Post-infectious glomerulonephritis

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Where does it all come from?

- **William Charles Wells 1812:** Dropsy that follows scarlet fever
  - Dark and scanty urine [*red matter of blood*]
  - Proteinuria [*probably serum was found in the urine*]
  - The siblings are much more likely to develop nephritis “due in part, to a similarity of constitution derived from both parents”

- **Von Pirquet 1911:** antigen-antibody reaction that causes renal disease
Epidemiology

- The most common cause of acute nephritis in children
- The vast majority of all cases occur in developing countries (9.5-28.5/10^5)
- In industrialized countries, the incidence has decreased over the last 3 decades (0.3/10^5)
- Increased risk among children between 5-12 yrs; rare in < 3 yrs
Sporadic vs Epidemic

- Sporadic

- Epidemics of group A streptococcal infection
  - 5-10% with pharyngitis
  - 25% with skin infection
Pathogenesis - Immune complex (IC) disease?

- Proposed mechanisms
  - Deposition of circulating IC
  - In situ IC formation - deposition of streptococcal antigens within the GBM
  - In situ IC formation - streptococcal antibodies that cross-react with glomerular components
  - Alteration of a normal renal antigen that elicits autoimmune reactivity
Who are the nephritogenic antigens?

- **NAPIr** - Nephritis-associated plasmin receptor
  - Present in renal biopsies
  - Antibodies in 92% of PSAGN and 60% of uncomplicated infection
  - In Latin America and Switzerland: Antibodies in 5/47 and in only one biopsy sample

- **SPE B** - Streptococcal pyrogenic exotoxin
  - Colocalizes with complement and within “humps” in kidney biopsies
  - Antibodies in convalescent sera in all 53 pts
Pathology

• **Light microscopy**
  – Endocapillary proliferation and neutrophils
  – *Crescent formation – uncommon*

• **Immunofluorescence studies**
  – *IgG and C₃ deposits in a diffuse granular pattern within the mesangium and capillary walls (occasionally IgM, IgA, fibrin)*
Postinfectious glomerulonephritis

Low power light micrograph showing diffuse, proliferative glomerulonephritis as may be seen in postinfectious glomerulonephritis. The glomeruli are so hypercellular (arrows) that open capillary lumens cannot be seen and the glomeruli may be hard to distinguish from the surrounding interstitium.

Courtesy of Helmut Rennke, MD.
Acute postinfectious glomerulonephritis. The glomeruli show global intracapillary hypercellularity with large numbers of polymorphonuclear leukocytes in the glomerular capillary lumina (hematoxylin and eosin stain, ×400). (Courtesy of Peter Degrell, University of Pécs Faculty of Medicine, Nephrological Center, Pécs, Hungary.)

Immunofluorescence microscopy shows granular deposition of complement in the glomerular tuft in postinfectious glomerulonephritis. IgG can also be seen in the same distribution.

*Courtesy of Helmut Rennke, MD.*
• **Electron microscopy**
  
  – Immune complexes (correspond to IgG and C₃ in IF)
  
  – Subepithelial electron dense deposits (humps) → epithelial damage and proteinuria
  
  – Subendothelial IC deposits and complement activation → local influx of inflammatory cells nephritic syndrome
  
  – Does the rate of clearance of the IC correlate with the clinical course?
Normal glomerulus

Electron micrograph of a normal glomerular capillary loop showing the fenestrated endothelial cell (Endo), the glomerular basement membrane (GBM), and the epithelial cells with its interdigitating foot processes (arrow). The GBM is thin and no electron dense deposits are present. Two normal platelets are seen in the capillary lumen.

*Courtesy of Helmut Rennke, MD.*
Postinfectious glomerulonephritis

Electron micrograph shows pathognomonic subepithelial deposits (D) with a semilunar, hump-shaped appearance in postinfectious glomerulonephritis. The humps sit on top of the glomerular basement membrane (GBM). A neutrophil is attached to the denuded GBM, contributing to the glomerular inflammation. Neutrophil attraction requires the initial presence of subepithelial immune deposits so that complement chemoattractants have access to the systemic circulation.

