Hello #MedTwitter
Let's talk about pediatric #MPGN / ‘Immune complex GN’ #ICGN today
A few pearls from the 1st @ASPNeph pathology webinar of 2021
#tweetorial #NephTwitter

Let's begin with a poll:

Which of the following is true about IC-MPGN?

2/ All the above

- There is limited data on epidemiology
- The estimated prevalence is 1 to 2/ million children, 5 to 15 years of age
MPGN denotes “pattern of injury” not etiology

Characteristic mesangial & endocapillary cellularity

Thickening of glomerular capillary walls due to subendothelial deposition of IC/complement factors

Image courtesy @Trumidor
4/ ⚫ Type III hypersensitivity reaction ⚫ is the hallmark of the disease

⚡ ”Anything” can form IC→IC deposition→activation of immune cells→‘complement activation’→Glomerular injury

⚡ complement dysregulation is the key ⚫ factor
Pathogenesis of IC-MPGN

1. Chronic circulating immune complexes (IC)
   - Persistent antigenemia
   - Impaired clearance

2. IC formation or deposition in glomeruli
   - Regulated by charge and size

3. Recruitment of platelets, neutrophils and macrophages
   - Complement activation with C5a generation
   - C3b- & Fc-mediated adherence
   - Chemokine production
   - LAM expression

4. Oxidant and protease mediated capillary wall damage
   - Proteinuria and fall in GFR

5. Cytokine and growth factor stimulation of mesangial cells
   - Mesangial cell matrix expansion

Adapted from comprehensive nephrology
5/ Currently, “triggers/ risk factors” for host injury are unknown

⚡Damage is inversely proportional to Antigen (Ag) clearing
⚡In other words, chronic antigenemia = chronic inflammation

6/ Latest classification is based on IF-

⚡C3 dominant deposits→ C3 Glomerulopathy (C3GN & DDD)- rare
⚡C3 + Ig deposits→ Ig- MPGN (Immunoglobulin asso. MPGN)
⚡No deposits MPGN→ Chr. TMA, transplant glomerulopathy, etc.
7/ **Etiopathogenesis:**

- **IC- MPGN is via CLASSICAL complement pathway activation,**

- **C3G is due to primary alternative complement pathway dysregulation**
<table>
<thead>
<tr>
<th>Antigens</th>
<th>IC- MPGN</th>
<th>C3G</th>
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<tbody>
<tr>
<td></td>
<td>Children- idiopathic</td>
<td>autoantibodies that protect C3 convertase</td>
</tr>
<tr>
<td></td>
<td>Adults- secondary to</td>
<td>from degradation (C3, C4,</td>
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<td></td>
<td>infection, autoimmune</td>
<td>or C5 nephritic factors)</td>
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<tr>
<td></td>
<td>disease, or monoclonal</td>
<td>genetic mutations resulting in</td>
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<tr>
<td></td>
<td>gammopathies</td>
<td>impaired function of alternative</td>
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<td></td>
<td></td>
<td>complement pathway regulators</td>
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<tr>
<td></td>
<td></td>
<td>idiopathic</td>
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<tr>
<td>Complement</td>
<td>activation of CLASSICAL</td>
<td>primary ALTERNATE pathway</td>
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<tr>
<td></td>
<td>pathway</td>
<td>dysregulation</td>
</tr>
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Kirpalani et al 2020

8/ MPGN is associated with a variety of disorders. Common one being

- Complement system abnormalities
- SLE
- Hepatitis B & C
- &gt;50y - monoclonal gammopathies
9/ ✮ What is the most common presentation of IC-MPGN?

