C1q nephropathy – the Diverse Disease

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Definition

• Dominant or codominant (≥2+), mesangial staining for C1q, usually with immunoglobulins
• Absence of clinical or laboratory evidence of SLE
  – Cases with histologic features of MPGN and the codominant staining for IgA were excluded?!

Clinical-pathologic categories

- FSGS or MCD
- Proliferative GN of unknown etiology
Clinical-pathologic categories

- FSGS or MCD
  - nephrotic syndrome

- Proliferative GN of unknown etiology
  - asymptomatic urinary abnormalities
  - heavy proteinuria
  - gross hematuria
  - rapidly progressive GN
  - chronic renal insufficiency

Children and young adult
Normal serum complement levels

Slovenia - 72 patients, all Caucasians, 68% male

• **Light microscopy**
  - no lesion 37.5%
  - FSGS 15.2%
  - proliferative GN 27.8%
  - other findings 19.4%

• **Clinical presentations**
  - nephrotic syndrome or nephrotic-range proteinuria 47%
  - renal insufficiency 46%
  - hematuria in 69%

• **Light microscopy and clinical presentation**
  1. No lesion (MCD-like disease) - 63% nephrotic syndrome
  2. FSGS – all nephrotic syndrome
  3. proliferative GN - asymptomatic urinary abnormalities (20%)
     or chronic kidney disease (75%)

Japan - 61 patients, age 1 - 67

• Biopsy findings
  – MCD 75%
  – FSGS 13%
  – mesangial proliferative glomerulonephritis 12%

• Clinical presentations
  – asymptomatic urinary abnormalities 59%
    • more common hematuria
  – nephrotic syndrome 41%
    • more common in MCD patients

Croatia – 10 patients, all Caucasian, age 2.7 – 64

- **Biopsy finding**
  - proliferative GN
    - 5 patients
  - MCD
    - 4 patients
  - membranous GN
    - 1 patient

- **Clinical presentation**
  - nephrotic syndrome
    - 7 patients
  - renal insufficiency
    - 2 patients
  - asymptomatic urinary abnormality
    - 1 patient
  - hematuria
    - 9 patients

Pathological features – light microscopy

- normal
- mesangial proliferation

Pathological features – light microscopy

- global endocapillary proliferation
- crescents

Galesic K, et. Al. Liječ Vjesn 2015;137:283
Pathological features – light microscopy

- FSGS – all variants were seen

Pathological features – light microscopy

• Membranous GN

PAS x400
Pathological features – light microscopy

• Membranous GN

Masson trichrome stain x400

Light microscopy – Summary

241 cases

<table>
<thead>
<tr>
<th>Series</th>
<th>Total cases</th>
<th>MCD</th>
<th>FSGS</th>
<th>PGN (immune mediated GN)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Markowitz et al. [3]</td>
<td>19</td>
<td>2 (11%)</td>
<td>17 (89%)</td>
<td>0</td>
</tr>
<tr>
<td>Fukuma et al. (children) [14]</td>
<td>30</td>
<td>22 (73%)</td>
<td>2 (7%)</td>
<td>6 (20%)</td>
</tr>
<tr>
<td>Hisano et al. [15]</td>
<td>61</td>
<td>46 (75%)</td>
<td>8 (13%)</td>
<td>7 (11%)</td>
</tr>
<tr>
<td>Vizjak et al. [10]</td>
<td>72</td>
<td>27 (38%)</td>
<td>11 (16%)</td>
<td>20 (28%)</td>
</tr>
<tr>
<td>Gunasekara et al. (children) [4]</td>
<td>35</td>
<td>19 (54%)</td>
<td>9 (26%)</td>
<td>7 (20%)</td>
</tr>
<tr>
<td>Said et al. (allografts) [13]</td>
<td>24</td>
<td>8 (33%)</td>
<td>5 (21%)</td>
<td>11 (46%)</td>
</tr>
</tbody>
</table>

Pathological features – **immunofluorescence**

- dominant or codominant C1q (≥2+)

  - mesangial deposits
  - mesangial and capillary wall deposits

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Slovenia - 72 patients
MCD 37.5%; FSGS 15.2%; proliferative GN 27.8%; others 19.4%

