MEMBRANOUS NEPHROPATHY

No longer ‘idiopathic’ but how should it be managed?

John Feehally
MANAGEMENT OF MEMBRANOUS NEPHROPATHY

Definitions

Aetiology & Pathogenesis

Predicting prognosis

Choosing therapy
MANAGEMENT OF MEMBRANOUS NEPHROPATHY

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DEFINING MEMBRANOUS NEPHROPATHY

- Histopathology
- Clinical
- Immune mechanisms
DEFINING MEMBRANOUS NEPHROPATHY

Histopathology

Clinical

Immune mechanisms
MEMBRANOUS NEPHROPATHY
MEMBRANOUS NEPHROPATHY
Electron-dense deposits on the subepithelial aspect of a thickened GBM
DEFINING MEMBRANOUS NEPHROPATHY

- Histopathology
- Clinical
- Immune mechanisms

‘Pattern’ *not* ‘disease’
DEFINING MEMBRANOUS NEPHROPATHY

- **Histopathology**
- **Clinical**
  - Usually nephrotic syndrome
- **Immune mechanisms**

‘Pattern’ *not* ‘disease’
MANAGEMENT OF MEMBRANOUS NEPHROPATHY

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MEMBRANOUS NEPHROPATHY – PATTERN OR DISEASE?

Idiopathic

Secondary
- Immune disease
- Infection
- Drugs
- Malignancy
# Aetiology of Secondary Membranous Nephropathy

<table>
<thead>
<tr>
<th>Common</th>
<th>Uncommon</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IMMUNE DISEASE</strong></td>
<td></td>
</tr>
<tr>
<td>Systemic lupus</td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td></td>
<td>Sarcoidosis</td>
</tr>
<tr>
<td><strong>INFECTION</strong></td>
<td></td>
</tr>
<tr>
<td>HBV</td>
<td>Malaria, leprosy, filariasis, schistosomiasis</td>
</tr>
<tr>
<td>HCV</td>
<td></td>
</tr>
<tr>
<td><strong>DRUGS</strong></td>
<td></td>
</tr>
<tr>
<td>Gold</td>
<td>Mercury, Captopril</td>
</tr>
<tr>
<td>Penicillamine</td>
<td></td>
</tr>
<tr>
<td><strong>OTHER</strong></td>
<td></td>
</tr>
<tr>
<td>Solid organ malignancies</td>
<td>Sickle cell disease</td>
</tr>
<tr>
<td>Transplant</td>
<td><strong>de novo or recurrent</strong></td>
</tr>
</tbody>
</table>
MEMBRANOUS NEPHROPATHY

- IgG4 dominant
- IgG1-3 suggests secondary MN
DEFINING MEMBRANOUS NEPHROPATHY

Histopathology

Clinical

Usually nephrotic syndrome

Immune mechanisms

The podocyte is the target, but what is the antigen?

‘Pattern’ not ‘disease’
MEMBRANOUS NEPHROPATHY
– PATTERN OR DISEASE?

Idiopathic
Diagnosis by exclusion

Secondary
Infection
Drugs
Malignancy
MEMBRANOUS NEPHROPATHY – PATTERN OR DISEASE?

- Idiopathic
  - Diagnosis by exclusion
- Antigen unknown
- Secondary
  - Infection
  - Drugs
  - Malignancy
MEMBRANOUS NEPHROPATHY – PATTERN OR DISEASE?

Idiopathic
Diagnosis by exclusion

Secondary
Infection
Drugs
Malignancy

Antigen unknown
MEMBRANOUS NEPHROPATHY – PATTERN OR DISEASE?

