Acute Post Streptococcal Glomerulonephritis in Pediatrics: An Updated Overview

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Abstract
A common infectious agent in childhood is group A streptococcus (GAS) which is responsible for a wide range of clinical diseases in humans. These diseases are classified into toxin mediated, superficial, invasive and post-infectious diseases. Auto-immune post-infectious sequelae of GAS, acute post-streptococcal glomerulonephritis and acute rheumatic fever are responsible for most of related mortality and morbidity.
Key words: Acute Post Streptococcal Glomerulonephritis

Acute post streptococcal glomerulonephritis (APSGN)
Pudendal nerve arises from the sacral plexus in the pelvis. It is the main nerve of both perineum and APSGN is the common post-infectious glomerulonephritis in childhood. Responsible microorganisms are mostly group A B-hemolytic streptococci (GABHS). It usually appears 1–2 weeks after a throat infection and 3–5 weeks after a skin infection. Macroscopic or microscopic hematuria, edema, azotemia, and hypertension are the major clinical findings. It usually appears in children aged between 4 and 14 years old. Its presentation may be as acute nephritic syndrome, nephrotic syndrome, rapidly progressive glomerulonephritis (RPGN), or it may be subclinical (1).
Congestive heart failure, pulmonary edema, and severe hypertension-induced encephalopathy might occur as a complication of hypervolemia in the acute phase. Although the short-term prognosis is mostly good, APSGN is still one of the important causes of acute renal failure and hospitalization in children (2).

Epidemiology
Frequency
APSGN may occur in epidemic outbreaks or in clusters of cases, and it may occur in isolated patients. Epidemic outbreaks reported in the past as a consequence of upper respiratory or skin streptococcal infections. Sporadic cases and small clusters occur yearly with larger and more widespread outbreaks occurring approximately every 5 years, associated with the circulation of a nephritogenic strain of streptococcus. In communities with high levels of scabies, skin sores and overcrowded living conditions new strains spread very quickly (3).
Over the last 2-3 decades, the incidence of APSGN has declined in the United States as well as in other countries, such as Japan, Central Europe, and Great Britain. The estimated worldwide burden of APSGN is approximately 472,000 cases per year, with approximately 404,000 cases being reported in children and 456,000 cases occurring in less developed countries.
APSGN associated with skin infections is most common in tropical areas where pyoderma is endemic, whilst pharyngitis associated APSGN predominates in temperate climates (4). Carapetis et al (5) analyzed 11 population studies and found that the annual burden of APSGN in developing countries was 9.3 cases per 100,000 people.

Epidemic poststreptococcal glomerulonephritis occurs mainly in developing countries in areas such as Africa, the West Indies, and the Middle East. Reasons for this changing epidemiology relate to the nutritional status of the community, the more liberal use of antibiotic prophylaxis, and possibly, the change in the nephritogenic potential of streptococci. Among epidemic infections with nephritogenic streptococci, the apparent clinical attack rate is 10-12% (6).

Pathogenesis

APSGN is an immune complex-mediated disease, the exact pathology remains unclear, but it is believed to be type III hypersensitivity reaction. Several mechanisms may participate in the pathogenesis of renal damage. Nephritogenic immune complexes are formed in circulation and deposited in the glomeruli; alternately, the antigen and antibody arrive separately and meet in or outside the glomerular basement membrane, causing in situ immune complex disease. Immune cell recruitment, production of chemical mediators and cytokines, and local activation of the complement and coagulation cascades drive an inflammatory response that is localized in the glomeruli. Complement activation leads to destruction of the basement membrane (3).

Glomerular deposition of circulating immune complexes depends on the antigen load, the antigen:antibody ratio, Post-Streptococcal Glomerulonephritis 3 and the size of the immune complexes. In situ formation of immune complexes is favored by cationic antigens that have a charge-dependent facilitated penetration into the polyanionic glomerular basement membrane(GBM), and tend to occur in conditions of antigen excess (7).

Table 1: Pathogenetic mechanisms participating in acute poststreptococcal glomerulonephritis (7).