Courtesy of Helmut Rennke, MD.
Clinical manifestations

- History of GAS infection
- Latent period: 1-3 wks following pharyngitis and 3-6 wks following skin infection
- Asymptomatic microscopic hematuria nephritic syndrome
- Gross hematuria in 30-50% (smoky, tea/coca cola)
Watch for signs of volume overload

• May be the sole presenting symptom/sign
• Hypertension (50-90%) varies in severity
  – May manifest as headache or significant neurologic signs
  – Hypertensive encephalopathy
• Edema (1/3)
• Respiratory distress due to pulmonary edema
Laboratory findings

• **Urinalysis** (freshly voided sample): hematuria ± casts, varying degrees of proteinuria (nephrotic range in 5%), pyuria

• **Complement**: $C_3$ and CH50 depressed in 90%; $C_4$ usually normal or slightly depressed
  - The combination of low $C_3$ and nl $C_4$ indicates activation of the alternative pathway
  - Normalizes within 6-8 wks
• Positive GAS culture in 25% (lag period), more in impetigo

• **Serology**: anti streptolysin O titers vs. streptozyme

• False negative
  – Following impetigo
  – Early antimicrobial therapy
When should we perform a kidney biopsy?

When another glomerular disorder is being considered

- Persistently low $C_3$ levels (MPGN, SLE...)
- Recurrent gross hematuria (IgA nephropathy? Alport syndrome?)
- Progressive kidney failure
- Unremitting nephrotic-range proteinuria
Further differential diagnosis

- Henoch-Schönlein purpura

- Post infectious GN associated with other agents
# Bacterial and viral agents associated with post-infectious glomerulonephritis

## Bacterial infections
- Skin or throat (Streptococcus group A)
- Endocarditis (Staphylococcus aureus, Streptococcus viridans)
- Visceral abcess (Staphylococcus aureus, E. coli, Pseudomonas, Proteus mirabilis)
- Shunt nephritis (Staphylococcus aureus, Staphylococcus albus, Streptococcus viridans)
- Pneumonia (Diplococcus pneumoniae, Mycoplasma)
- Typhoid fever (Salmonella typhi)

## Viral infections
- Epstein Barr virus
- Parvovirus B19
- Varicella
- Cytomegalovirus infection
- Coxsackie
- Rubella
- Mumps
- Hepatitis B

## Parasitic infections
- Schistosoma mansoni
- Plasmodium falciparum
- Toxoplasma gondii
- Filaria

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Management

• No specific therapy

• Penicillin administered to children with persistent GAS infection (prevent spread to household)

• Prophylactic penicillin to households in epidemics

• Supportive
  – Volume overload: salt restriction, loop diuretics
  – Hypertensive encephalopathy
  – Dialysis
Rapidly progressive glomerulonephritis (RPGN)

- The clinical correlate of crescentic GN
- Children tend to recover spontaneously
- Consider:
  - Corticosteroids (I.V. pulse methylprednisolone and/or oral prednisone)
  - I.V. cyclophosphamide (every 3-4 wks)
  - Plasmapheresis
Course

• Rapid resolution
• Diuresis begins within one week
• Serum creatinine normalizes within 3-4 wks
• Microscopic hematuria resolves within 3-12 months with episodes of gross hematuria during intercurrent infections
• Proteinuria improves rapidly; if in the nephrotic range - may persist for 6 months or more [correlates with removal of humps?]
Prognosis

- Recurrent episodes are rare
- Overall outcome in children is excellent

- Long term outcome (5-18 years):
  - 20% abnormal urinalysis (hematuria or proteinuria)
  - 92-99% normal or only modestly reduced renal function
  - Long-term follow-up in patients with a complicated course
An additional risk factor for CKD

- The prognosis is significantly worse in specific communities in which other risk factors for CKD exists.
- In Australian Aboriginal communities LBW (low nephron number), diabetes and metabolic syndrome are prevalent.
- PSGN may represent an additional risk factor that would explain why the incidence of ESRD is several-fold higher compared to the non-Aboriginal population.
Thank you