- **Idiopathic**
  - Diagnosis by exclusion

- **Secondary**
  - Infection
  - Drugs
  - Malignancy

2009

~ 70 %

PLA2 receptor
PLA2R and the pathogenesis of membranous nephropathy

TWO SEMINAL OBSERVATIONS
PLA2R and the pathogenesis of membranous nephropathy

TWO SEMINAL OBSERVATIONS

PLA2R (M-type Phospholipase A2 Receptor) is the target autoantigen in MN
M-type PLA2 Receptor as the Target Antigen in Idiopathic Membranous Nephropathy

Beck LH et al. NEJM 2009; 361: 11
Colocalization of the M-Type Phospholipase A₂ Receptor (PLA₂R) and IgG4 and Reactivity of Eluted IgG4

PLA2R and the pathogenesis of membranous nephropathy

TWO SEMINAL OBSERVATIONS

**PLA2R (M-type Phospholipase A2 Receptor)**

is the target autoantigen in MN

**HLA DQ1 & PLA2R1**

are the two risk alleles in MN
Manhattan Plot for GWAS for Idiopathic Membranous Nephropathy

Stanescu H et al. NEJM 2011; 364: 616
Manhattan Plot for GWAS for Idiopathic Membranous Nephropathy

Stanescu H et al. NEJM 2011; 364: 616
**Table 3. Odds Ratios for Idiopathic Membranous Nephropathy, According to Single-Nucleotide Polymorphism (SNP) and Genotype Combinations.**

<table>
<thead>
<tr>
<th>SNP rs2187668 (HLA-DQA1)</th>
<th>SNP rs4664308 (PLA2R1)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GG</td>
</tr>
<tr>
<td>GG</td>
<td>No. of cases/total no. of subjects</td>
</tr>
<tr>
<td></td>
<td>Odds ratio (95% CI)</td>
</tr>
<tr>
<td>GA</td>
<td>No. of cases/total no. of subjects</td>
</tr>
<tr>
<td></td>
<td>Odds ratio (95% CI)</td>
</tr>
<tr>
<td>AA</td>
<td>No. of cases/total no. of subjects</td>
</tr>
<tr>
<td></td>
<td>Odds ratio (95% CI)</td>
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* Persons who were homozygous for the low-risk allele (GG) constituted the reference category. Numbers of cases and total numbers of subjects are from the joint analysis. OR denotes odds ratio.
MEMBRANOUS NEPHROPATHY – PATTERN OR DISEASE?

**Idiopathic**

- Diagnosis by exclusion

**Secondary**

- Infection
- Drugs
- Malignancy

2009

- 70% - PLA2 Receptor
- 30% - ?
PLA2R is not the only antigen in membranous nephropathy

• **Endogenous antigens**
  – **Podocyte membrane (Primary)**
    • PLA2R (70% of idiopathic MN)
    • Neutral endopeptidase (NEP) (alloimmune MN in neonates)
  – **Podocyte cytoplasm (Probably secondary intramolecular epitope spreading)**
    • Superoxidase dismutase (SOD)
    • Aldose reductase (AR)
    • aEnolase

• **Exogenous antigens**
  • **Cationic BSA** (Debiec H et al. NEJM;364:2101, 2011)
    – 4 Children <2.5 years old, Probably milk-derived
Anti-PLA2R as a marker in ‘idiopathic’ MN
Anti-PLA2R as a marker in ‘idiopathic’ MN

Is anti-PLA2R specific for ‘idiopathic’ MN?
Is Anti-PLA2R specific for ‘idiopathic’ MN?

8 published studies – 616 IMN

3 different methods: Indirect IF (259) ELISA (207) Western blot (150)

<table>
<thead>
<tr>
<th>Healthy controls</th>
<th>Other renal disease</th>
<th>‘Idiopathic’ MN</th>
<th>Secondary MN</th>
</tr>
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<tbody>
<tr>
<td>0/115 +ve</td>
<td>0/276 +ve</td>
<td>72%</td>
<td>5 – 30%</td>
</tr>
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</table>

Clinically active
No immunosuppression

Tumours, lupus, viral infection
Anti-PLA2R as a marker in ‘idiopathic’ MN

Is anti-PLA2R specific for ‘idiopathic’ MN?

