Rapidly Progressive Glomerulonephritis (RPGN)

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Objectives

- Understand the pathogenesis of RPGN
- Understand the clinical features and management of two specific types of RPGN:
  - Anti-GBM antibody disease
  - ANCA-associated disease
Glomerulonephritis in Children

- **Definition**
  - Varying degrees of hematuria, proteinuria, edema, hypertension, and decreased kidney function
Glomerulonephritis in Children

- **Definition**
  - Varying degrees of hematuria, proteinuria, edema, hypertension, and decreased kidney function

- **Clinical classification**
  - Acute glomerulonephritis
  - Recurrent macroscopic hematuria
  - Chronic glomerulonephritis
  - Rapidly progressive glomerulonephritis
Glomerulonephritis in Children

• **Clinical classification**
  – **Acute glomerulonephritis**
    • Sudden onset of hematuria, proteinuria, nephritic urinary sediment, edema, hypertension, and decreased kidney function
    • Most commonly due to post-streptococcal and HSP nephritis
  – Recurrent macroscopic hematuria
  – **Chronic glomerulonephritis**
  – Rapidly progressive glomerulonephritis
Glomerulonephritis in Children

• **Clinical classification**
  
  – Acute glomerulonephritis
    • Sudden onset of hematuria, proteinuria, nephritic urinary sediment, edema, hypertension, and decreased kidney function
    • Commonly due to post-streptococcal and HSP nephritis
  
  – Recurrent macroscopic hematuria
    • Transient episodes of gross hematuria following URIs
    • Commonly due to IgA nephropathy or Alport syndrome
  
  – Chronic glomerulonephritis
  
  – Rapidly progressive glomerulonephritis
Glomerulonephritis in Children

• **Clinical classification**
  – **Acute glomerulonephritis**
    - Sudden onset of hematuria, proteinuria, nephritic urinary sediment, edema, hypertension, and decreased kidney function
    - Commonly due to post-streptococcal and HSP nephritis
  – **Recurrent macroscopic hematuria**
    - Transient episodes of gross hematuria following URIs
    - Commonly due to IgA nephropathy or Alport syndrome
  – **Chronic glomerulonephritis**
    - Usually asymptomatic microscopic hematuria and proteinuria
    - Hypertension and decreased kidney function in later stages
    - Commonly due to IgA nephropathy, MPGN, and lupus
  – **Rapidly progressive glomerulonephritis**
RPGN in Children

• Definition
  – Features of acute glomerulonephritis (hematuria, proteinuria, edema, hypertension, nephritic urinary sediment), but with progressive loss of kidney function over days or weeks
  – Histologically characterized by glomerular crescent formation
Glomerular Crescents

Normal glomerulus

Active hypercellular crescent (gaps in glomerular basement membrane)

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Glomerular Crescents

Normal glomerulus
Active hypercellular crescent
(gaps in glomerular tuft and capsule)

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Glomerular Crescents

Active hypercellular crescent

Active hypercellular crescent

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Glomerular Crescents

Fibrous crescent

Fibrous crescent

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Glomerular Crescents

- a: GBM, Parietal Epithelial Cell, Bowman Capsule, Bowman Space, Mesangial Space, Endothelial Cell, Podocyte
- b: Plasma Proteins, Fibrin, Inflammatory Cells, Gaps or Holes in GBM Caused by Glomerular Disease
- c: Interstitial Fibroblast, Infiltrating Macrophage, Proliferating Parietal Epithelial Cells
- d: Fibrocellular Crescent
RPGN in Children

- **Mechanism of primary glomerular injury**
  - Immune complex
  - Anti-GBM antibody
  - Pauci-immune
RPGN in Children

- Mechanism of primary glomerular injury
  - Immune complex
    - Circulating immune complexes
    - Immune deposits in various parts of the glomeruli
    - Postinfectious GN, IgA nephropathy, lupus nephritis
  - Anti-GBM antibody
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RPGN in Children

• Mechanism of primary glomerular injury
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  – Anti-GBM antibody
    • Circulating antibodies directed to an antigen intrinsic to GBM
    • Linear deposition of IgG along the GBM
    • Anti-GBM antibody disease (Goodpasture’s)
  – Pauci-immune
RPGN in Children

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  – Pauci-immune
    • Circulating anti-neutrophil cytoplasmic antibody (ANCA)
    • Necrotizing glomerulonephritis with no immune deposits
    • ANCA-associated vasculitis

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RPGN in Children

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  - Immune complex
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Anti-GBM Antibody Disease

- Circulating autoantibodies directed against alpha-3 (and sometimes alpha-5) chain of type IV collagen, which is highly expressed in the GBM and alveoli
- Inciting stimulus for anti-GBM antibody is unknown
- Usually presents with RPGN (nephritic urine and progressive loss of kidney function)
- About half the patients also have pulmonary hemorrhage
- **Goodpasture’s disease** = RPGN + pulmonary hemorrhage + anti-GBM antibody
- Other systemic signs are usually absent
- Some patients also test positive for ANCA – they have signs of a systemic vasculitis