<table>
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<tr>
<th>Mechanism</th>
<th>Evidence</th>
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<tr>
<td><strong>Nephritogenic antigens</strong> (NAPr, SPEB, streptokinase, others)</td>
<td>NAPr and SEPB demonstrated in renal biopsies</td>
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<tr>
<td>Circulating immune complexes</td>
<td>Circulating anti-SPEB and anti-NAPr antibodies in APSGN patients</td>
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<tr>
<td>In situ Immune complexes (cationic antigens)</td>
<td>SPEB co-localized with complement in glomeruli and demonstrated in the subepithelial electron-dense deposits (“humps”) in APSGN</td>
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<tr>
<td>Autoimmunity (anti-IgG, other)</td>
<td>Neuraminidase is produced by some nephritogenic streptococci. Serum neuraminidase activity in APSGN patients</td>
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The size of GBM pores and the molecular size of the streptococcus-Ig complex are also important determinants. The molecular size of the streptococcus-Ig complex is about 15 nm (10 nm for streptococcus group A and 5 nm for immunoglobulin). The GBM pore sizes in children and adults are 2-3 nm and 4-4.5 nm, respectively. Therefore, the immune complex molecule can be more easily rodded into the glomerulus in children than in adults and, thus, may explain the increased frequency of APSGN in children compared to that in adults (8).

Some studies revealed 2 antigens isolated from nephritogenic streptococci in APSGN, these include the cationic cysteine protease streptococcal pyrogenic exotoxin B (SPEB) or nephritis strain–associated protein (NSAP), and nephritis-associated streptococcal plasmin receptor (NAPlr), which is a plasmin-binding protein with glyceraldehyde phosphate dehydrogenase (also known as presorbing antigen or PA-Ag). These fractions have an affinity for glomeruli and have been shown to induce specific, long-lasting antibody responses in biopsy specimens from patients with APSGN. Glomerular deposits of and antibody response to exotoxin B were more consistently present in APSGN than were deposits of and antibody response to PA-Ag (9).

PA-Ag is also known to activate the alternate pathway of the complement cascade, which happens to be preferentially activated in persons with APSGN. The observation that some patients may only have C3 deposition may relate to this mechanism (10).

**Diagnosis of APSGN :**

**A) History:**
A delay in the diagnosis of APSGN is sometimes related to the absence of a clear history of a preceding documented streptococcal infection. This may be due to more stringent definition criteria that require documented evidence of past infection by streptococci. Typically, an acute nephritic syndrome develops 1-2 weeks after an antecedent streptococcal pharyngitis, whereas a lapse of 3-6 weeks is common before a nephritic syndrome develops following streptococcal pyoderma, this latent period, more clearly defined after pharyngeal infections than after pyoderma, averages approximately 10 days (11).
Other factors contributing to a delay in the diagnosis of APSGN include the sporadic occurrence of disease, because this often requires a high index of suspicion, as opposed to epidemics; the history of an upper respiratory tract infection alone during the preceding month, which may not be diagnostically helpful, because upper respiratory tract infections are common during winter; the misdiagnosis of severe volume overload in a child as primarily due to a cardiac cause, because volume overload in children is relatively rare; and the absence of visible hematuria (a presentation that is relatively common) (12).

B) Clinical manifestation:
Cardinal features of APSGN are hematuria, edema, and hypertension.

Hematuria:
It may be microscopic and not identified by the patient. It may be macroscopic and lead to dark brown or smoky urine, the urine is often dark, typically described as “rusty,” “tea,” or “cola” colored. Frank hematuria may occur in severe cases (11).

Edema:
Starts in the eyelids and face then the lower and upper limbs then generalized (e.g. hydrocele, ascites, pericardial and pleural effusion). It may be migratory: appearing in eyelid in the morning, disappearing in the afternoon, and reappearing around the ankle in ambulatory patients by the end of the day (13).