Does anti-PLA2R correlate with disease activity?
Anti-PLA2R is elevated in membranous nephropathy with active disease and much lower or absent in remission.
Anti-PLA2R antibodies & disease activity in Membranous Nephropathy

Anti-PLA2R antibodies & disease activity in Membranous Nephropathy

Hofstra J et al. CJASN 2011; 6: 1286
Anti-PLA2R as a marker in ‘idiopathic’ MN

Is anti-PLA2R specific for ‘idiopathic’ MN?

Does anti-PLA2R correlate with disease activity?

What is the temporal association of anti-PLA2R & proteinuria in

• spontaneous remission?
• therapeutic remission?
• relapse?
Rituximab-induced Depletion of anti-PLA2R Autoantibodies Predicts Response in Membranous Nephropathy

Beck L et al. JASN 2011; 22: 1543
Variable temporal relationship between anti-PLA2R antibodies & disease activity in Membranous Nephropathy

Cyclosporin x 2

Spontaneous remission

Anti-PLA2R as a marker in ‘idiopathic’ MN

Is anti-PLA2R specific for ‘idiopathic’ MN?

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What is the temporal association of anti-PLA2R & proteinuria in
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  • therapeutic remission?
  • relapse?

Does anti-PLA2R correlate with clinical outcome?
Anti-PLA2R levels & time to doubling of serum creatinine in membranous nephropathy

Kanigicherla D et al. KI 2013; 83: 940
Anti-PLA2R levels & outcome in membranous nephropathy
N = 79

Anti-PLA2R levels *did not* predict:

- Complete remission
- Partial remission
- Renal failure

Anti-PLA2R levels in lower tertile *did* predict:

- Spontaneous remission

Hofstra J et al. JASN; 2012; 23: 1735
Anti-PLA2R as a marker in ‘idiopathic’ MN

Is anti-PLA2R specific for ‘idiopathic’ MN?

Does anti-PLA2R correlate with disease activity?

What is the temporal association of anti-PLA2R & proteinuria in
  • spontaneous remission?
  • therapeutic remission?
    • relapse?

Does anti-PLA2R correlate with clinical outcome?

How should anti-PLA2R be measured?
How should anti-PLA2R antibodies be measured?

Which antibody: rabbit? guinea pig?

Which technique: Western blot? ELISA? Indirect IF?

Hofstra J et al. JASN 2012; 23: 1735
Anti-PLA2R & Membranous Nephropathy

Should we measure anti-PLA2R routinely

... for diagnosis?

.... to guide therapy ?

....not yet .....
MEMBRANOUS NEPHROPATHY

Terminology

Idiopathic

Primary ?

Secondary
Infection
Drugs
Malignancy
MANAGEMENT OF MEMBRANOUS NEPHROPATHY

Definitions

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MEMBRANOUS NEPHROPATHY

Can we predict prognosis at presentation?

Pathological features?

Clinical features?

Serology?
MEMBRANOUS NEPHROPATHY

Can we predict prognosis at presentation?

Pathological features?

- Glomerulosclerosis
- Tubular atrophy & interstitial fibrosis
PATHOLOGICAL CLASSIFICATION
OF MEMBRANOUS NEPHROPATHY

ELECTRON MICROSCOPY

Stage 1: subepithelial EDDs, no BM reaction

Stage II: ‘spikes’

Stage III: EDDs surrounded by BM

Stage IV: lucency of deposits

Ehrenreich & Churg, 1968
PATHOLOGICAL CLASSIFICATION
OF MEMBRANOUS NEPHROPATHY

- Logical & systematic
- Covers ‘progression’ of lesions

**BUT**

11 reports 1979-1992

8/11 suggested this classification did not predict outcome or duration of disease

Ehrenreich & Churg, 1968
MEMBRANOUS NEPHROPATHY

Can we predict prognosis at presentation?

Pathological features?

