بسم الله الرحمن الرحيم

PEDIATRICS **Nephrology**

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Acute Poststreptococcal Glomerulonephritis (APSGN)

This disease is a **classic example of the acute nephritic syndrome** characterized by the sudden onset of **gross hematurea, edema, hypertension, & renal insufficiency**. It is one of the most common glomerular causes of gross hematurea in children & is a major cause of morbidity following **group A β-hemolytic streptococcl hnfection (GAS).**

Etiology & epidemiology

It follows infections of the throat or the skin by certain **" nephritogenic "** strains of GAS. **97% of cases occur in less- developed countries** & the overall incidence has decreased in industrialized nations, presumably due to improved hygienic conditions. It follows **streptococcal pharyngitis during cold weather & follows skin infection (pyoderma) during warm weather.** Although epidemics of nephritis have been described in association with throat (serotype 12) & skin (serotype 49) infections, this disease is **most commonly sporadic.**

Pathology

The kidneys appear **symmetrically enlarged**. Glomeruli appear enlarged & relatively bloodless & show diffuse mesangeal cell proliferation with increase in mesangeal matrix. Polymorphnuclear leukocyte infiltration is common in glomeruli during the early stage of the disease. Immunofluorescence microscopy reveals "lumpy-bumpy" deposits of immunoglobulins & complements on the glomerular basement membrane & in the mesangium. On electron microscopy, electron dense deposits (humps) are observed on the epithelial side of the glomerular basement membrane.

Pathogenisis

Morphologic studies & the depression in the serum complement (C3) level provide strong evidence that APSGN is mediated by **immune complexes**. Precise mechanisms by which nephritogenic streptococci induce immunologic injury continue to be elucidated. GAS possess **M proteins**, & nephritogenic strains are related to the M protein serotype.

Clinical presentations

- It is most common in children aged **5-12 years** & uncommon below the age of 3 year.
- Symptoms usually develop 1-2 weeks after an antecedent streptococcal pharyngitis or 3-6 weeks after streptococcal pyoderma. The history of a specific infection may be absent (mild symptoms or no seek for treatment).
- **The severity of renal involvement varies** from a symptomatic microscopic hematuria with normal renal functions to gross hematuria with acute renal failure.
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- Depending on the severity of renal involvement, patients may develop various degrees of **edema, hypertension & oliguria**. Patients may develop **encephalopathy** (blurred vision, severe headache, altered mental status, seizure) &/or **heart failure** (respiratory distress, orthopnea, cough) owing to hypertension or hypervolemia.
- Encephalopathy may also result directly from the toxic effects of streptococcal bacteria on the CNS.
- Peripheral edema typically results from salt & water retention & is common & **nephrotic syndrome may develop in < 5% of cases.**
- **Nonspecific symptoms** as malaise, lethargy, abdominal or flank pain, & fever are common.
- **The acute phase generally resolves within 6-8 weeks.**
- Although urinary protein excretion & hypertension usually normalize by 4-6 weeks after the onset, **persistent microscopic hematuria may persist for 1-2 years after the initial presentation.**

