University of Diyala – College of Medicine
Pediatrics department – Nephrology & Urology
ا.د.مهدي شمخي جبر الزهيري

Acute Post-streptococcal Glomerulonephritis (APSGN)

- This disease is a classic example of the acute nephritic syndrome characterized by the sudden onset of gross hematuria, edema, hypertension & renal insufficiency.
- It is one of the most common glomerular causes of gross hematuria in children & is a major cause of morbidity following group A β-hemolytic streptococcal infection (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 M1, M4, M25 & some strains of M12) & skin (serotype M49) 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.

Pathogenesis

- 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.
- The search for the precise nephritogenic antigens suggests a possible role for streptococcal pyogenic exotoxin (SBE) B & nephritis-associated streptococcal plasmin receptor.

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.
- 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 is common & typically results from salt & water retention. Nephrotic syndrome may develop in < 5% of cases.
- Atypical presentations include those with subclinical disease & those with severe symptoms but an absence of initial urinary abnormalities. In individual who presents with purpuric rash, it is difficult to distinguish APSGN from HSLP without a renal biopsy.
- 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 , often with RBC casts, proteinuria & 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 B level.
- If available, a positive streptozyme screen (which measures multiple antibodies to different streptococcal 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 posterior reversible encephalopathy syndrome in the parieto-occipital areas.
- CXR is indicated in heart failure, respiratory distress, heart gallop, decreased breath sounds, rales & hypoxemia.
- The clinical diagnosis of APSGN is quite likely with acute nephritic syndrome, evidence of recent streptococcal infection & low C3 level. However, it is important to consider other diagnoses as SLE, endocarditis, membranoproliferative GN & acute exacerbation of chronic GN .
- 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, thin glomerular basement membrane nephropathy, membranous nephropathy, membranoproliferative GN, rapidly progressive GN, FSGS, SLE

nephritis, HSLP nephritis, HUS, sickle cell glomerulopathy, endocarditis, pyelonephritis, acute tubular necrosis, UTI, trauma, coagulopathy, tumor, factitious syndrome, urolithiasis, acute exacerbation of chronic GN, & acute GN following other infections like staphylococci, streptococcus pneumonia, G-ve bacteria, certain fungi, rickettsial, parotozoal, parasitic & viral disease (particularly influenza & parvovirus)

Complications

- Hypertension: seen in 60% of cases & is associated with hypertensive encephalopathy in 10% of cases. Although the neurologic sequelae are often reversible with appropriate management, severe prolonged hypertension can lead to intracranial bleeding.
- Acute renal dysfunction: hyperkalemia, hyperphosphatemia, hypocalcemia, acidosis, seizure, & uremia (may require dialysis).
- 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 considered at risk & be cultured for GAS & treated if positive.
- 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 (400 ml/m^2 surface area).

- 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. Treatment of heart failure.
3. Treatment of renal failure (dialysis)

Prognosis

- Complete recovery occurs in > 95% of children with APSGN.

- 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.

Hemolytic–Uremic Syndrome (HUS)

- HUS is a common causes of community-acquired acute kidney injury in young children. It is the most common form of thrombotic microangiopathy (TMA) in children. Like all TMA, 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 & other TMA allow classification into:

1. Infection-induced: the most common form of HUS is caused by Shiga toxin-producing *E.coli* (STEC) that cause prodromal acute enteritis & is commonly termed STEC-HUS or diarrhea-associated HUS.
- In the subcontinent of Asia & southern Africa, the toxin of *Shigella dysenteria* type 1 is causative, whereas in Western countries, verotoxin-producing *E. coli* (VTEC) or STEC is the usual cause.
- Several serotypes of *E. coli* can produce the toxin & the O157:H7 type is most common in Europe & the Americas. A large epidemic of HUS in Europe was caused by STEC-O104:H4. The reservoir of STEC is the intestinal tract of domestic animals, usually cows. Disease is usually transmitted by undercooked meat or unpasteurized milk or apple cider. Local outbreaks have followed the ingestion of undercooked, contaminated hamburger or other foods cross-contaminated on unwashed cutting boards at fast food restaurants, contaminated municipal water supply, petting farms, swimming in contaminated ponds, lakes or pools.
- With broad food distribution, wider epidemics have been traced to lettuce, raw spinach & bean sprouts contaminated STEC. Less often, STEC 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*. HUS is typically severe, develops during the acute infection & presented with pneumonia & empyema. A thrombotic microangiopathy, similar to HUS or TTP, also occurs in untreated HIV & influenza infections.

2. Genetic: (second major category, inherited deficiency of either VWF-cleaving protease or some complement factors, but 50% of familial cases without specific gene defect, mostly without preceding diarrhea prodrome, can be indolent & unremitting or have a relapsing pattern precipitated by infectious illness, severe prognosis, can benefit from alternative treatment)
3. Medication-induced: (as cyclosporine, tacrolimus, mithramycin, quinine & cocaine)

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

Pathology & Pathogenesis

- There are narrowing of the capillary lumens & platelet- fibrin thrombi which lead to renal cortical necrosis.
- 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 intra-renal platelets adhesion or damage.