Clinical features?

Serology?
NATURAL HISTORY of “IDIOPATHIC” MEMBRANOUS NEPHROPATHY with NEPHROTIC SYNDROME

- **ONE THIRD**: spontaneous complete remission in 3 to 5 years
  25% who enter remission subsequently relapse

- **ONE THIRD**: Partial remission (24hr uProt< 2g) with persistent proteinuria but no loss of GFR

- **ONE THIRD**: ESRD over 5 to 10 years

- Remission or maintain normal GFR for > 3 years - prognosis is excellent
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There is now no such thing as:

- ‘the natural history of membranous nephropathy’
- BP control
- Renin-angiotensin blockage
- Salt restriction
PREDICTING RISK IN MEMBRANOUS NEPHROPATHY – Toronto Registry

**LOW RISK**
- normal renal function
- proteinuria < 4g/day for 6/12

**MEDIUM RISK**
- normal renal function
- proteinuria > 4g/d < 8g/d for 6/12

**HIGH RISK**
- abnormal renal function or/and
- persistent proteinuria >8g/d for >6/12
VALUE OF PARTIAL REMISSION IN IDIOPATHIC MEMBRANOUS NEPHROPATHY

TORONTO GN REGISTRY - 343 patients

Survival free from renal failure

CR: 102, 67, 33, 12
PR: 135, 74, 32, 9
NR: 106, 34, 9, 4

P < 0.001
NR < PR < CR

Troyanov S et al. KI 2004; 66: 1199
NATURAL HISTORY OF GOLD-INDUCED MEMBRANOUS NEPHROPATHY

MEMBRANOUS NEPHROPATHY

Can we predict prognosis at presentation?

Pathological features?

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MEMBRANOUS NEPHROPATHY

Can we predict prognosis at presentation?

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*Anti-PLA2R antibodies are promising, but not of proven value*
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CLINICAL PRACTICE GUIDELINE FOR GLOMERULONEPHRITIS
## Examples of Rating Guideline Recommendations

**QUALITY of Supporting Evidence is shown as A, B, C or D**

<table>
<thead>
<tr>
<th>Level 1</th>
<th>We recommend….</th>
<th>1A</th>
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<tbody>
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<td></td>
<td>We suggest….</td>
<td>1D</td>
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- **Level 1**: We recommend….
  - Most patients should receive the recommended course of action
  - Supported by evidence from high quality RCTs

- **Level 2**: We suggest…
  - Different choices will be appropriate for different patients.
  - Each patient needs help to arrive at a management decision appropriate for them
  - No RCTs
  - Supported by limited observational data

---

**Of 19 recommendations or suggestions for ‘idiopathic’ Membranous Nephropathy**

- **Only 3 (16%) are 1A or 1B**
Examples of Rating Guideline Recommendations

QUALITY of Supporting Evidence is shown as A, B, C or D

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The recommendations or suggestions  
*only apply* to nephrotic syndrome  
*not* to asymptomatic proteinuria

<table>
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<th>Level 2</th>
<th>We suggest</th>
<th>2D</th>
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<td>Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision appropriate for them</td>
<td>Supported by limited observational data</td>
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Examples of Rating Guideline Recommendations

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<td>Level 2</td>
<td>Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision appropriate for them</td>
<td>No RCTs Supported by limited observational data</td>
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**NONE** of the available RCT evidence has relevant information about anti-PLA2R status
Basics of treatment in idiopathic membranous nephropathy

Exclude secondary causes

Anti-proteinuric therapy
BP control; RAS blockade

Disease-specific immunotherapy
“Should I treat this patient?”

“Should I treat this patient with an immunosuppressive regimen with a significant adverse event profile?”