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Normal GBM
Anti-GBM Antibody Disease
Anti-GBM Antibody Disease

GBM
Type IV collagen network
Type IV collagen molecules
Protomer
NC1
Hexamer
Anti-GBM Ab
Monomer α3(IV)NC1

Epithelial cell foot processes
Endothelial cells

Fibrocellular Crescent
Interstitial Fibroblast
Proliferating Parietal Epithelial Cells
Infiltrating Macrophage

Caps or Holes in GBM Caused by Glomerular Disease
Inflammatory Cells
Plasma Proteins
Fibrin
Anti-GBM Antibody Disease

- Rare condition – 1 case per million population per year
- Usually seen in older children and in adults
- Diagnosis established by testing for anti-GBM antibodies (direct ELISA) – but false negative results may occur in patients with low titers
- Kidney biopsy is recommended for establishing the diagnosis
Anti-GBM Antibody Disease

Linear deposition of IgG along the GBM

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Anti-GBM Antibody Disease

- If untreated, anti-GBM antibody disease progresses rapidly to end-stage renal disease
- Early diagnosis is important for best response to treatment
- Patients who already require dialysis at the start of specific treatment rarely recover kidney function
- Specific treatment includes both plasmapheresis (to remove circulating anti-GBM antibody) and immunosuppression (to minimize new antibody formation)
Anti-GBM Antibody Disease

- Plasmapheresis should be performed initially daily until symptoms improve and anti-GBM antibody titers decrease
- Then switched to alternate days until all symptoms resolve and anti-GBM antibody titers become negative (usually 2-3 weeks)
Anti-GBM Antibody Disease

- Immunosuppression should be initiated as soon as possible, concurrent with plasmapheresis
- Steroids: IV methylprednisolone (20 mg/kg/day up to a maximum of 1 gm daily) for 3 days, then oral prednisolone (1-2 mg/kg/day) for 3-4 weeks followed by a slow taper over 6 months
- Oral cyclophosphamide (2 mg/kg/day) for 3 months
- Appropriate prophylaxis against potential side effects of steroids and cyclophosphamide
ANCA-associated vasculitis

- Circulating autoantibodies directed against neutrophil cytoplasmic antigens proteinase 3 (PR3) or myeloperoxidase (MPO)
- Inciting stimulus for ANCA production include respiratory infections and inhaled environmental toxins
- Usually presents with RPGN (nephritic urine and progressive loss of kidney function) and many other systemic signs of vasculitis
- Granulomatosis with polyangiitis (GPA) (Wegener’s)
- Microscopic polyangiitis (MPA)
- Churg-Strauss syndrome (CSS)
Antineutrophil Cytoplasmic Ab (ANCA)

• Detected using
  • Indirect immunofluorescence assay (IF)
  • Direct enzyme-linked immunosorbent assay (ELISA)
Antineutrophil Cytoplasmic Ab (ANCA)

- Detected using

  - **Indirect immunofluorescence assay (IF)**
    - Incubate ANCA-positive sera with fixed human neutrophils
    - Observe immunofluorescence pattern
    - Subjective, visual interpretation, not standardized
    - Sensitive but not specific
    - Used for screening

  - **Direct enzyme-linked immunosorbent assay (ELISA)**
    - Standardized assays for antibodies to PR3 and MPO
    - Specific but not sensitive
    - Used for confirmation

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ANCA – Indirect Immunofluorescence

Cytoplasmic

Perinuclear

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ANCA – Indirect Immunofluorescence

- **Cytoplasmic pattern**
- Antibodies against proteinase 3 (PR3)
- 90% of patients with granulomatosis with polyangiitis (GPA)

- **Perinuclear pattern**
- Antibodies against myeloperoxidase (MPO)
- 70% of patients with microscopic polyangiitis (MPA)

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ANCA-associated vasculitis
ANCA-associated vasculitis

Summary of the Pathogenesis of MPO-ANCA Vasculitis

- TNF
- IL-18
- GM-CSF
- LPS
- Complement
- Neutrophil
- Apoptosis
- NETosis
- Dendritic Cell
- INFECTION
- DRUGS
- TOXINS
- GENETICS

Legend:
- Neutrophil
- Activated Neutrophil
- Dendritic cell
- CD4 + T cell
- B cell
- NET
- ANCA
- LAMP2 Antibody
- MPO
- Adhesion molecules
- Cytokines

Neutrophil degranulation
Complement activation
TLR ligation

Glomerular Endothelial cell

Crescentic Glomerulonephritis
Granulomatosis with polyangiitis and Microscopic polyangiitis

- Usually seen in adults but can affect all ages
- Incidence in childhood is 1-6 cases/million/year
- Some recent reports suggest incidence in childhood now approaching that in adults
- GPA (Wegener’s) is more common than MPA, although there are regional differences

Sacri et al. NDT 2015, 30:1104
Granulomatosis with polyangiitis and Microscopic polyangiitis

