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REVIEW

Post-streptococcal acute glomerulonephritis in children: clinical features and pathogenesis

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Abstract Post-streptococcal acute glomerulonephritis (PSAGN) is one of the most important and intriguing conditions in the discipline of pediatric nephrology. Although the eventual outcome is excellent in most cases, PSAGN remains an important cause of acute renal failure and hospitalization for children in both developed and underdeveloped areas. The purpose of this review is to describe both the typical and less common clinical features of PSAGN, to outline the changes in the epidemiology of PSAGN over the past 50 years, and to explore studies on the pathogenesis of the condition with an emphasis on the search for the elusive nephritogenic antigen.

Keywords Acute glomerulonephritis · Group A beta-hemolytic streptococcus · Nephritogenic

Historical perspective

In 1812, Wells described the clinical features of acute nephritis that included a latent period between scarlatina and development of edema and urine that contained both a red substance and a coagulable substance (protein) [1]. He also observed that the siblings of a child with nephritis were more likely to develop nephritis after scarlatina than the siblings of non-nephritic children. A decade later, Richard Bright combined the finding of the coagulable substance in the urine with the clinical features of dropsy and autopsy evidence of kidney "derangement" [2]. The term "Bright's disease" became the acceptable name for both acute and chronic glomerulonephritis until the mid-20th century. The form of the disorder associated with scarlatina became known as acute hemorrhagic Bright's disease [3]. During the last decades of the 19th and first decades of the 20th century, several descriptions of post-scarlatina glomerulonephritis appeared, and were termed "acute glomerulonephritis" [4–6].

The association between β-hemolytic streptococcal infection and acute glomerulonephritis was noted by Longcope et al., who stated that "no evidence could be obtained...that the streptococcus caused the glomerular nephritis by actual invasion of the kidney, for blood cultures and urine cultures were negative" [5]. The work of Dick and Dick [7] and Dochez and Sherman [8], demonstrating that a β-hemolytic streptococcus was the pathogenic species in scarlet fever, led to use of the term "post-streptococcal acute glomerulonephritis".

By 1940 serologic findings of anti-streptococcal antibodies [9] and depression of complement [10] were noted in patients with post-streptococcal acute glomerulonephritis (PSAGN) and it became clear that glomerulonephritis followed both upper respiratory and cutaneous infections with β-hemolytic streptococci [11, 12]. In 1941, Seegal and Earle developed the concept of nephritogenic strains of streptococci that were different from those that caused rheumatic fever [13]. Thus, the concept that acute glomerulonephritis was a non-suppurative, immunologically mediated complication of group A β-hemolytic streptococcal infections became firmly established.

Dedication This review is dedicated to the memory of Shane Roy III (1936–2009). Dr. Roy was the first pediatric nephrologist in Tennessee. His scholarly interest in post-streptococcal acute glomerulonephritis spanned his 40-year career in Memphis, resulting in seminal clinical observations on the condition.

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Epidemiology

Post-streptococcal acute glomerulonephritis remains an important non-suppurative complication of group A streptococcal infection worldwide. The estimated worldwide yearly burden of PSAGN is 472,000 cases; approximately 404,000 of those cases occur in children [14]. By far, most of the burden of PSAGN is borne by developing countries [14]. Pyoderma-associated PSAGN continues to prevail in tropical areas, where streptococcal skin infections may be endemic [15]. In contrast, in more temperate areas pharyngitis-associated PSAGN now predominates [16, 17].

The epidemiology of PSAGN has long been noted to differ from that of acute rheumatic fever [13, 18, 19] and led to the conclusion that certain strains of group A streptococci are either rheumatogenic or nephritogenic, while others are neither [13, 20]. Group A streptococci are most commonly typed by their surface M proteins [21], which are virulence factors. However, group A streptococci can also be divided into two groups based on the presence or absence of a lipoproteinase that causes serum to become opaque (serum opacity factor) [22, 23]. Each of these two groups contains a characteristic group of M proteins. The opacity factor-negative group contains the "rheumatogenic" strains, while the opacity factor-positive group contains the "nephritogenic" strains [24]. Thus, acute rheumatic fever and PSAGN should not result from the same streptococcal infection, making the reports of such associations difficult to explain [25, 26]. In addition, nephritogenic strains can be subdivided into those primarily associated with pyoderma and those that most often cause pharyngitis [27, 28]. This distinction is made more complicated by the fact that pyoderma-associated strains sometimes cause a simultaneous pharyngitis, presumably by transfer of bacteria from the skin to the oropharynx [20].