In acute glomerulonephritis, glomerular filtration is reduced by the glomerular capillary obstruction caused by the immunological injury. The reduced glomerular filtration results in a fall in the filtered load of sodium and water, leading to expanded extracellular volume. The hemodynamic characteristics of this disease are increased blood volume, hypertension and normal or increased cardiac output. Blood volume expansion increases peripheral capillary filtration by increasing arterial and venous pressures. The return of filtered fluid into venules and via lymphatics is impaired by the high venous pressure. The primary event of edema formation in acute glomerulonephritis is the increased blood volume, edema also results as decreased serum protein reduces the osmotic pressure in the circulating blood volume. This reduced colloid osmotic gradient results in fluctuation of transcapillary fluid. The resulting insufficient osmotic pressure for fluid reabsorption into the circulating blood volume allows it to remain in the colloid rich tissue (14).

Hypertension:
The current definition of hypertension in children is based on the normative distribution of BP in healthy children, characterized by sex and height, as outlined in the recently updated clinical practice guidelines.

Oliguria:
Urine output is less than 0.5 ml/kg/hour. It may not be observed by the patient (13).

Proteinuria:
Varying degrees of proteinuria are also typically present, but nephrotic syndrome is rare, occurring in 2-4% of cases. Both microscopic proteinuria and mild proteinuria may persist for several months
after the acute presentation (15).

**Laboratory studies:**

**Urinalysis:**
Results are always abnormal, urine output is most often reduced, concentrated and acidic. Hematuria and proteinuria are present in all cases. Urine sediment has red blood cells, red blood cell casts, white blood cells, granular casts, and, rarely, white blood cell casts. Dysmorphic red blood cells indicative of glomerular hematuria can usually be detected by performing phase-contrast microscopy. Red blood cell casts are best detected in first, early- morning urine specimens examined by the physician immediately after the patient voids. Hematuria usually resolves within 3-6 months but may persist as long as 18 months (7).

Proteinuria may be mild or so severe that it causes nephrotic syndrome. Approximately 5-10% of patients with APSGN have nephrotic-range proteinuria. Proteinuria usually disappears in 6 months. Patients with nephrotic-range proteinuria in the acute phase or persistent heavy proteinuria have a worse prognosis. This is often associated with an evolution to a garlandlike pattern of immune deposits as the disease progresses (7).

**Evidence of preceding streptococcal infection:**
Antibody titers to extracellular products of streptococci are positive in more than 95% of patients with pharyngitis and 80% of patients with skin infections. The Antistreptolysin (ASO), antinicotinamide Adenine Dinucleotidase (anti-NAD), Antihyaluronidase (AHase), and anti-DNAse B are commonly positive after pharyngitis, and anti-DNAse B and AHase titers are more often positive following skin infections. ASO titers are frequently used to document streptococcal infection, but a more sensitive test is the streptozyme test, which tests antibodies to ASO, anti–DNAse B, AHase, and anti-NAD (16).

**Complement profiles:**
Low serum complement levels indicative of an antigen-antibody interaction are a universal finding in the acute phase of APSGN. Most patients have marked depression of serum component CH50 and serum concentrations of C3. The activation of the alternative pathway of the complement system is thought to be responsible for the hypocomplementemia. In some patients, the levels of C2 and C4 may also be decreased, but to a lesser extent, suggesting that both classic and alternate pathways of the complement system are activated. In most uncomplicated cases, the complement levels return to normal in 6-8 weeks. Prolonged hypocomplementemia suggests an alternative diagnosis. Occasionally, low complement levels persist for 3 months (8).

**Elevated BUN and creatinine values:**
This reflects the decrease in the glomerular filtration rate that occurs in the acute phase. The elevations are usually transient. Their failure to normalize within several weeks or months indicates that the patient may not have a true APSGN and suggests seeking an alternative diagnosis (17).

**Hyperkalemia:**
The most common cause of hyperkalemia in infants and children is “pseudo hyperkalemia” from hemolysis of the blood sample when the sample is obtained from a heel stick or a small bore
intravenous line. Although hyperkalemia is defined as a serum potassium concentration of > 5.5 mEq/L, it is moderate (6 to 7 mEq/L) and severe (>7 mEq/L) cases of hyperkalemia that are life threatening and require immediate therapy. When pseudo hyperkalemia is suspected, the test to determine the serum potassium level should be repeated from a free-flowing venous sample before any treatment is administered. Otherwise, hyperkalemia is most commonly seen in patients with end-stage renal disease or in those who experience acute renal failure (18).