Clinical presentations

- HUS (diarrheal form) is most common in preschool & school-age children, but it can occur in adolescents & adult. It can be relatively mild, or may be severe & fatal
- The onset is abrupt with manifestation of:

1. Microangiopathic hemolytic anemia as intense pallor, weakness & lethargy. 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. Thrombocytopenic purpura which may be mild (platelets count is about 120,000/mm^3) to severe (platelets count < 20,000/mm^3).

Complications

- Anemia, acidosis, hyperkalemia, fluid overload, heart failure, hypertension, uremia
- Extrarenal manifestations: 1. CNS (irritability, seizure, & comma) 2. GIT (colitis, intestinal perforation, intussusception, & hepatitis) 3. Heart (pericarditis, myocardial dysfunction, & arrhythmias) 4. Other rare complications as focal pancreatic necrosis, skin necrosis, parotitis,& adrenal dysfunction.

Diagnosis & differential diagnosis

- The diagnosis is made by a combination of microangiopathic hemolytic anemia with schistocytes, thrombocytopenia & kidney involvement. Anemia can be mild at presentation but it rapidly progress. Platelet counts usually 20000-100000/mm^3.
- PTT & PT are normal. Coombs test is negative except in pneumococcal-induced HUS. Leucocytosis is often present & significant. Urinalysis typically shows microscopic hematuria & low-grade proteinuria.
- The renal insufficiency can vary from mild elevations in serum BUN & creatinine to acute, anuric kidney failure. Stool culture is often negative in diarrhea-associated HUS.
- genetic form of HUS should be considered in the absence of diarrheal prodrome or pneumococcal infection.
- other causes of acute kidney injury with microangiopathic hemolytic anemia should be considered & excluded as SLE, malignant hypertension, bilateral renal vein thrombosis. A kidney biopsy is rarely indicated to diagnose HUS.

Prognosis &Treatment

- With early recognition & intensive supportive care, the mortality rate for diarrhea-associated HUS is < 5%. Up to 50% of 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 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 (> 80% require dialysis) 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, prompt correction of volume deficit, control of hypertension, early institution of dialysis if the patient becomes anuric or significantly oliguric, & RBC transfusion (in pneumococcal-HUS, RBC should be washed before transfusion to avoid complications). 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 in STEC can result in increased toxin release & therefore not recommended but prompt treatment of causative pneumococcal infection is important. Binders of Vero or Shigatoxin in the gut are unsuccessful.
- Plasma infusion or plasmapharesis has been proposed for patients suffering severe manifestations of HUS, primarily serious CNS involvement (especially genetic HUS but contraindicated with pneumococcal associated- HUS).
- Eculizumab (inhibit complement activation) is approved for treatment of atypical HUS including HUS following renal transplantation (with giving meningococcal vaccine before treatment).
- Most patients with diarrhea-associated 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 (particularly significant proteinuria) require careful follow-up. Patients who recover completely or no residual urinary abnormalities after 1 yr are unlikely to develop long-term sequelae but require out-patient annual examination.

Henoch-Schonlein Purpura (HSP)

- Henoch-Schonlein Purpura (HSP) is the most common vasculitis of childhood & is characterized by leucocytoclastic vasculitis & IgA deposition in the small vessels of skin, joints, GIT & kidney (also called IgA vasculitis).

Epidemiology

- HSP occurs worldwide & affects all ethnic groups but is more common in white & Asian populations. The incidence is about 14-20/100000 children/yr & affects males more than females by 1.2-1.8:1 ratio.
- About 90% of cases occur in children, usually 3-10 yr. HSP is less common in adults & often with sever & chronic complications. HSP is more common in winter & spring (many cases follows URT infection) & is unusual in summer.

Pathogenesis

- The exact pathogenesis remains unknown. Infections triggers as GAS, *Staphylococcus aureus*, mycoplasma & adenovirus are suspected. HSP is mediated by IgA & Ig immune complexes with occasional familial occurrence.
- Patients with familial Mediterranean fever, hereditary periodic fever syndromes & complement deficiencies are at increased risk of HSP (may be due to genetically determined immune dysregulation).

