Membranous nephropathy

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Antalya, November 27, 2016
Lecture overview

- Definition
- Epidemiology
- Clinical features
- Histopathology
- Pathogenesis
- Treatment
- Summary
Definition

• Membranous Nephropathy (MN) = Membranous Glomerulonephritis

• Histologic description of glomerular pathology (not one single disease!) characterized by immune complex deposition in the subepithelial space of glomeruli

• MN:
  ✓ Idiopathic
  ✓ Secondary (autoimmune disease, infections, medications)
Epidemiology

• Incidence of MN:
  - adults:  1.2/100,000/year (25-30% of NS adults)
    McCogan et al. NDT 2011
  - children:  0.05-0.1/100,000/year (< 5% of NS children)
    Filler et al. AJKD, 2003
  - increasing incidence during adolescence (up to 18% of NS patents)
    Mubarak et al. NDT 2011
Clinical features of idiopathic MN

• Proteinuria: asymptomatic >> nephrotic range
• Nephrotic syndrome: 25 – 100% of patients in pediatric series
• Hematuria: 70-90% of patients
  ✓ macroscopic: up to 40%  Lee et al. Pediatr Nephrol 2011
• Hypertension: < 10%
• Thromboembolic events: <5%

Histopathology

• 1968: initial description by Ehrenreich and Churg

  • Normocellular glomerulus
  • Prominent capillary loops with thickened wall
  • Subepithelial immune complex deposits
Pathogenesis of idiopathic MN

• Heymann et al. 1959: animal model of MN – Heymann nephritis:
  ✓ Immunization of Lewis rats with brush boarder fraction of rat proximal tubules → immune complex deposition in subepithelial space

• Van Damme et al. 1978: *in situ* immune complex formation in Heymann nephritis

• Kerjaschki & Farquhar 1982: megalin as the autoantigenic target in Heymann nephritis
Preformed circulating immune complexes

Immune deposits

Endogenous antigen

- Heymann nephritis
- Idiopathic MN

Exogenous antigen

Immune deposits

Activation of complement pathways

In-situ formation of immune deposits

Adapted from Ronco & Diebec, Lancet 2015
Rats ≠ Humans

Human kidney antigen in idiopathic MN?
Fetomaternal alloimmunization in newborn

• Male born at 38 weeks GA
  ✓ Starting from 34 weeks GA: oligohydramnios, enlarged fetal kidneys
  ✓ At birth: oliguria, massive proteinuria, respiratory distress

• Family history
  ✓ Unrelated healthy parents
  ✓ Mother: miscarriage at 14 weeks of previous pregnancy
<table>
<thead>
<tr>
<th>Age</th>
<th>Serum Creatinine Concentration (mg/dl)</th>
<th>Urinary Protein Excretion (mg/mg of creatinine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 day</td>
<td>ND</td>
<td>14.2</td>
</tr>
<tr>
<td>2 days</td>
<td>1.9</td>
<td>15.2</td>
</tr>
<tr>
<td>4 days</td>
<td>2.7</td>
<td>ND</td>
</tr>
<tr>
<td>5 days</td>
<td>2.2</td>
<td>ND</td>
</tr>
<tr>
<td>6 days</td>
<td>1.6</td>
<td>14.0</td>
</tr>
<tr>
<td>22 days</td>
<td>1.4</td>
<td>28.3</td>
</tr>
<tr>
<td>31 days</td>
<td>1.3</td>
<td>16.2</td>
</tr>
<tr>
<td>40 days</td>
<td>0.8</td>
<td>8.4</td>
</tr>
<tr>
<td>52 days</td>
<td>0.6</td>
<td>4.2</td>
</tr>
<tr>
<td>4 mo</td>
<td>0.5</td>
<td>7.9</td>
</tr>
<tr>
<td>9 mo</td>
<td>0.6</td>
<td>3.9</td>
</tr>
<tr>
<td>11 mo</td>
<td>0.6</td>
<td>1.3</td>
</tr>
</tbody>
</table>
Kidney biopsy at 4 weeks of age: unusual MN

Fetomaternal Alloimmunization with Antenatal Glomerulopathies (FMAIG)

- FMAIG is caused by formation of antibodies to neutral endopeptidates (NEP) in mothers deficient for NEP due to mutations in MME gene (3q25.2) due to exposure to NEP on placenta and fetal cells, with subsequent transplacental IgG transfer and fetal alloimmunization.

- NEP (zink metallopeptidase) degrades glucagon, enkephalins, substance P, oxytocin, bradikinin, ANP, endothelin, β-amyloid and others, is expressed on podocytes starting from S-shape body.