The serotype most frequently associated with pyoderma-associated pharyngitis is M49, "the Red Lake strain" [28, 29]. Other pyoderma-associated strains are M2, M42, M56, M57, and M60 [24]. The common pharyngitis-associated PSAGN M types are 1, 4, 25, and some but not all M12 strains [19, 30].

Two epidemics on the Red Lake Chippewa Indian Reservation in northern Minnesota provided important early insight into the epidemiology of PSAGN [31, 32]. In both epidemics, the nephritis followed cases of pyoderma due to the M49 serotype, which was discovered in the first epidemic in 1953 [28]. The second epidemic, in 1966, affected only children that were too young to have been alive during the first epidemic. This absence of nephritis in older children and young adults in the second epidemic was presumed to be due to immunity gained from exposure to the M49 serotype in the first epidemic [31].

Most of the well-studied PSAGN epidemics or clusters were pyoderma-associated [28, 29, 33–35]. However, a few epidemics/clusters included a predominance of pharyngitis-associated strains [36, 37]. In geographical areas having distinct seasons, pyoderma-associated cases tend to occur in the late summer or early fall months [18, 33, 34, 38], while in regions with a constant tropical climate cases occur year round [31].

The incidence of PSAGN often varies over time in a population. In a health district in Santiago, Chile, the annual incidence of PSAGN doubled to 13.2 cases per 100,000 population in an "epidemic" period (1984–1989) compared to an earlier "endemic" period (1980–1983) [33]. Subsequently (1990–1999), the incidence decreased to a low of 1.7 cases per 100,000 population per year. Most cases during the epidemic period were pyoderma-associated and correlated significantly with family size and household overcrowding.

The apparent decline in the incidence of PSAGN in the United States over the past 40 years is assumed to be largely from the near eradication of streptococcal pyoderma due to better hygiene and/or a decreased prevalence of skin infection-associated nephritogenic M serotypes [39]. Most new cases now admitted to the Le Bonheur Children's Medical Center in Memphis, TN, appear to be pharyngitis-associated [40]. This trend was documented in a 1990 study that found a marked overall decline in the number of children hospitalized for PSAGN from the period 1961–1970, when the average was 31 patients per year (70% pyoderma-associated), to the period of 1979–1988, when the average was 9.5 patients per year (38% pyoderma-associated) [17]. Thus, over these periods the prevalence of pharyngitis-associated PSAGN did not change significantly while that of pyoderma-associated PSAGN fell markedly. A similar decline in pyoderma-associated PSAGN was shown for northeast Florida for the period 1999–2006 as compared to 1959–1973 [16]. In the current era, since the near-disappearance of pyoderma-associated PSAGN in developed countries, virtually no epidemiologic data have been published on M types in PSAGN.

Pathogenesis

The concept of immune complex formation resulting in PSAGN dates to the early 20th century observations of Schick and Von Pirquet likening human PSAGN to acute serum sickness, with its similar latent interval [41, 42]. However, the exact mechanism by which PSAGN occurs remains a source of debate. Theories proposed have included glomerular trapping of circulating immune complexes as well as in situ immune complex formation resulting from antibodies reacting with either streptococcal components deposited in the glomerulus or with components of the glomerulus itself ("molecular mimicry"). Evidence has also been presented to support the anti-immunoglobulin activity

or glomerular plasmin binding activity of streptococcal components as causative of PSAGN.