<table>
<thead>
<tr>
<th>Immune Reactants</th>
<th>Frequency (n [%])</th>
<th>Intensity (Mean ± SD)</th>
<th>Intensity (Median)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG</td>
<td>48 (66.7)</td>
<td>2.2 ± 0.8</td>
<td>2</td>
</tr>
<tr>
<td>IgM</td>
<td>58 (80.6)</td>
<td>1.8 ± 0.8</td>
<td>2</td>
</tr>
<tr>
<td>IgA</td>
<td>34 (47.2)</td>
<td>1.7 ± 0.9</td>
<td>1</td>
</tr>
<tr>
<td>C1q</td>
<td>72 (100.0)</td>
<td>2.9 ± 0.7</td>
<td>3</td>
</tr>
<tr>
<td>C3</td>
<td>60 (83.3)</td>
<td>1.9 ± 0.9</td>
<td>2</td>
</tr>
<tr>
<td>C4</td>
<td>25 (34.7)</td>
<td>1.4 ± 0.6</td>
<td>1</td>
</tr>
</tbody>
</table>

A “full house” pattern was found in 30.6% patients, predominantly in those with proliferative GN

Japan - 61 patients
MCD 75%; FSGS 13%; proliferative GN 12%

Asymptomatic urinary abnormalities 59%

<table>
<thead>
<tr>
<th>IgG</th>
<th>69%</th>
<th>C3</th>
<th>58%</th>
<th>IgG+C3</th>
<th>38%</th>
<th>IgG+IgM+C3</th>
<th>38%</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgM</td>
<td>14%</td>
<td>48%</td>
<td>IgM</td>
<td>20%</td>
<td>32%</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>C3</td>
<td>58%</td>
<td></td>
<td>C3</td>
<td>48%</td>
<td></td>
<td>3%</td>
<td>IgG+IgM+C3</td>
</tr>
<tr>
<td>IgG+C3</td>
<td>38%</td>
<td></td>
<td></td>
<td>IgG+IgM+C3</td>
<td>4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgM+C3</td>
<td>3%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>IgG+IgM+C3</td>
<td>38%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4%</td>
<td></td>
</tr>
</tbody>
</table>

Nephrotic syndrome 41%

There was no patient with positive IgA.
A “full house” pattern was not found.

Croatia – 10 patients
MCD 4; proliferative GN 5, membranous GN 1

C1q 3+ 6 patients
C1q 2+ 4 patients
IgG 1 patient
C3 1 patient
IgM+C3 3 patients
IgG+IgM+C3 3 patients
IgG+IgA+IgM 1 patient
IgG+IgA+IgM+C3 1 patient, “full house” pattern

Immunofluorescence – Summary

• Most cases together with C1q have staining for IgG, IgM and C3, alone or combination

• IgA may be also present, but codominant staining for IgA is diagnostic of IgA nephropathy and excludes the diagnosis of C1 nephropathy

• The “full house” pattern may be also present, in one study in 30.6% of cases
Pathological features – Electron Microscopy

- mesangial deposits
- mesangial and capillary wall deposits

References:
Pathological features – Electron Microscopy

• subepithelial and intramembranous deposits
Pathological features – Electron Microscopy

• foot process effacement
Slovenia - 72 patients
MCD 37.5%; FSGS 15.2%; proliferative GN 27.8%; others 19.4%

<table>
<thead>
<tr>
<th>Electron Microscopy Features</th>
<th>Light Microscopy Findings (n [%])</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No Lesions (n = 5)</td>
</tr>
<tr>
<td>Mesangial deposits</td>
<td>4 (80.0)</td>
</tr>
<tr>
<td>Mesangial-SED deposits</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Mesangial-SED-SEP deposits</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Mesangial-SEP deposits</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Podocyte foot process effacement(^b)</td>
<td></td>
</tr>
<tr>
<td>( \geq 50% )</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>&lt;50%</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Podocyte cytoskeleton condensation</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

Japan - 61 patients
MCD 75%; FSGS 13%; proliferative GN 12%

<table>
<thead>
<tr>
<th>Deposits</th>
<th>Asymptomatic urinary abnormalities</th>
<th>Nephrotic syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesangial</td>
<td>78%</td>
<td>96%</td>
</tr>
<tr>
<td>Mesangial+subepithelial</td>
<td>14%</td>
<td>0%</td>
</tr>
<tr>
<td>Mesangial+subendothelial</td>
<td>8%</td>
<td>4%</td>
</tr>
<tr>
<td>Mesangial+subendothelial +subepithelial</td>
<td>3%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Croatia – 10 patients
MCD 4; proliferative GN 5, membranous 1

<table>
<thead>
<tr>
<th>Deposits</th>
<th>Number of patients</th>
<th>Foot processes effacement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesangial</td>
<td>4</td>
<td>all- diffuse</td>
</tr>
<tr>
<td>Mesangial+subendothelial</td>
<td>1</td>
<td>diffuse</td>
</tr>
<tr>
<td>Mesangial+subendothelial+subepithelial+intramembranous</td>
<td>5</td>
<td>4 focal and 1 diffuse</td>
</tr>
</tbody>
</table>

Electron microscopy – Summary

• In MCD like pictures and FSGS with nephrotic syndrome deposits are present only within mesangium and they are usually associated with diffuse foot processes effacement.

