Membranous nephropathy

By
Mohammed Kamal Nassar, MD
Lecturer of Nephrology
Mansoura University
Membranous nephropathy

- **Definition:**
  - Immune complex glomerular disease in which immune deposits of IgG and complement components develop predominantly or exclusively beneath podocytes on the subepithelial surface of the glomerular capillary wall.

- **Epidemiology:**
  - Most common cause of primary nephrotic syndrome in older (>60 years) Caucasian adults
    - 25 - 35% of cases
    - 20% progress to ESRD
### Etiology

#### Primary

| Anti-PLA₂R associated (70%-80%) | Idiopathic (20%-30%) |

#### Secondary

<table>
<thead>
<tr>
<th><strong>Common</strong></th>
<th><strong>Uncommon</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoimmune diseases</td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td></td>
<td>Class V lupus nephritis</td>
</tr>
<tr>
<td></td>
<td></td>
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<tr>
<td>Infections</td>
<td></td>
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<td></td>
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<td></td>
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<tr>
<td>Malignancy</td>
<td>Non-Hodgkin lymphoma</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Drugs or toxins</td>
<td>Mercury-containing compounds</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Sarcoidosis</td>
</tr>
</tbody>
</table>

#### Alloimmune

- Graft-versus-host disease following hematopoietic stem cell transplantation
- *De novo* membranous nephropathy in renal allograft
- Fetomaternal alloimmunization to neutral endopeptidase
Pathogenesis

1. Antigens

- Neutral endopeptidase (NEP) – alloimmune antenatal MN
- Phospholipase A₂ receptor (PLA₂R) – Primary MN
- Megalin – Heymann nephritis in rats
- Anti-NEP, anti-PLA₂R or anti-megalin
Extrinsic Planted Antigens

- \textcolor{red}{\textbullet} Cationized BSA – rabbit and mouse models, childhood MN
- \textcolor{blue}{\textbullet} Anti-BSA
M-Type Phospholipase A₂ 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.

B Reactivity to the 185-kD Protein

<table>
<thead>
<tr>
<th></th>
<th>Nonreactive</th>
<th>Reactive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic MN</td>
<td>35</td>
<td>15</td>
</tr>
<tr>
<td>Secondary MN</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>Other Diseases</td>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td>Normal</td>
<td>0</td>
<td>5</td>
</tr>
</tbody>
</table>

No. of Subjects

<table>
<thead>
<tr>
<th></th>
<th>No. of Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reactive serum</td>
<td>26</td>
</tr>
<tr>
<td>Nonreactive serum</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>30</td>
</tr>
</tbody>
</table>
autoantibodies against PLA$_2$R were found in 70 to 80% of patients with idiopathic membranous nephropathy but not in those with secondary membranous nephropathy or other renal diseases. It has been suggested that the serum level of PLA$_2$R autoantibody could be used for the diagnosis of and therapeutic implications. The absence of circulating PLA$_2$R autoantibody at the time of kidney biopsy does not rule out a diagnosis of PLA$_2$R-related membranous nephropathy.

Hanna Debiec, Ph.D.
Pierre Ronco, M.D., Ph.D.
Serum PLA2R auto antibodies test is a good +ve but not good -ve marker for MN.
Anti-PLA2R Titers Clinical Significance (2)

• anti-PLA2R titers strongly correlated with clinical status

• lower anti-PLA2R titers were associated with a higher rate of spontaneous remission

• a decline in anti-PLA2R predicted the clinical response to immunosuppressive therapy

Anti-PLA2R antibodies measured by ELISA predict long-term outcome in a prevalent population of patients with idiopathic membranous nephropathy

Durga Kanigicherla¹, Jennet Gummadova², Edward A. McKenzie², Stephen A. Roberts³, Shelley Harris¹, Milind Nikam¹, Kay Poulton¹, Lorna McWilliam¹, Colin D. Short¹, Michael Venning¹ and Paul E. Brenchley¹,⁴
Anti-PLA2R

Is it only related to Idiopathic MN?

Anti-Phospholipase A2 Receptor Antibody in Membranous Nephropathy

Weisong Qin,* Laurence H. Beck, Jr., † Caihong Zeng,* Zhaohong Chen,* Shijun Li,* Ke Zuo,* David J. Salant, † and Zhihong Liu*

Anti-PLA2R Titers Clinical Significance
(3)

• Highly suggestive of primary MN

• But does not exclude the coexistence of:
  – hepatitis virus infection,
  – malignancy,
  – another associated rheumatologic or inflammatory disease.