- Clinical presentation of GPA and MPA are similar
- Upper and lower airway involvement is more frequent in GPA
- Adults typically present with prolonged prodromal symptoms of fever, malaise, weight loss – specific organ involvement is often delayed by months
- Children exhibit a much shorter prodrome and develop kidney or lung symptoms early – time to diagnosis is usually less than one month

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# Granulomatosis with polyangiitis and Microscopic polyangiitis

<table>
<thead>
<tr>
<th></th>
<th>Cabral GPA (n=65)</th>
<th>Sacri GPA (n=28)</th>
<th>Sacri MPA (n=38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>14 (4-17)</td>
<td>13 (10-15)</td>
<td>11 (9-12)</td>
</tr>
<tr>
<td>Fever/malaise</td>
<td>90%</td>
<td>82%</td>
<td>80%</td>
</tr>
<tr>
<td>ENT</td>
<td>80%</td>
<td>75%</td>
<td>0%</td>
</tr>
<tr>
<td>Lung</td>
<td>80%</td>
<td>70%</td>
<td>30%</td>
</tr>
<tr>
<td>Kidney</td>
<td>76%</td>
<td>78%</td>
<td>95%</td>
</tr>
</tbody>
</table>

*Cabral et al. Arthritis Rheum 2009, 60:3413*

*Sacri et al. NDT 2015, 30:1104*
Granulomatosis with polyangiitis

- ENT manifestations
  - Chronic nasal crusting and purulent/bloody discharge
  - Chronic sinusitis and otitis
  - Cartilage destruction (saddle deformity)

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Granulomatosi with polyangiitis

- Lung manifestations
  - Cough, dyspnea, hemoptysis
  - CXR: nodules, cavities, infiltrates, effusions
Granulomatosis with polyangiitis

- Kidney manifestations
  - Hematuria, proteinuria, hypertension
  - Nephritic urine and progressive loss of kidney function
  - Necrotizing crescentic GN with no immune deposits
  - Granulomas are uncommon
Granulomatosis with polyangiitis and Microscopic polyangiitis

- If untreated, ANCA-associated vasculitis progresses rapidly to end-stage renal disease
- Early diagnosis is important for best response to treatment
- Specific treatment includes initial therapy to induce remission and maintenance therapy to prevent relapses
ANCA – Initial Treatment

- **Glucocorticoids** for all cases
- **Cyclophosphamide** in combination with steroids
- **Rituximab** as an alternative to cyclophosphamide
- **Plasma Exchange** in the most severe cases
ANCA – Initial Treatment

• **Glucocorticoids**
  - If severe, daily IV pulse methylprednisolone for 3 days, followed by oral prednisone for 4 weeks, then slow taper over 6 months
  - If less severe, skip the IV pulses
ANCA – Initial Treatment

• **Glucocorticoids**
  – If severe, daily IV pulse methylprednisolone for 3 days, followed by oral prednisone for 4 weeks, then slow taper over 6 months
  – If less severe, skip the IV pulses

• **Cyclophosphamide**
  – Daily oral for 3-6 months or monthly intravenous for 6 months

• **Rituximab**
  – Alternative to cyclophosphamide (equally effective)
  – Once a week intravenous dose of 375 mg/m² for 4 weeks

• **Plasma Exchange**
  – Usually reserved for severe RPGN or severe pulmonary involvement
ANCA – Maintenance Therapy

- Glucocorticoids in low doses for all cases
- Azathioprine in combination with steroids
- Methotrexate as an alternative to azathioprine
- Rituximab as an alternative to azathioprine
- Duration is 18-24 months
ANCA – Maintenance Therapy

- **Glucocorticoids** in low doses for all cases

- **Azathioprine** in combination with steroids
  - Daily oral doses for 24 months

- **Methotrexate** as an effective alternative to azathioprine
  - Weekly oral doses for 24 months
  - Avoid if eGFR < 50 ml/min

- **Rituximab** as an effective alternative to azathioprine
  - Dosed at 6, 12, and 18 months after initial remission
Childhood ANCA - Outcomes

66 children included

Response (N=66, 100%)

Initial remission (N=46, 70%)

Secondary remission (N=15)
Adjuvant therapies:
CYP (N=8), IVIG (N=2), PE (N=3), RTX (N=3)

Remission (N=61, 92%)

Relapses (N=17)
15 remissions (3 ESRD)

No relapse (N=29)
29 remissions (11 ESRD)

Relapses (N=10)
9 remissions (4 ESRD, 2 deaths)

No relapse (N=5)
5 remissions (3 ESRD)

Refactory disease (N=16, 24%)

No remission (N=4, 6%)
1 early death, 3 patients with incomplete data

No remission (N=1)
Active disease until death (ESRD)
Objectives

- Understand the pathogenesis of RPGN
- Understand the clinical features and management of two specific types of RPGN:
  - Anti-GBM antibody disease
  - Pauci-immune

Thank You for your Attention!

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