Diagnosis

- **GUE:** RBC , RBC casts, proteinurea, & polymorphnuclear leukocytes.
- There may be mild normochromic **anemia** due to hemodilution & low-grade hemolysis.
- **The serum C3** level is significantly reduced in >90% in acute phase & return to normal level after 6-8 weeks after the onset (C4 is most often normal or mildly depressed).
- The diagnosis is confirmed by the clear **evidence of prior streptococcal infections :**
  1. Positive **throat culture** may support diagnosis or represent carrier state.
  2. A rising **antibody titer** to streptococcal antigen(s) confirms a recent streptococcal infection. These include :
     - The antistreptolysin O titer **(ASOT)** is commonly elevated after pharyngeal infection but rarely increases after streptococcal skin infections.
     - The best single antibody titer to document cutaneous infection is the anti-deoxyribo-nuclease **(DNase) B** level.
     - If available, a positive **streptozyme** screen (which measures multiple antibodies to different streptpcoccal antigen) is a valuable diagnostic tool.
     - Serologic evidence for streptococcal infections is **more sensitive** than the history of recent infections & far more sensitive than positive bacterial culture.
- **MRI of the brain** is indicated in patients with severe neurologic symptoms & can demonstrate reversible posterior leukoencephalopathy in the parieto-occipita areas.
- **CXR** is indicated in heart failure, respiratory distress, heart gallop, decreased breath sounds, rales & hypoxemia.
- **Renal biopsy** should be considered only in **acute renal failure**, **nephrotic syndrome**, **absence of evidence of streptococcal infection & normal complement level.** It should be considered when (hematuria & proteinuria, diminished renal infection &/or low C3 level persist more than 2 months after onset). Persistent hypocomplementemia can indicate a chronic form of postinfectious GN or another disease such as membranoproliferative GN.

Differential diagnosis

It includes several causes of ***hematuria*** as :

• Ig A nephropathy • Alport syndrome • Membranous nephropathy • Membranoproliferative glomerulonephritis • SLE nephritis • Acute exacerbation of chronic glomerulonephritis • Acute glomerulonephritis following other infections like staphylococci, streptococcus pneumonia, G-ve bacteria, bacterial endocarditis, certain fungi, rickettsial & viral disease particularly influenza • Pyelonephritis

Complications

- Hypertension : seen in 60% of cases & is associated with hypertensive encephalopathy in 10% of cases.
- Acute renal dysfunction: hyperkalemia, hyperphosphatemia, hypocalcemia, acidosis, seizure, & uremia.
- Heart failure.

Prevention

- Early systemic antibiotic treatment for streptococcal throat & skin infection does not eliminate the risk of GN.
- Family members of the patient, especially young children, should be cultured for GAS & treated if appropriate
- Family pets, particularly dogs, have also been reported as carriers.

Treatment

- *General measures* :
    1. Bed rest : only indicated during the oliguric phase (1^{st} week).
    2. Diet : increase carbohydrates diet to provide adequate calories & decrease protein & salts during oliguric phase & with complications as severe hypertension & marked vascular congestion.
    3. Fluid balance : During the oliguric phase, measurement of the daily urinary output is important. The total daily fluid intake should be equal to the urinary output + insensible water loss.
- *Specific measures :*
    1. Although a 10-days course of systemic penicillins is recommended to limit the spread of nephritogenic organisms, antibiotic therapy does not affect the natural history of GN.
    2. Control of hypertension : sodium restriction, diuresis usually with IV furosemide, & pharmacotherapy with calcium channel antagonists, vasodilators, or angiotensin-converting enzyme inhibitors are standard therapies.
    3. Control of edema : In most cases, edema subsides spontaneously at the end of 1^{st} week & with the onset of diuresis. ↓ fluid & salt intake during the 1^{st} week is usually important. In more severe cases, negative fluid balance is required. Diuretics as furosemide may be used.

- *Treatment of complications :*
    1. Severe hypertension (hypertensive crisis) : Na^+ nitroprusside infusion (0.5-10 microgram/kg/minute), Labetalol infusion (0.25-3 mg/kg/hour), Esmolol infusion (150-300 microgram/kg/minute).
    2. Heart failure.
    3. Renal failure.

Prognosis

- **Complete recovery occurs in > 95% of patients.**
- Mortality rate in the acute phase can be avoided by appropriate treatment of acute renal failure, heart failure, & hypertension.
- Infrequently, the acute phase is severe & leads to glomerulosclerosis & chronic renal disease in **<2%** of affected children.
- Recurrences are extremely rare.
- The true incidence of chronic renal disease that emerges later in adulthood as a result of childhood APSGN & reduction of functioning nephron number remains unknown.