• In proliferative glomerulonephritis mesangial deposits are usually accompanied with subendothelial and/or subepithelial and/or intramembranous deposits.
Differential diagnosis

• Lupus nephritis
• HIV-related “lupus-like” GN
• Primary MPGN

EXCLUSION CRITERIA

• Hypocomplementemia
• Tubuloreticular inclusions
• Codominant staining for IgA
Clinicopathological study of originally non-lupus “full-house” nephropathy

Yao-Ko Wen & Mei-Ling Chen

To cite this article: Yao-Ko Wen & Mei-Ling Chen (2010) Clinicopathological study of originally non-lupus “full-house” nephropathy, Renal Failure, 32:9, 1025-1030, DOI: 10.3109/0886022X.2010.510614

Idiopathic non-lupus full-house nephropathy is associated with poor renal outcome

Emilie C. Rijnink¹, Y.K. Onno Teng², Tineke Kraaij², Ron Wolterbeek³, Jan A. Bruijn¹ and Ingeborg M. Bajema¹

Nephrol Dial Transpl 2017
Idiopathic non-lupus “full house” nephropathy

• “Full house” pattern by IF in the absence of signs of SLE

• some of the patients described as C1 nephropathy had a “full house” pattern, in one study 30%!

• it is necessary to establish clear cut criteria to differentiate C1q nephropathy and idiopathic non-lupus full-house nephropathy
Etiology and Pathogenesis 1

Diagram:
- **Antigen** and **Antibody (IgG)** form the **C1 complex**.
- **C2a and C4b fragments**.
- **C3 convertase**.
- **C3 hydrolysis** leads to **C3b and C3a fragments**.
- **C3b cleaves C5 into C5a and C5b**.
- **Cell swells and bursts**.
- **C5b, C6, C7, C8 and C9 together form the cylindrical membrane attack complex**.
Etiology and Pathogenesis 1

- the frequent co-deposition of IgG or IgM in C1q nephropathy supports the concept of an immune complex–mediated glomerulonephritis, particularly in cases that show features of proliferative glomerulonephritis

Etiology and Pathogenesis 2

C1q-binding proteins:
- IgG
- IgM
- CRP (C-reactive protein)
- SAP (serum amyloid protein)
- PTX3 (pentraxin 3)
- Gram-negative bacteria
- LPS (lipopolysaccharide)
- Viral proteins, e.g. gp41 of HIV-1, gp21 of HTLV-1
- Beta amyloid peptide
- CR1 (complement receptor 1)
- cC1qR or CRT (calreticulin)
- gC1qR
- etc.

Etiology and Pathogenesis 2

- mesangial staining for C1q may reflect interactions other than immune complex deposition, such as binding to neoepitopes released by apoptotic cells or other proteins trapped in the glomerulus, or binding to cell surface C1q receptors on mesangial cells
- C1q may become fixed to immunoglobulin or other anionic molecules that have been trapped nonspecifically in the mesangium in the course of glomerular proteinuria
- in the setting of podocytopathy with heavy proteinuria (e.g., MCD or primary FSGS), the presence of C1q staining might reflect defective clearing of plasma proteins, rather than complement activation by immune complexes.

C1q nephropathy in two young sisters

Jameela A. Kari · Sawsan M. Jalalah

- steroid resistant nephrotic syndrome
- presenting before 2 years of age
- role for genetic factors?
- exposure to a same environmental trigger?
Etiology and Pathogenesis - Summary

• Immune complex–mediated GN
  – Proliferative C1q nephropathies

• Nonspecific trapping of C1q in the mesangium
  – C1q with MCD or FSGS presentation

Role of the genetic and environmental factors?
Treatment and Prognosis

• Data about therapy and prognosis are limited.

• There are no randomized, prospective, controlled clinical trials.

• There are no official therapeutic guidelines.
Slovenia - 53 patients follow-up 4 months to 20 years, mean 5.4±5.1