**Kidney biopsy:**
Kidney biopsy is generally not recommended in the evaluation of patients with APSGN since the clinical history is usually highly suggestive and resolution of APSGN typically begins within 1 week of presentation. However, the performance of a renal biopsy is indicated in patients whose clinical presentation, laboratory findings, or disease course is atypical. Kidney tissue is required to make a definitive diagnosis that might affect treatment or provide information about disease progression or prognosis. A biopsy should be contemplated for certain patients with acute kidney injury (AKI), proteinuria, or hematuria. In such persons, study of the histology by light, immunofluorescent, and electron microscopy may be diagnostic (19).

**Management of APSGN:**
**General measures:**
Management is directed at treating the acute effects of renal insufficiency and hypertension. Patients with subclinical disease may be followed as outpatients but patients with the acute nephritic syndrome with severe hypertension and complication require hospitalization. Bed rest is difficult to enforce and is of unproven value, yet most children keep it on their own while they are in the acute phase. Restrictions of fluid and sodium intake are the cornerstones of the treatment of patients with APSGN (20).

**Antibiotics**
There is no specific treatment for post-streptococcal glomerulonephritis. Treatment is focused on relieving symptoms. The first question to be considered is when to give antibiotic treatment to a suspected nephritogenic streptococcal infection. Rapid, high sensitivity streptococcal test are good guide to treat if they are positive but a negative test requires confirmation. However, a recent report indicates that a decision to treat or not to treat based on the results of these tests is not associated with a higher incidence of APSGN after sore throat and skin infection. The diagnosis of PSGN carries with it the indication of treatment with penicillin or, in allergic individuals, erythromycin. If infection is present at the time of diagnosis, it requires treatment. Early administration of penicillin is reported to prevent or ameliorate the severity of acute glomerulonephritis and at least one report suggests that APSGN patients that receive antibiotic treatment have a milder clinical course. If infection is not apparent at the time of diagnosis, antibiotic treatment should be given anyway because positive cultures are sometimes obtained in apparently healthy patients and cross infection of household members and siblings of index cases is very high. Although a 10-day course of oral antibiotic therapy with penicillin is recommended to limit the spread of the nephritogenic organisms, antibiotic therapy does not affect the natural history of glomerulonephritis. Corticosteroids and other anti-inflammatory medications are generally not effective (21).

**Cases with Edema and Hypertension:**
Cases that present significant edema, hypertension and circulatory congestion benefit from the administration of loop diuretics (1-2 mg/kg, maximum upto 10 mg/kg IV or orally every 12 h). This therapy facilitates the resolution of edema and ameliorates the hypertension that is driven by
extracellular volume expansion. Diuretic therapy seldom if ever is required for longer than 48 h. Other diuretics are without effect (thiazide diuretics) or dangerous because of the possibility of hyperkalemia (aldosterone antagonists) (22).

Patients who present severe hypertension may require antihypertensive treatment and Nifedipine (0.5 – 2 mg/kg in children, every 4–6 h) is usually effective. Sublingual Nifedipine and intravenous Nicardipin can also be used. Beta blockers are usually avoided as patients develop some degree of respiratory compromise except Metoprolol which is a super selective beta blocker. Parenteral hydralazine, Labetolol, Diazoxide may be required for hypertensive emergency but the possibility of tachycardia requires close observation. Angiotensin converting enzyme inhibitors and type 1 receptor blockers carry the risk of hyperkalemia and should not be used when GFR is < 30% and serum potassium is > 5.8 mmol/L. Exceptionally, nitroprusside is required to control hypertensive encephalopathy (21).

Corticosteroids:
A renal biopsy is indicated for patients with rapidly progressive renal failure. If the biopsy findings show evidence of crescentic glomerulonephritis with more than 30% of the glomeruli involved, a short course of intravenous pulse steroid therapy is recommended (500 mg to 1 gm/1.73 m2 of methylprednisoneqrd for 3-5 days). However, no controlled clinical trials have evaluated such therapy. Long-term treatment with steroids or immunosuppressives is not recommended (23)

Renal Dialysis:
Dialysis is indicated in the setting of severe renal impairment leading to volume excess or electrolyte abnormalities that cannot otherwise be medically managed (24).

References