Hemolytic–Uremic Syndrome (HUS)

HUS is one of the most common causes of community-acquired acute kidney failure in young children. It is characterized by the **triad of microangiopathic hemolytic anemia, thrombocytopenia & renal insufficiency.** HUS has a clinical features in common with thrombotic thrombocytopenia purpura (TTP) which can include also CNS involvement & fever with more gradual onset. Most cases of HUS (but few cases of TTP) occur after an acute gastrointestinal illness (usually diarrheal).

Etiology

The various etiologies of HUS allow classification into:

1. Infection-induced: the most common form of HUS is caused by toxin-producing E.coli that cause prodromal acute enteritis & is commonly termed diarrhea-associated HUS. In the subcontinent of Asia & southern Africa, the **shiga toxin of Shigella dysenteria type 1** is causative, whereas in Western countries, **verotoxin-producing E. coli (VTEC)** are the usual cause. Several serotypes of E. coli can produce verotoxin & the **O157:H7** type is most common in Europe & the Americas. The reservoir of VTEC is the intestinal tract of domestic animals, usually cows. Disease is usually transmitted by **undercooked meat or unpasteurized milk** or apple acidar. HUS outbreaks have also been associated with municipal water supply, petting farms, swimming in contaminated pools & consuming cheese lettuce or raw spinach contaminated with toxin. Less often, HUS **may spread by person-person** contact (within families or child care centers).

A rare but distinct form of HUS is related to **neuraminidase-producing S. pneumonia** which is typically presented with pneumonia & empyema. A thrombotic microangiopathy , similar to HUS or TTP , also occurs in untreated **HIV infections**.

2. Genetic: (second major category, **mostly without preceding diarrhea prodrome**, can be **indolent & unremitting or have a relapsing** pattern precipitated by infectious illness)

3. Medication-induced: (cyclosporine, tacrolimus, chemotherapy as mitomycin C & cisplatinum, clopidogrel & ticlopidine, quinine).

4. HUS associated with systemic diseases characterized by microvascular injury: (as malignant hypertension, SLE, antiphospholipid syndrome, following bone marrow or solid organ transplantation).

Clinical presentations

The onset is abrupt with manifestation of :

1. ***Microangiopathic hemolytic anemia*** as intense pallor. The examination of blood smear is important to identify RBC fragment, Burr cells, & schistocytes, as well as severe anemia & reticulocytosis.
2. ***Acute renal failure*** which is usually but not always oligoanuric with acidotic breathing & altered consciousness (↑ blood urea, ↑ serum creatinine, ↑ serum K^+, & metabolic acidosis).
3. ***Throbocytopenic purpura*** which may be mild (platelets count is about 120,000/mm^3) to severe (platelets count < 20,000/mm^3).

Pathogenesis

The primary event is the ***endothelial cell injury.*** Capillary & arterial endothelial injury in the kidneys lead to **localized clotting.** The microangiopathic hemolytic anemia results from **mechanical damage of RBC^S** as they pass through the altered vasculature. Thrombocytopenia is caused by **intrarenal platelets** adhesion or damage.

Complications

• *Anemia* • *Acidosis* • *Hyperkalemia* • *Fluid overload* • *Heart failure*
• *Hypertension* • *Uremia*
• *Extrarenal manifestations* : 1. CNS (irritability, seizure, & comma) 2. GIT (colitis, intestinal perforation, intususception, & hepqtitis) 3. Heart (pericarditis, myocardial dysfunction, & arrythmias) 4. Other rare complications as focal pancreatic necrosis, skin necrosis, parotitis,& adrenal dysfunction.

Prognosis &Treatment

- The acute prognosis, with careful supportive care, for diarrhea-associated HUS has **<5% mortality.** Half of the patients require dialysis support during the acute phase of the disease. Most recover renal function completely, but of surviving patients, 5% remain dependent on dialysis, & up to 20-30% are left with some level of chronic renal insufficiency.