Thrombospondin type-1 domain-containing 7A (THSD7A)

- A transmembrane protein expressed on podocytes.
- Responsible Ab in 10% of idiopathic MN with negative anti-PLA2R Ab.
Thrombospondin Type-1 Domain-Containing 7A in Idiopathic Membranous Nephropathy

**B European Cohort**
- Reactivity with a 250-kD protein
- No. of Patients:
  - Idiopathic MN (anti-PLA2R1-positive): 0/74
  - Secondary MN: 0/44
  - Other glomerular disease: 1/34
  - Healthy controls: 0/76

**C Boston Cohort**
- Reactivity with a 250-kD protein
- No. of Patients:
  - Idiopathic MN (anti-PLA2R1-positive): 0/255
  - Secondary MN (anti-PLA2R1-positive): 9/110
  - Secondary MN (3 anti-PLA2R1-positive): 1/33
  - Secondary MN (30 anti-PLA2R1-negative): 0

2. Antibodies

<table>
<thead>
<tr>
<th>IGg1</th>
<th>IGg2</th>
<th>IGg3</th>
<th>IGg4</th>
</tr>
</thead>
</table>

- **Idiopathic**
  - +
  - +
  - +
  - or
  - -

- **Lupus Nephritis**
  - +++
  - ++
  - +
  - or
  - -

- **Malignancy**
  - +++
  - ++
  - +
  - +

---

**Figure B: Specificity of Anti-PLA$_2$R Antibody**

<table>
<thead>
<tr>
<th>IgG Subclass</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>MN1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MN2</td>
<td></td>
<td></td>
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<tr>
<td>MN3</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>MN4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MN5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MN6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Legend**: Black arrows indicate the specific binding sites for each subclass.
3. Podocyte damage
4. New ECM formation
Clinical features

- **Proteinuria:**
  - Subnephrotic (20 – 30%)
  - Nephrotic range proteinuria (70 – 80%)
  - Non selective
- **Microscopic hematuria** (30 – 40%)
- **Normal complement level**
  - In primary MN, serologic tests for anti-PLA2R are positive in 75% to 80% of cases
- **Other autoantibodies (ANA, ANCA, RF)** –ve
- **Hypertension** (10 – 20%)
- **Normal renal functions** (90%)
- **Thromboemolic disease** (DVT, RVT, PE)
Pathology
### Diagnosis

<table>
<thead>
<tr>
<th>Patient Groups</th>
<th>Test</th>
</tr>
</thead>
</table>
| All patients   | Blood pressure  
                 | Renal function (serum creatinine and creatinine clearance)  
                 | Urine protein excretion (24-hour urine or urine protein-creatinine ratio)  
                 | Serum albumin  
                 | Serum cholesterol, including LDL-HDL ratio  
                 | Urinalysis  
                 | Renal biopsy  
                 | Anti-PLA₂R |
| Associated disease | Hepatitis B (HBs antigen)  
                 | Hepatitis C (HCV antibody)  
                 | Antinuclear antibody (ANA), anti-double-stranded DNA (hallmark of systemic lupus erythematosus)  
                 | Complement C₃, C₄ (usually normal in idiopathic MN) |
| Select Patients | Renal venous Doppler ultrasound  
                 | Contrast CT, MRI  
                 | Anti-GBM antibody  
                 | Antineutrophil cytoplasmic antibody (ANCA)  
                 | Assess for interstitial nephritis  
                 | Cancer screening (see text) |

With suspected thromboembolic events, flank pain, hematuria, acute renal failure

With sudden decrease in renal function, development of active urine sediment

Suggestive symptoms or age >50 years
<table>
<thead>
<tr>
<th>Primary</th>
<th>Secondary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunofluorescence Microscopy</td>
<td></td>
</tr>
<tr>
<td>IgG4 &gt; IgG1, IgG3</td>
<td>IgG1, IgG3 &gt; IgG4</td>
</tr>
<tr>
<td>IgA, IgM absent</td>
<td>IgA, IgM may be present.</td>
</tr>
<tr>
<td>Mesangial Ig staining absent</td>
<td>Mesangial Ig staining may be present.</td>
</tr>
<tr>
<td>C1q negative or weak</td>
<td>C1q positive</td>
</tr>
<tr>
<td>PLA₂R positive and co-localizes with IgG</td>
<td>PLA₂R negative</td>
</tr>
<tr>
<td>Electron Microscopy</td>
<td></td>
</tr>
<tr>
<td>Subepithelial deposits only ± mesangial deposits rarely</td>
<td>Subepithelial deposits ± mesangial and subendothelial deposits</td>
</tr>
</tbody>
</table>
Malignancy Screening

When to screen?