- NEP deficiency in humans and in mice is asymptomatic.
Homozygous or compound heterozygous truncating mutations in the MME gene

graphic: placenta diagram

anti-NEP IgG

Formed after miscarriage or during ongoing pregnancy

Adapted from: Diebec & Ronco PNAS, 2007
M-Type Phospholipase A$_2$ Receptor as Target Antigen in Idiopathic Membranous Nephropathy

Laurence H. Beck, Jr., M.D., Ph.D., Ramon G.B. Bonegio, M.D., Gérard Lambeau, Ph.D., David M. Beck, B.A., David W. Powell, Ph.D., Timothy D. Cummins, M.S., Jon B. Klein, M.D., Ph.D., and David J. Salant, M.D.
Phospholipase A2 receptor (PLA2R)

- 185-KD glycoprotein expressed by podocytes
- Found in immune deposits in MN
- PLA2R and IgG co-localize in biopsy specimens from patients with idiopathic MN
- ~70% of patients with idiopathic MN have antibodies against PLA2R
Beck et al. NEJM, 2009
Rees & Kain. Nat Rev Nephrology, 2009
Genetic predisposition to MN (GWAS study)

<table>
<thead>
<tr>
<th>SNP rs2187668 (HLA-DQA1)</th>
<th></th>
<th>SNP rs4664308 (PLA2R1)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GG</td>
<td>GA</td>
<td>AA</td>
<td></td>
</tr>
<tr>
<td>No. of cases/total no. of subjects</td>
<td>14/354</td>
<td>79/944</td>
<td>97/659</td>
<td></td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
<td>1.00</td>
<td>2.22 (1.24–3.97)</td>
<td>4.19 (2.36–7.46)</td>
<td></td>
</tr>
<tr>
<td>GA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cases/total no. of subjects</td>
<td>23/115</td>
<td>94/363</td>
<td>178/348</td>
<td></td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
<td>6.07 (3.01–12.27)</td>
<td>8.49 (4.73–15.22)</td>
<td>25.43 (14.32–45.16)</td>
<td></td>
</tr>
<tr>
<td>AA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cases/total no. of subjects</td>
<td>5/11</td>
<td>23/41</td>
<td>42/55</td>
<td></td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
<td>20.24 (5.51–74.38)</td>
<td>31.03 (13.72–70.19)</td>
<td>78.46 (34.55–178.17)</td>
<td></td>
</tr>
</tbody>
</table>

Anti-PLA2R antibodies can be used for clinical monitoring of MN

Ronco & Debiec, Nephron Clin Pract, 2014
Heymann nephritis

MN caused by anti-NEP, anti-PLA2R, anti-THSD7A Ab
Early-Childhood Membranous Nephropathy Due to Cationic Bovine Serum Albumin

Hanna Debiec, Ph.D., Florence Lefeu, M.Sc., Markus J. Kemper, M.D.,
Patrick Niaudet, M.D., Ph.D., Georges Deschênes, M.D., Ph.D.,
Giuseppe Remuzzi, M.D., Tim Ulinski, M.D., Ph.D.,
and Pierre Ronco, M.D., Ph.D.
Cationic bovine serum albumin (BSA) as a cause of MN in children

• In children < 5 years old with MN BSA was detected in subepithelial immune deposits
• High serum titer (IgG1 and IgG4) of anti-BSA antibodies
• Absence of anti-PLA2R antibodies
• Source of cationic BSA? Antibodies are formed against peptide comprising amino acids 147-161

Cationic BSA can penetrate negatively charged GBM and reside in subepithelial space to form immune complexes.
Heymann nephritis
MN caused by anti-NEP, anti-PLA2R, anti-THSD7A Ab
MN caused by anti-BSA Ab

Adapted from Ronco & Diebec, Lancet 2015
## Causes of secondary MN

<table>
<thead>
<tr>
<th>Infections</th>
<th>Autoimmune</th>
<th>Medications</th>
<th>Neoplasia</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B</td>
<td>SLE</td>
<td>Penicillamine</td>
<td>Ovarian tumor</td>
<td>Sickle cell hemoglobinopathy (SS and SA)</td>
</tr>
<tr>
<td>Streptococcal infection</td>
<td>Sjogren’s</td>
<td>Tiopronine</td>
<td>Neublastoma’s</td>
<td></td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>Primary biliary cirrhosis</td>
<td>Cysteamine</td>
<td>Angiomatoid fibrous histiocytoma</td>
<td>De novo post-renal graft</td>
</tr>
<tr>
<td>Syphilis</td>
<td>Autoimmune hepatitis</td>
<td>NSAIDs</td>
<td></td>
<td>Mercury</td>
</tr>
<tr>
<td>CMV</td>
<td>Sarcoidosis</td>
<td>Captopril</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EBV</td>
<td></td>
<td>Infliximab</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malaria</td>
<td></td>
<td>Etanercept</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>ERT (aryl sulfatase B for Pompe disease)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Treatment of idiopathic MN

- Very few studies in children, no randomized studies
- Disease course in adults might differ from children
- In most patients renal biopsy performed after steroid treatment because of steroid resistance
- Spontaneous remission occurs also in children
- Thrombotic complications are rare in children and frequent in adults
## Differences between pediatric and adult MN