- **The prognosis of HUS not associated with diarrhea is more severe.** Pneumococcal-associated HUS causes increased morbidity with 20% mortality. The familial genetic form of HUS can be insidiously progressive or relapsing diseases with poor prognosis. Identification of specific factor deficiencies in some of these genetic forms provides opportunity for specific replacement therapy to improve outcome.
- The primary approach for HUS include **early recognition of the disease, monitoring for potential complications & meticulous supportive care** as **fluid & electrolytes balance, control of hypertension, early institution of dialysis if the patient becomes anuric or significantly oliguric, & RBC transfusion.** Platelets should generally not administered, regardless of platelet count because they are almost immediately consumed by the active coagulation. Despite low platelet count, serious bleeding is very rare.
- **Anticoagulation, antiplatelet & fibrinolytic therapy is contraindicated** because they increase the risk of serious hemorrhage.
- **Antibiotic** therapy to clear the toxigenic organism can result in increased toxin release & therefore not recommended. Prompt treatment of any underlying pneumococcal infection is important. Binders of Vero or Shigatoxin in the gut are unsuccessful.
- **Plasma infusion or plasmapheresis** has been proposed for patients suffering severe manifestations of HUS, primarily serious CNS involvement (especially genetic HUS).
- **Most patients with diarrhea-associated acquired HUS recover completely with little risk of long-term sequelae.** However, patients with hypertension, any level of renal insufficiency, or residual urinary abnormalities persisting a year after an episode of diarrhea-positive HUS require careful follow-up.

Henoch-Schonlein Purpura (HSP)

(Anaphylactoid Purpura; Vascular Purpura)

Henoch-Schonlein Purpura (HSP) is an **inflammation of the blood vessels** in the skin and other body organs. It is the **most common cause of nonthrombocytopenic purpura in children**. People of all ages may develop HSP, but it is most common in children. Most cases occur between **2-8 yrs** of age & **males** are affected twice as frequently as females The exact **cause of HSP is unknown** (possibly due to a disorder of the **immune** system). HSP frequently occurs in the winter, often after an upper respiratory infection. It is not contagious. The overall incidence is estimated to be **9/100,000** population.

The clinical presentation may be acute, with the appearance of several manifestations **simultaneously, or insidious**, with sequential occurrence of symptoms over a period of weeks or months. **Low-grade fever and fatigue** are present in more than half of affected children. Symptoms may last for **4 to 6 weeks**. These may include: **Skin rash** of reddish-purple spots, usually on the buttocks or legs, occasionally on the elbows that is not itch (the **hallmark** of HSP), **arthritis** especially knees and ankles (**3/4** of cases), **Abdominal pain & bloody stool(1/2** of cases), **hematuria & proteinuria (1/3** of cases).

Diagnosis : Patients with HSP show evidence of systemic inflammation with **elevated ESR, CRP, and WBC count.** The platelet count is the most important test because HSP is characterized by nonthrombocytopenic purpura with a **normal, or even high, platelet count.** The presence of normal platelet numbers differentiates HSP from other causes of purpura that are associated with thrombocytopenia, such as autoimmune thrombocytopenia, SLE, or leukemia. The **urine** should be screened by urinalysis for evidence of hematuria, and serum **BUN and creatinine** should be obtained to evaluate renal function. Testing the **stool** for blood may identify evidence of gut ischemia. Any question of gut perforation requires **radiologic** investigation. **Definitive diagnosis of vasculitis is confirmed by skin biopsy, which is obtained when the clinical presentation is atypical.**

Treatment may include: Nonsteroidal anti-inflammatory drugs **(NSAIDs)**—to lessen joint pain and arthritis, **Steroids**—for significant abdominal pain or kidney disease, **Antibiotics**—to treat infection, **Cyclophosphamide** —to suppress the immune system when you have symptoms of severe kidney disease

The prognosis in HSP nephritis is **generally favorable**, although the risk of chronic kidney disease is less than 1%.

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