<table>
<thead>
<tr>
<th>Clinical Outcomes</th>
<th>No Lesions (n = 6)</th>
<th>No Lesions (with NS) (n = 13)</th>
<th>FSGS (with NS) (n = 9)</th>
<th>Proliferative GN (n = 14)</th>
<th>Other (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up (yr; range)</td>
<td>0.5 to 15.0</td>
<td>0.3 to 21.0</td>
<td>1.0 to 9.0</td>
<td>0.5 to 12.0</td>
<td>0.5 to 14.0</td>
</tr>
<tr>
<td>Follow-up (yr; mean ± SD)</td>
<td>5.4 ± 6.0</td>
<td>7.1 ± 7.4</td>
<td>2.9 ± 2.5</td>
<td>4.9 ± 3.5</td>
<td>6.5 ± 4.7</td>
</tr>
<tr>
<td>Normal/complete remission (n [%])</td>
<td>2 (33.3)</td>
<td>10 (76.9)</td>
<td>3 (33.3)</td>
<td>2 (14.3)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Partial remission (n [%])</td>
<td>1 (16.7)</td>
<td>3 (23.1)</td>
<td>2 (22.2)</td>
<td>0 (0.0)</td>
<td>2 (18.2)</td>
</tr>
<tr>
<td>Treatment resistant NS (n [%])</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (11.1)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Stable renal disease (n [%])</td>
<td>3 (50.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>8 (57.1)</td>
<td>4 (36.4)</td>
</tr>
<tr>
<td>Progression of renal disease (n [%])</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>2 (14.3)</td>
<td>2 (18.2)</td>
</tr>
<tr>
<td>ESRD (n [%])</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>3 (33.3)</td>
<td>2 (14.3)</td>
<td>3 (27.2)</td>
</tr>
</tbody>
</table>

Japan - 61 patients follow-up 3 to 8 years, mean 7.2±4.4

- **Asymptomatic abnormality - 36 patients**
  - 9 received steroids
    - biopsy findings of FSGS or proliferative GN
    - 2 progress to ESRD
  - 24 persistent urinary abnormalities
  - 10 normal urinalysis

- **Nephrotic syndrome – 25 patients**
  - All received steroids
    - 8 complete remissions
    - 3 persistent proteinuria
    - 13 frequent relapses
    - 1 ESRD

Croatia – 10 patients
MCD 4; proliferative GN 5, membranous GN 1

<table>
<thead>
<tr>
<th>Patient</th>
<th>Treatment</th>
<th>Follow-up (months)</th>
<th>EGFR at the time of biopsy (ml/min)</th>
<th>Last EGFR (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Glucocorticoids + cyclophosphamide</td>
<td>26</td>
<td>48</td>
<td>47</td>
</tr>
<tr>
<td>2</td>
<td>Glucocorticoids</td>
<td>33</td>
<td>104</td>
<td>120</td>
</tr>
<tr>
<td>3</td>
<td>Glucocorticoids + cyclosporine</td>
<td>23</td>
<td>100</td>
<td>99</td>
</tr>
<tr>
<td>4</td>
<td>Glucocorticoids + azathioprine</td>
<td>6</td>
<td>27</td>
<td>10</td>
</tr>
<tr>
<td>5</td>
<td>Glucocorticoids + cyclophosphamide</td>
<td>30</td>
<td>66</td>
<td>60</td>
</tr>
<tr>
<td>6</td>
<td>Glucocorticoids + cyclophosphamide</td>
<td>15</td>
<td>12</td>
<td>24</td>
</tr>
<tr>
<td>7</td>
<td>Symptomatic treatment</td>
<td>12</td>
<td>122</td>
<td>106</td>
</tr>
<tr>
<td>8</td>
<td>Glucocorticoids</td>
<td>60</td>
<td>144</td>
<td>96</td>
</tr>
<tr>
<td>9</td>
<td>Glucocorticoids + cyclosporine</td>
<td>60</td>
<td>112</td>
<td>100</td>
</tr>
<tr>
<td>10</td>
<td>Symptomatic treatment</td>
<td>28</td>
<td>105</td>
<td>128</td>
</tr>
</tbody>
</table>

Treatment and Prognosis - Summary

• C1q nephropathy with MCD-like features responds well to steroids but may have a higher rate of relapses.
• Cases with FSGS pictures had generally poor responses (steroid resistance in 60%), and additional immunosuppressive therapy is needed.
• Majority of patients with proliferative lesions who received immunosuppressive therapy have stable renal function.
• Rituximab has shown clinical benefit in same patients.

C1q deposition in the renal allograft: a report of 24 cases

Samar M Said¹, Lynn D Cornell¹, Anthony M Valeri², Sanjeev Sethi¹, Mary E Fidler¹, Fernando G Cosio³ and Samih H Nasr¹

Mod Pathol 2010;23:1080

C1q-dominant mesangial deposition in the renal allograft is a morphological pattern with no apparent clinical significance in the majority of patients. It is usually detected after the first year.
Conclusion

- Clinical presentation, histology and outcomes of C1q nephropathy are heterogeneous.
- There are two basic clinical-pathologic categories:
  - MCD-like and FSGS
  - proliferative GN
- Etiology and pathogenesis are unknown.
- It remains to be determined whether C1q nephropathy represents a single disease with diverse clinical and pathologic features or different diseases that share a common immunopathologic finding of C1q predominant deposits.
Thank you!