If the anti-PLA2R antibody test is negative

+ the kidney histology is consistent with secondary MN

+ there is no other clear cause of secondary MN

+ risk factors or alarm signs:
  • extensive smoking history,
  • guaiac-positive stools,
  • unexplained anemia or weight loss

Malignancy Screening

How to screen?

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Young Adult</th>
<th>Older Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>Chest x-ray</td>
<td>Computed tomography</td>
</tr>
<tr>
<td>Kidney</td>
<td>Ultrasonography, malignant cells in the urine</td>
<td>Ultrasonography, malignant cells in the urine</td>
</tr>
<tr>
<td>Breast</td>
<td>Physical examination</td>
<td>Mammography</td>
</tr>
<tr>
<td>Stomach</td>
<td>Fecal occult blood?</td>
<td>Gastroscopy</td>
</tr>
<tr>
<td>Colon</td>
<td>Fecal occult blood?</td>
<td>Colonoscopy</td>
</tr>
<tr>
<td>Prostate</td>
<td>Rectal digital examination, percentage PSA</td>
<td>Ultrasonography, prostate biopsy</td>
</tr>
<tr>
<td>Uterus</td>
<td>Gynecologic examination</td>
<td>Colposcopy</td>
</tr>
</tbody>
</table>

In young patients, fecal occult blood is usually searched for only in the case of anemia. MN, membranous nephropathy; PLA2R1, phospholipase A2 receptor 1; PSA, prostate specific antigen.

Malignancy Screening

How to screen?

Examination:
- LN.
- Systemic exam for any mass.

Male > 50 = PSA
Female > 50 = Mammogram

Body CT Scan (+ other imaging) if cause is not evident.
Malignancy Screening
Frequency of screening

Cancer screening should continue for a period of five to ten years after the diagnosis of MN (since cancers associated with MN are typically diagnosed within this time frame.)

Clinical course

- Spontaneous remission in up to 30%
- 25% ESRD after 8 years

<table>
<thead>
<tr>
<th>Factors</th>
<th>Predictor</th>
<th>PPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Features</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>Older &gt; younger</td>
<td>43</td>
</tr>
<tr>
<td>Gender</td>
<td>Male &gt; female</td>
<td>30</td>
</tr>
<tr>
<td>HLA type</td>
<td>HLA/B18/DR 3/Bfll present</td>
<td>71</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Present</td>
<td>39</td>
</tr>
<tr>
<td><strong>Serum Levels</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin</td>
<td>&lt;1.5 g/dL</td>
<td>56</td>
</tr>
<tr>
<td>Creatinine</td>
<td>Above normal</td>
<td>61</td>
</tr>
<tr>
<td><strong>Urine Protein</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td>Present</td>
<td>32</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>&gt;8 g for &gt;6 months</td>
<td>66</td>
</tr>
<tr>
<td>IgG excretion</td>
<td>&gt;250 mg/day</td>
<td>80</td>
</tr>
<tr>
<td>β2-Microglobulin excretion</td>
<td>&gt;54 μg/mmol creatinine &lt;54</td>
<td>79</td>
</tr>
<tr>
<td>C5b-9 excretion</td>
<td>&gt;7 mg/mg creatinine</td>
<td>67</td>
</tr>
<tr>
<td><strong>Biopsy Changes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glomerular focal sclerosis</td>
<td>Present</td>
<td>34</td>
</tr>
<tr>
<td>Tubulointerstitial disease</td>
<td>Present</td>
<td>48</td>
</tr>
</tbody>
</table>
Management
Renal Disease Risk Categories

<table>
<thead>
<tr>
<th>Low Risk</th>
<th>Medium Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal serum creatinine and creatinine clearance plus proteinuria &lt;4 g/day over 6 months of observation</td>
<td>Normal or near-normal creatinine clearance and persistent proteinuria &gt;4 g/day to &lt;8 g/day over 6 months despite maximum conservative treatment</td>
<td>Deteriorating renal function and/or persistent proteinuria &gt;8 g/day for 3 (up to 6) months of observation</td>
</tr>
</tbody>
</table>
Definitions

**Complete Remission:** Urinary protein excretion <0.3 g/d (uPCR <300 mg/g or <30 mg/mmol), confirmed by two values at least 1 week apart, accompanied by a normal serum albumin concentration, and a normal SCr.