10/ Ans: Hematuria

✮ Clinical presentation is heterogeneous

⚡ ranges from asymptomatic hematuria to AKI

⚡ In a pediatric study: hematuria &gt; HTN &gt; NS

https://www.kireports.org/article/S2468-0249(20)31534-5/fulltext#sectsectitle0030
A 14 yr old adolescent male patient presented with HTN, hematuria, nephrotic syndrome, and AKI. Kidney biopsy revealed IC-MPGN. What will be your initial workup?
GOAL: identifying Treatable Target

Rule out PIGN prior to assigning IC-GN/ C3GN diagnosis

Hx driven work-up: Viral titers, Autoimmune/Rheum. evaluation, Immune Cell Abnormality, etc

If no etiology is found --> assess complement dysregulation

- History driven work-up is appropriate
  - Viral titers: Hepatitis B&C, EBV, CMV, HIV
  - Autoimmune/ Rheumatologic evaluation: AN, C3.C4, ENAs
  - Immune Cell Function/ Abnormality
  - >50y: monoclonal gammopathy

- Assessment of Complement pathways

<table>
<thead>
<tr>
<th>Functional assays</th>
<th>CH50, AP50, FH function</th>
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<tbody>
<tr>
<td>Quantification of complement components and regulators</td>
<td>C3, C4, FI, FH, FB, Properdin</td>
</tr>
<tr>
<td>Measurement of complement activation</td>
<td>C3d, Bb, sMAC</td>
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<tr>
<td>Autoantibodies</td>
<td>Anti-FH, anti-FB, nephritic factors (C3, C4, C5)</td>
</tr>
<tr>
<td>Genetic Testing</td>
<td>C3, CFH, CFI, CFB, CFHR-5</td>
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<tr>
<td>Plasma Cell disorders</td>
<td>Serum free light chains, Serum and urine electrophoresis, and Immunofixation</td>
</tr>
<tr>
<td>IF on kidney biopsy specimen</td>
<td>IgA, IgG, IgG, C1q, C3, fibrinogen, kappa, lambda, C4d (usually bright C3 +/- Ig, negative C4d)</td>
</tr>
</tbody>
</table>
Kidney Biopsy in IC-MPGN shows:

- **LM:** Mesangial proliferation and GBM thickening.
  “smashed blueberry pancake” appearance - by @Trumidor

- **IF:** C3 deposits + Ig deposits

- **EM:** Mesangial proliferation, GBM thickening, mesangial deposits

![Silver stain](Image courtesy @Trumidor)
14/ § Rx: treating the etiology, ↓ underlying immune dysregulation & burden of HTN & proteinuria
⚡ No curative option
⚡ Mostly expert-opinion based Rx data
⚡ RAASi, HTN & Lipid-lowering agents - all
⚡ Steroids, MMF & rarely CNI
⚡ PLEX, Rituximab, Eculizumab - inconsistent data
Clinical parameters at first presentation ($n = 14$) and after 1 year of follow-up ($n = 13$). Data are shown as median (line), interquartile range (box), and 1.5× interquartile range (whiskers). a Shows protein/creatinine ratio, b age-height-adapted blood pressure percentiles, c estimated glomerular filtration rate (eGFR) according to the Schwartz formula, and d serum C3 levels.
Prognosis:

- Pediatric pts with IC-MPGN/ C3G have better outcomes than adults
- Progression to advanced CKD - rare in children
- HTN & proteinuria remain suboptimally controlled
- Poor prognosis: NS, low eGFR at the onset, persistent HTN & proteinuria remain suboptimally controlled

Long-Term Outcomes of C3 Glomerulopathy and Immune-Complex MPGN in Children

- 165 patients
- 17 hospitals
- 3 countries
- Largest pediatric cohort

85 biopsy reports available
42% initially diagnosed as MPGN reclassified as C3G

Survival without eGFR < 30 mL/min/1.73 m²
50% reduction in eGFR or kidney replacement therapy

CONCLUSION:
Many patients initially diagnosed as MPGN would meet criteria for C3G. Longer follow-up may reveal a worse kidney prognosis in C3G vs. IC-MPGN.

Kirpalani et al, 2020
Thank you for scrolling till the end!

For case-based discussion on this topic logon to @ASPNeph January pathology webinar
Until next time...
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@priti899 @RoshanPGeorgeMD

@rattibha unroll please

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