BP control
Renin-angiotensin blockade
Salt restriction
Statin
10 YEAR FOLLOW UP OF ‘PONTICELLI REGIMEN’ FOR IDIOPATHIC MEMBRANOUS NEPHROPATHY WITH NEPHROTIC SYNDROME

Treated Patients
42 42 41 40 40 39 37 37 36 35 34 34 33 32 30 30 30 30

Untreated Patients
39 38 36 35 32 29 29 28 28 27 26 25 23 22 20 20 20 20 17

Ponticelli C et al. KI 1995; 48: 1600
‘PONTICELLI REGIMEN’
FOR IDIOPATHIC MEMBRANOUS NEPHROPATHY
WITH NEPHROTIC SYNDROME

Why is there controversy?
Why is there controversy?

Toxicity

Are old trials relevant to modern practice?

Does ethnicity matter?

Is it necessary to treat all patients?
In 6 months the patient receives:

9 grams Methylprednisolone
and oral Prednisolone 0.4mg/kg/alt day for 3 months

plus

Chlorambucil 0.2 mg/kg/day for 3 months
or
Cyclophosphamide 2.5 mg/kg/day
CALCINEURIN INHIBITORS FOR IDIOPATHIC MEMBRANOUS NEPHROPATHY WITH NEPHROTIC SYNDROME

Cyclosporine
Catran D et al. ......

Tacrolimus
Praga M et al.

Both are effective

BUT not been compared ‘head to head’ with ‘Ponticelli’
Why is there controversy?

Toxicity

Are old trials relevant to modern practice?

Does ethnicity matter?

Is it necessary to treat all patients?
ARE OLDER RCTs RELEVANT TO MODERN MANAGEMENT OF GN?

BP targets

Renin-angiotensin system blockade
Blood pressure defined as > 160/90

Renin-angiotensin blockade?
RCT OF CORTICOSTEROIDS AND CYCLOPHOSPHAMIDE FOR IDIOPATHIC MEMBRANOUS NEPHROPATHY WITH NEPHROTIC SYNDROME

Significant benefit of steroid/cyclo regimen

Median BP

Baseline  113/78

10 years  132/83

Not different between treatment groups

Jha V et al. JASN 2007;  18: 1899
‘PONTICELLI REGIMEN’
FOR IDIOPATHIC MEMBRANOUS NEPHROPATHY
WITH NEPHROTIC SYNDROME

Why is there controversy?

Toxicity

Are old trials relevant to modern practice?

Does ethnicity matter?

Is it necessary to treat all patients?
PROGNOSIS OF IDIOPATHIC MEMBRANOUS NEPHROPATHY IN JAPAN

949 patients followed for up to 20 years
No RCTs

374 corticosteroids
257 alkylating agents
157 other immunosuppressives
161 ‘supportive therapy’

Shiiki H et al. Kidney Int 2004; 5: 1400
PROGNOSIS OF IDIOPATHIC MEMBRANOUS NEPHROPATHY IN JAPAN

Shiiki H et al. Kidney Int 2004; 5: 1400
‘PONTICELLI REGIMEN’
FOR IDIOPATHIC MEMBRANOUS NEPHROPATHY
WITH NEPHROTIC SYNDROME

Why is there controversy?

Toxicity

Are old trials relevant to modern practice?

Does ethnicity matter?

Is it necessary to treat *all* patients?
EARLY vs. LATE START OF IMMUNOSUPPRESSIVE TREATMENT IN IDIOPATHIC MEMBRANOUS NEPHROPATHY WITH NEPHROTIC SYNDROME

RCT
Prednisolone/cyclophosphamide
Immediately or delayed until renal function declined

EARLY TREATMENT
Earlier remission
Shorter duration of nephrotic syndrome

No difference at 6 years in
Remission
Renal function
Relapse rate
Adverse events

Hofstra J et al. NDT 2010; 25: 129
TREATMENT OF
IDIOPATHIC MEMBRANOUS NEPHROPATHY

Select high risk patients

‘Head to head’