<table>
<thead>
<tr>
<th>Disease type/subtype:</th>
<th>Pediatric MN</th>
<th>Adult MN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of primary nephrotic syndrome cases that are MN</td>
<td>&lt;5% (children) 5–20% (adolescents)</td>
<td>15–30%</td>
</tr>
<tr>
<td>MN that is primary (“idiopathic”)</td>
<td>Minority</td>
<td>Majority</td>
</tr>
<tr>
<td>Proportion of primary MN that is PLA₂-R-associated</td>
<td>45% (more common in adolescents)</td>
<td>70–80%</td>
</tr>
<tr>
<td>Demographic and clinical features:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male predominance</td>
<td>Variable</td>
<td>Yes</td>
</tr>
<tr>
<td>Full nephrotic syndrome</td>
<td>40–75%</td>
<td>75%</td>
</tr>
<tr>
<td>Microscopic hematuria</td>
<td>70–90% (can be macroscopic)</td>
<td>50%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>&lt; 10%</td>
<td>30%</td>
</tr>
<tr>
<td>Thromboembolic events</td>
<td>&lt; 5%</td>
<td>10–20%</td>
</tr>
<tr>
<td>Spontaneous remission</td>
<td>Common</td>
<td>30%</td>
</tr>
<tr>
<td>Progressive renal impairment</td>
<td>&lt; 25%</td>
<td>30–40%</td>
</tr>
<tr>
<td>Pathological features:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mesangial deposits</td>
<td>Up to 50%</td>
<td>30%</td>
</tr>
<tr>
<td>Segmental distribution of deposits</td>
<td>Occasional</td>
<td>Very rare</td>
</tr>
</tbody>
</table>

Guideline 7.2: **When to start immunosuppression:**
- Treat only in nephrotic syndrome AND either: Urinary protein persistently >4 g/day and >50% of the baseline x6 mos observation (1B)
- **severe**, disabling, life-threatening **symptoms** of nephrotic syndrome (1C)
- Creatinine rise >30% within 6-12 months from diagnosis but eGFR still >25–30 ml/min/1.73 m2 (2C)

Guideline 7.3: **Initial therapy:**
- 6-month course of alternating monthly cycles of oral and i.v. corticosteroids, and oral alkylating agents (1B).
- Monitor x6 months post-therapy before considering treatment failure (1C)

Guideline 7.4: **Alternative initial regimen:** cyclosporine or tacrolimus x at least 6 months (1C)

Guideline 7.5: **DON’T start with:** corticosteroid or MMF monotherapy (1B/1C)

Guideline 7.6: **Resistant membranous:** If failed steroids/alkylators → try calcineurin inhibitor, and vice versa (2C)
Treatment recommendations in children

• Asymptomatic patients with sub-nephrotic proteinuria (protein/creat (mg/mg) < 2): anti-proteinuric treatment with ACEi or ARBs

• In patients with SRNS: 12-week course of cyclophosphamide (2 mg/kg/day) + AD steroids
  ✓ Calcineurin inhibitors might be an alternative treatment, although even less evidence in children

Menton & Valenti. Pediatr Nephrol 2010
Alternative treatment regimens: rituximab

- $N=100$
  - 68 as 1st line therapy
  - 32 as 2nd line therapy
- Partial+Complete remissions = 65/100
- Complete remissions = 27/100
- Median time to remission 7.1 months (IQR 3.2-12.0 months)
- Median total followup 29 months
- 18/65 relapsed
- 11/18 went back in remission (PR+CR) after more rituximab

No studies in children

Alternative treatment regimens: ACTH

No studies in children

Beck et al. JASN, 2009
Summary

- MN is a histologic description of an immune complex glomerulopathy
- Search for underlying causes is mandatory
- In young children: specific causes (FMAIG, cationic BSA)
- No treatment guidelines for children:
  - Asymptomatic children with not-nephrotic proteinuria: anti-proteinuric treatment
  - In SRNS patients: alkylating agents with AD steroids or CNI inhibitors, or rituximab?
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- Committee meeting minutes
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Thrombospondin Type-1 Domain-Containing 7A in Idiopathic Membranous Nephropathy

Nicola M. Tomas, M.D., Laurence H. Beck, Jr., M.D., Ph.D., Catherine Meyer-Schwesinger, M.D., Barbara Seitz-Polski, M.D., Hong Ma, Ph.D., Gunther Zahner, Ph.D., Guillaume Dolla, M.S., Elion Hoxha, M.D., Udo Helmchen, M.D., Anne-Sophie Dabert-Gay, Ph.D., Delphine Debayle, Ph.D., Michael Merchant, Ph.D., Jon Klein, M.D., Ph.D., David J. Salant, M.D., Rolf A.K. Stahl, M.D., and Gérard Lambeau, Ph.D.
Reactivity to THSD7A was found in 10% of patients with no antibodies against PLA2R