Clinical manifestations

- The hallmark of HSP is rash which is palpable purpura starting as pink macule or wheals & developing into petechiae, raised purpura or large echymoses with occasional bullae & ulcerations. Skin lesions are usually symmetric & occur in gravity-dependent areas (lower extremities), extensor aspect of upper extremities or in pressure points (buttocks).
- The skin lesions often evolve in groups, typically lasting 3-10 days & may recur up to 4 months after initial presentations. Subcutaneous edema localized to the dorsa of hand & feet, periorbital area, lip, scrotum or scalp is also common.
- Musculoskeletal involvement, including arthritis & arthralgia occurs in up to 75% of cases. The arthritis tend to be self-limited & oligo-articular, with predilection for large joints as knee & ankle, & does not lead to deformities. Peri-artiular swelling & tenderness without erythema or effusions are common. Arthritis usually resolves within 2 wk but can recur.
- GIT manifestations occur in up to 80% of children & include abdominal pain, vomiting, diarrhea, paralytic ileus & melena. Intussusception, mesenteric ischemia & intestinal perforation are rare but serious complications. Endoscopic evaluation is usually not needed but may identify vasculitis of intestinal tract.
- Renal involvement occurs in up to 30% of cases, manifesting as microscopic hematuria, proteinuria, hypertension, frank nephritis, nephrotic syndrome & acute or chronic renal failure. However, progression to ESRD is uncommon in children. Renal manifestations can be delayed for several months after the initial illness, so close follow-up with serial urinalysis & blood pressure monitoring is necessary.
- Neurologic manifestations may be caused by hypertension (posterior reversible encephalopathy syndrome) or CNS vasculitis (intracerebral hemorrhage, seizures, headaches, depressed level of consciousness, cranial or peripheral neuropathies & behavior changes).
- Other less common potential manifestations are inflammatory eye disease, carditis, pulmonary hemorrhage, orchitis & testicular torsion.

Diagnosis

- The diagnosis of HSP is clinical & often straightforward when the typical rash is present. In 25% of cases, the rash appears after other manifestations, making early diagnosis challenging. Most patients are afebrile.
- No laboratory finding is diagnostic of HSP. Common but nonspecific findings include leukocytosis, thrombocytosis, mild anemia & elevation of ESR & CRP. The platelet count is normal. Occult blood in stool is frequently found. Serum albumin level may be low due to renal or intestinal protein loss.
- Autoantibody testing such as ANA is not useful diagnostically but to exclude other diseases. Serum IgA are often elevated but are not routinely measured. Assessment of renal involvement with blood pressure, urinalysis & serum creatinine is necessary.

- U/S is often used in GIT complaints to look for bowel wall edema or rare intussusception. Barium enema can also be used for diagnosis & treatment of intussusception. Although not necessary in typical HSP, biopsies of skin & kidney can be helpful in atypical or severe cases (characteristically shows leukocytoclastic vasculitis with IgA deposition).

Differential diagnosis

- It depends on specific organ involvement but usually involve other small vessel vasculitides, infections, APSGN, HUS, coagulopathies & other acute intra-abdominal processes. Other differential include popular-pupuric gloves & socks syndrome, SLE, urticarial, hypersensitivity & thrombocytopenia.
- Infantile acute hemorrhagic edema (AHE) is an isolated cutaneous leukocytoclastic vasculitis that affects infants <2 yr of age, resembles HSP clinically. AHE manifests as fever, tender edema of the face, scrotum, hands & feet & echymoses (usually larger than the purpura of HSP) on the face & extremities. The trunk is spared, but petichiae may be seen in mucus membranes. The patient usually appears well except for the rash. The platelet count is normal or elevated & the urinalysis is normal. The younger age, the nature of the lesions, absence of other organ involvement & biopsy may help distinguish infantile AHE from HSP.

Treatment

- Treatment for mild & self-limited HSP is supportive (adequate hydration, nutrition & analgesia.
- Corticosteroids are most often used to treat significant GI involvement or other life threatening manifestations. Glucocorticoids such as oral prednisone (1-2 mg/kg/day) or in severe cases, IV methylprednisolone for 1-2 wk followed by taper reduce abdominal pain & joint pain but do not alter overall prognosis.
- Corticosteroids are not routinely recommended for prevention of complications such as nephritis. Rapid tapering of corticosteroids may lead to a flare of symptoms.
- IVIG & plasma exchange are sometimes used for severe disease. In some patients, chronic HSP renal disease is managed with immunosuppressants as azathioprine, cyclophosphamide, cyclosporine & mycophenolate mofetil. ESRD develops in <5% of children with HSP nephritis.

Complications

- Serious GI involvement as intussusception & intestinal perforation imparts significant morbidity & mortality.
- Renal disease is the major long-term complication, occurring in 1-2% of children with HSP. Renal disease can develop up to 6 months after diagnosis but rarely dose so if the initial urinalysis is normal. Therefore, it is recommended to do serial monitoring of blood pressure & urinalysis for at least 6 mo after diagnosis to monitor for development of nephritis.

Prognosis

- Overall, the prognosis is excellent & most children experience an acute, self-limited course lasting on average 4 wk. 15-60% of children have 1 or more recurrences, typically within 4-6 mo of diagnosis. With each relapse symptoms are usually milder than the presentation. Children with more severe initial course are at higher risk of relapse.
- The long-term prognosis usually depends on the severity & the duration of GIT or renal involvement. Chronic renal disease develops in 1-2% of children with HSP, & <5% of those with HSP nephritis develop ESRD. The risk of HSP recurrences & graft loss following renal transplantation is estimated at 7% after 10 yr.

****