Is ‘Ponticelli’ or CNI more effective?
Tight BP control
125/75

Full renin-angiotensin blockade

Statin
Tight BP control
125/75

Full renin-angiotensin blockade

Statin

Deteriorating renal function or intractable nephrotic syndrome
Tight BP control
125/75

Full renin-angiotensin blockade

Statin

Deteriorating renal function or intractable nephrotic syndrome

What is the evidence that immunosuppressive regimens give additional benefit?
Tight BP control
125/75

Full renin-angiotensin blockade – 92%

Statin

At least 20% decline in GFR or intractable nephrotic syndrome

RCT

Continue supportive therapy
37

‘Ponticelli’ Regimen
33

Cyclosporin
36
THE UK RANDOMISED CONTROLLED TRIAL OF IMMUNOSUPPRESSION FOR PROGRESSIVE MEMBRANOUS NEPHROPATHY

**Primary end point: further 20% decline in GFR**

At least 20% decline in GFR or intractable nephrotic syndrome

- **Tight BP control**: 125/75
- **Full renin-angiotensin blockade**: 92%
- **Statin**

**Intention to treat analysis**
Time to 20% fall in GFR

% remaining

0% 25% 50% 75% 100%

0 1 2 3

Time (years)

Cyclosporin
Pred / Chlor
Support Care

40%
18%
16%
Hazard Ratio (95% CI):

Pred/Chlorambucil vs Supportive care: HR 0.44 (0.24, 0.78), 2p=0.0042
RITUXIMAB FOR IDIOPATHIC MEMBRANOUS NEPHROPATHY

2003-2012

90 references on PubMed

Hundreds of patients treated
RITUXIMAB FOR IDIOPATHIC MEMBRANOUS NEPHROPATHY

2003-2012

90 references on PubMed

Hundreds of patients treated

No RCT
RITUXIMAB FOR IDIOPATHIC MEMBRANOUS NEPHROPATHY WITH NEPHROTIC SYNDROME

n = 100

Persistent uP >3.5g/d after 6 months ACE inhibitor

10 year experience, at least 6 months follow up

32% previous immunosuppression

RITUXIMAB - most had 2 doses, second dose when peripheral blood B cells recovering

Ruggenenti P et al. JASN 2012; 23: 1416
RITUXIMAB

Perception –

A powerful B-cell specific targeted therapy

Replacing more toxic agents

Remarkably safe
ADVERSE EFFECTS OF RITUXIMAB

Up to 10% infusion reaction

Short term infection risk < ‘Ponticelli regimen’

Increased tumour risk in rheumatology studies

Progressive multifocal leucoencephalopathy in nephrotic children

? relates to extent of other immunosuppressive exposure

Ruggenenti P et al. JASN 2012; 23: 1416
COST OF RITUXIMAB

1 dose of rituximab: $4,000

Ponticelli regimen for 6 months: $ 600

Does avoiding one hospital admission for a septic episode save the cost of rituximab?

Ruggenenti P et al. JASN 2012; 23: 1416
MEembranous Nephropathy Trial Of Rituximab (MENTOR)

Mayo Clinic

3 months run in ....

Cyclosporine for 6 months
vs.
Rituximab – minimum 2 doses

ClinTrials.gov: NCT01180036
ECULIZUMAB [C5 COMPLEMENT INHIBITOR] IN MEMBRANOUS NEPHROPATHY

Logical treatment
Prevents assembly of C5b-9 membrane attack complex

RCT

No benefit

Incomplete complement inhibition

Appel G et al. JASN 2002; 13: 668A
TREATMENT OF IDIOPATHIC MEMBRANOUS NEPHROPATHY

“Should I treat this patient?”
“Should I treat this patient?”

“Should I treat this patient with an immunosuppressive regimen with a significant adverse event profile?”
TREATMENT OF IDIOPATHIC MEMBRANOUS NEPHROPATHY

- Do the simple things properly
- Minimise adverse effects of treatment
- Use guidelines with judgment
- Wait for evidence
- Help create the evidence