Hello #MedTwitter #nephtwitter

We recently had an interesting case-based discussion in @ASPNeph pathology webinar about #membranousnephropathy @IPNA_pedneph

Let’s start with a poll!

Which of these is true about Membranous Nephropathy (MN)?

Correct Answer: D

- MN rare in children &lt;12y (~1-3%)
- Incidence ↑ in adolescents (18-22%)
- Incidence of MN appears to be ↑ worldwide

PMC4074564

Presentation in peds:
- Most common: proteinuria +/- microscopic hematuria
- Nephrotic syndrome: 40-75%
- Hypertension: &lt;10%
- Thromboembolic events: &lt;5%
- Gross hematuria noted in some patients
<table>
<thead>
<tr>
<th>Types of MN:</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Primary: Antibody (Ab) to a known podocyte antigen</td>
</tr>
<tr>
<td>- Idiopathic: no identified target antigen</td>
</tr>
<tr>
<td>- Secondary: due to illness/exposure (75% of peds cases)</td>
</tr>
<tr>
<td>- Alloimmune: Ab to foreign antigen</td>
</tr>
</tbody>
</table>

**Table: Differences between pediatric and adult membranous nephropathy (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 PLA3R-associated</td>
<td>45% (more common in adolescents)</td>
<td>70–80%</td>
</tr>
</tbody>
</table>

**Demographic and clinical features:**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Pediatric MN</th>
<th>Adult MN</th>
</tr>
</thead>
<tbody>
<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>
</tbody>
</table>

**Pathological features:**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Pediatric MN</th>
<th>Adult MN</th>
</tr>
</thead>
<tbody>
<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>

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Which of the following are identified antigens for primary MN?

Correct Answer: D

Although PLA2R was the first antigen discovered in 2009 followed by THSD7A in 2014 (these are the most common antigens), all the above antigens have now been identified with distinct disease entities causing MN.
PLA2R:
- Phospholipase A2 receptor (PLA2R) antibodies bind to antigens on podocytes
- Present in 70% of adults with primary MN
- 45-50% of pediatric patients with primary MN
- Does not seem to be associated with secondary MN

What is the classic histological pattern seen in MN?

Correct Answer: C

Classic MN Histology:
- **LM:** thickened GBM (“cheerios” appearance)
- **Silver Stain:** Spike pattern along GBM
- **IF:** IgG & C3 staining along GBM
- **EM:** finely granular electron dense deposits on subepithelial GBM

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**Fig. 1** Primary membranous nephropathy (MN) (hematoxylin and eosin; x200). Glomerular capillary walls are uniform with mild thickening (arrows)

**Fig. 2** Primary membranous nephropathy (MN) (periodic acid-methenamine silver-Jones stain; x400). Characteristic spike-like epimembranous projections of basement membrane material on capillary walls (arrows)
Natural History:
- No specific peds data
- In adults course is remitting/relapsing and:
  - ~1/3 spontaneously remit without treatment
  - ~1/3 persistent proteinuria with preserved kidney function
  - ~1/3 progress to ESKD

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Management:

Due to rarity of disease and favorable prognosis without treatment, there are no RCTs comparing treatments of MN in children.

Treatment:
- Varies based on severity
- Remission may occur spontaneously
- Can take months/years to achieve

Management cont:

- Asymptomatic subnephrotic proteinuria:
  - Non-immunosuppressants (ACEi or ARBs)
- Nephrotic Syndrome, worsening proteinuria or antibody levels:
  - Immunosuppression (Rituximab, Tacrolimus)
MENTOR Trial:

- Randomized controlled trial
- 130 adult patients with MN and proteinuria \( \geq 5 \text{g/day} \)
- Rituximab (Ritux) vs. Cyclosporine
- Ritux superior in achieving complete or Partial remission at 2y (60% vs. 20%)

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STARMEN Trial:
- Randomized open label controlled trial
- Adults with primary MN and persistent NS x 6months
- Steroid+CYC vs. Tacro+Ritux
- Complete remission higher with Steroid+CYC (60% vs 26%)
Prognosis:
- Progression to ESKD in childhood is rare
- Spontaneous remission possible
- Younger children have better outcomes
- Primary diagnosis in 0.5% of children with CKD and 0.4% on dialysis


Recurrence after transplant:
- Adult rates 7-45%
- anti-PLA2R Ab at the time of transplant ↑ risk
- No peds-specific data

PMID: 31811540
Now you are mem-BRAINY-ous about membranous nephropathy!

For a case-based clinical discussion with pathology expert login to @ASPNeph website, May webinar. Answer questions to get #MOC2credits #Membereducation #ASPNFOAMgroup

Thanks to @drM_sudha @RoshanPGeorgeMD @prit899