PIGN)</th>
<th>‘Atypical’ postinfectious glomerulonephritis (aPIGN)</th>
<th>C3 glomerulonephritis (C3GN)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LM</td>
<td>Diffuse proliferative, less commonly mesangial proliferative, or crescentic</td>
<td>Diffuse proliferative, less commonly mesangial proliferative, or crescentic</td>
<td>Membranoproliferative and less commonly mesangial proliferative</td>
</tr>
<tr>
<td>IF</td>
<td>Bright mesangial and capillary wall C3, usually with Iggs (garland pattern)</td>
<td>Bright mesangial and capillary wall C3, usually without Iggs. If present IgG (trace to 1+)</td>
<td>Bright mesangial and capillary wall C3, usually without Iggs</td>
</tr>
<tr>
<td>EM</td>
<td>Numerous subepithelial humps, few mesangial, and subendothelial deposits</td>
<td>Numerous subepithelial humps, many mesangial and subendothelial deposits, and ± intramembranous deposits</td>
<td>Many mesangial and subendothelial deposits, ± few intramembranous, and subepithelial humps</td>
</tr>
</tbody>
</table>

Abbreviations: EM, electron microscopy; IF, immunofluorescence; Ig, immunoglobulin; LM, light microscopy.

<table>
<thead>
<tr>
<th>9</th>
<th>No mutations</th>
<th>No mutations</th>
<th>Negative</th>
<th>9% Abnormal</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>c.1699A &gt; G, p.Arg567Gly</td>
<td>No mutations</td>
<td>Negative</td>
<td>0%, Normal</td>
</tr>
<tr>
<td>11</td>
<td>No mutations</td>
<td>No mutations</td>
<td>Negative</td>
<td>0%, Normal</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Positive (both assays)</th>
<th>ND</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive (both assays)</td>
<td>2.03 mg/l</td>
</tr>
<tr>
<td>Positive (C3CSAP)</td>
<td>0.21 mg/l</td>
</tr>
</tbody>
</table>

Long-Term Outcomes of C3 Glomerulopathy and Immune-Complex MPGN in Children

IC-MPGN & C3G cohort
- 165 patients
- 17 hospitals
- 3 countries
- Largest pediatric cohort

Reclassification
- 85 biopsy reports available
- 42% initially diagnosed as 'MPGN' reclassified as C3G

Clinical outcomes in IC-MPGN vs. C3G

CONCLUSION:
Many patients initially diagnosed as MPGN would meet criteria for C3G. Longer follow-up may reveal a worse kidney prognosis in C3G vs. IC-MPGN.