**Partial Remission:** Urinary protein excretion <3.5 g/d (uPCR <3500 mg/g or <350 mg/mmol) *and* a 50% or greater reduction from peak values; confirmed by two values at least 1 week apart, accompanied by an improvement or normalization of the serum albumin concentration and stable SCr.
7.1: Evaluation of MN

7.1.1: Perform appropriate investigations to exclude secondary causes in all cases of biopsy-proven MN. (Not Graded)
7.2: Selection of adult patients with IMN to be considered for treatment with immunosuppressive agents (see 7.8 for recommendations for children with IMN)

7.2.1: We recommend that initial therapy be started only in patients with nephrotic syndrome AND when at least one of the following conditions is met:

- urinary protein excretion persistently exceeds 4 g/d AND remains at over 50% of the baseline value, AND does not show progressive decline, during antihypertensive and antiproteinuric therapy (see Chapter 1) during an observation period of at least 6 months; (1B)

- the presence of severe, disabling, or life-threatening symptoms related to the nephrotic syndrome; (1C)

- SCr has risen by 30% or more within 6 to 12 months from the time of diagnosis but the eGFR is not less than 25–30 ml/min per 1.73 m² AND this change is not explained by superimposed complications. (2C)
Treatment

IMGN TREATMENT ALGORITHM

Mild proteinuria
<4g/day + normal renal function

ACEI ± ARB, dietary protein restriction, Maintain BP ≤ 125/75 mm Hg, Continue to monitor proteinuria and renal function

Moderate proteinuria
≥4 to <8 g/day + normal renal function

ACEI ± ARB, dietary protein restriction, Maintain BP ≤ 125/75 mm Hg, Observe for 6 months

Persistent nephrotic range proteinuria**

Cytotoxic/steroids**

Cyclosporine**

Heavy proteinuria
≥8 g/day with or without renal insufficiency

ACEI ± ARB, dietary protein restriction, Maintain BP ≤ 125/75 mm Hg, Observe for ≤ 6 months*

Persistent heavy proteinuria and/or decreasing renal function**

Cyclosporine**

Cytotoxic/steroids**

*Decreasing function or complication: start treatment early

**Introduction of risk reduction strategies

Catran D JASN 2005;16:1188-1194
Table 15 | Cyclical corticosteroid/alkylating-agent therapy for IMN (the “Ponticelli Regimen”)  

Month 1: i.v. methylprednisolone (1 g) daily for three doses, then oral methylprednisolone (0.5 mg/kg/d) for 27 days  
Month 2: Oral chlorambucil (0.15–0.2 mg/kg/d) or oral cyclophosphamide (2.0 mg/kg/d) for 30 days"a"  
Month 3: Repeat Month 1  
Month 4: Repeat Month 2  
Month 5: Repeat Month 1  
Month 6: Repeat Month 2  

IMN, idiopathic membranous nephropathy.  
"a"Monitor every 2 weeks for 2 months, then every month for 6 months, with serum creatinine, urinary protein excretion, serum albumin, and white blood cell count. If total leukocyte count falls to < 3500/mm³, then hold chlorambucil or cyclophosphamide until recovery to > 4000/mm³.
CNI-based regimens

*Cyclosporine:* 3.5–5.0 mg/kg/d given orally in two equally divided doses 12 hours apart, with prednisone 0.15 mg/kg/d, for 6 months. We suggest starting at the low range of the recommended dosage and gradually increasing, if necessary, to avoid acute nephrotoxicity (Sandimmune®, Neoral®, and generic cyclosporin considered equivalent).

*Tacrolimus:* 0.05–0.075 mg/kg/d given orally in two divided doses 12 hours apart, without prednisone, for 6–12 months. We suggest starting at the low range of the recommended dosage and gradually increasing, if necessary, to avoid acute nephrotoxicity.
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Results</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroids alone</td>
<td>No benefit</td>
<td>Although ineffective, frequently used by practitioner</td>
</tr>
<tr>
<td>Steroids-alkylating agents</td>
<td>Can significantly increase the probability of complete or partial remission. Protect renal function in the long term</td>
<td>The results are confirmed by randomized controlled trials. Risk of side effects (infection, leucopenia). Avoid frequent repetitions (risk of oncogenic or gonadotoxic effects)</td>
</tr>
<tr>
<td>CNI</td>
<td>Can significantly reduce the amount of proteinuria and increase the probability of complete or partial remission. Little information about their effects on renal function</td>
<td>Relapse of proteinuria is frequent after CNI withdrawal. Risk of hypertension, nephrotoxicity. Little information about long-term safety</td>
</tr>
<tr>
<td>Mycophenolate salts</td>
<td>Ineffective when given alone. Can reduce proteinuria when given together with steroids</td>
<td>Only small-sized studies with short-term follow-up are available. High relapse rate. No information about the long-term safety and efficacy</td>
</tr>
<tr>
<td>ACTH</td>
<td>Can reduce proteinuria</td>
<td>Only few small-sized studies with short-term follow-up are available. A randomized controlled trial is in progress</td>
</tr>
<tr>
<td>Rituximab</td>
<td>Can reduce proteinuria</td>
<td>Large observational studies available. No head-to-head comparison with other treatments</td>
</tr>
</tbody>
</table>

CNI, calcineurin inhibitors; ACTH, adrenocorticotropic hormone.
Resistant IMN

7.6: Treatment of IMN resistant to recommended initial therapy

7.6.1: We suggest that patients with IMN resistant to alkylating agent/steroid-based initial therapy be treated with a CNI. (2C)

7.6.2: We suggest that patients with IMN resistant to CNI-based initial therapy be treated with an alkylating agent/steroid-based therapy. (2C)
Relapsing IMN

7.7: Treatment for relapses of nephrotic syndrome in adults with IMN

7.7.1: We suggest that relapses of nephrotic syndrome in IMN be treated by reinstitution of the same therapy that resulted in the initial remission. (2D)

7.7.2: We suggest that, if a 6-month cyclical corticosteroid/alkylating-agent regimen was used for initial therapy (see Recommendation 7.3.1), the regimen be repeated only once for treatment of a relapse. (2B)
ANTI-PLA2R ANTIBODY and TREATMENT DECISIONS

• **Absent or low-titer** anti-PLA2R portends spontaneous remission, and is a reason to delay introduction of IS therapy

• **Elevated** Anti-PLA2R antibody titer does not predict the initial response to a specific treatment modality, regardless of choice of regimen

• **Declining** anti-PLA2R antibody titers (>50% of BL) during treatment predict remission or a decline in proteinuria in next 1-3 months

• **Persistently** positive anti-PLA2R at end of a course of therapy or re-appearance after a remission portend a subsequent relapse
Primary Membranous Nephropathy: 
A proposal for personalized care-2016

• Patients with NS need only be tested for anti-PLA2R antibody if MN is suspected- If positive then a diagnosis of a lesion of MN is established (without renal biopsy)- but may be 1° or 2°

• All patients with a biopsy lesion of MN should be tested for anti-PLA2R antibody (ELISA preferred) and PLA2R Ag in glomeruli prior to treatment. Negative tests indicate an evaluation for 2° MN is needed or that a SR is likely

• In suspected 1° MN initial tests for anti-PLA2R antibody results do not greatly influence the choice of drug for initial treatment but low titres suggest likely SR
Primary Membranous Nephropathy: 
*A proposal for personalized care-2016*

- Testing for anti-PLA2R antibody (ELISA preferred) should occur in all 1° MN patients at 1-2 month intervals during therapy and at the end of therapy. A 50% decline in titer predicts a 50% decline in proteinuria 3-6 months later.

- After a remission, a rising titer predicts relapse—but monitoring may not be required during prolonged remission.

- All patients with ESRD due to 1° MN should be tested pre-transplant. Recurrence of MN expected in 75-80%, if positive, and <25% if negative.
Thank You