In the 1960s and 1970s, work from the laboratories of Germuth, Dixon, and Michael [43–46] demonstrated similarities between PSAGN and an acute "one shot" serum sickness model in the rabbit: a latent interval, low levels of serum complement, glomerular deposition of antigen, antibody and complement, and the self-limited nature of both diseases. Such findings supported a circulating immune complex etiology for PSAGN [47, 48].

Serum levels of circulating immune complexes detected by a C1q binding assay were found in 67% of patients with PSAGN [49]. However, circulating immune complexes occurred with the same frequency in patients with uncomplicated group A streptococcal infections [50], and levels of circulating immune complexes were not correlated with clinical features of PSAGN [51]. Nordstrand et al. [52] noted that the time course of C3 deposition before that of IgG argues for complement activation by the alternative pathway, or by non-immune activation of the classical pathway that is now recognized as characteristic for the lectin pathway of complement activation [53]. Thus, the order of immune component deposition argued against glomerular deposition of the pre-formed immune complexes necessary for classical complement pathway activation [52].

The cross-reactivity of streptococci and mammalian tissue was demonstrated in the 1930s and 1940s [54, 55]. Experiments implicating molecular mimicry in acute rheumatic fever (ARF) [54, 56–59] led to evidence of a similar mechanism behind PSAGN [60]. Sera of patients with PSAGN contain antibodies to glomerular basement membrane (GBM) components laminin and type IV collagen [61]. Initially, cross-reactivity of streptococcal antigens with the GBM was demonstrated in the nephritogenic M12 strain [62]. However, later studies showed cross-reactivity with glomeruli of non-nephritogenic strains [63–65]. Kraus and Beachey [66] localized the antigenic determinant for cross-reactivity with human renal glomeruli of type 1 streptococcal M protein to a tetrapeptide (Ile-Arg-Leu-Arg) near the amino terminus. However, the similar cross-reactivity patterns of rheumatogenic and nephritogenic strains of streptococci argue against molecular mimicry involving M proteins [67].

Much of the early work on the pathogenesis of PSAGN focused on the group A-specific streptococcal M proteins, as nephritogenicity is restricted to certain M protein serotypes. M protein–fibrinogen complexes deposit in the glomeruli [68, 69]. However, not all strains of a nephritis-associated M protein serotype are nephritogenic [19], and while PSAGN only rarely recurs, many M protein serotypes do not confer lifetime immunity [48]. Additional evidence against an M protein etiology is the inability of convalescent serum to recognize free antigenic sites in early renal biopsies in patients with PSAGN, even after incubation of the sera with M protein [70]. Recently, *Streptococcus zooepidemicus* (group C) has been associated with outbreaks of PSAGN [71, 72], providing further evidence against M protein as the nephritogenic antigen.

M protein serotype 12 streptococci isolated from a patient with pharyngitis-associated PSAGN altered the carbohydrate composition of IgG in vitro, leading to the hypothesis that auto-immunogenic streptococcal-altered immunoglobulins underlie PSAGN [73]. Acute glomerulonephritis was induced in rabbits by administration of IgG altered by the same strain [74]. The autoimmunity-inducing IgG alteration in these studies was attributed to the actions of neuraminidase [75]. Anti-IgG antibodies were detected in the serum of 32% of patients with PSAGN [76], and in the glomeruli of 86% [77]. The arguments of Nordstrand et al. against the involvement of neuraminidase in the initiation of PSAGN are that (1) this would result in antibody deposition before C3, which is not observed in PSAGN [52], and (2) rheumatogenic and nephritogenic strains of streptococci both may produce neuraminidase [78].

Many studies have focused on the antigenic potential of certain components from nephritogenic strains of streptococci. As the glomerular basement membrane is negatively charged, cationic streptococcal components were investigated as the nephritogen, particularly histone-like proteins [79, 80]. In situ immune complex formation was proposed to result from anti-histone-like protein antibodies coupled with the ready adsorption of histone-like proteins to heparan sulfate-proteoglycans in the GBM [81]. However, anti-histone-like protein antibodies in the serum of patients with PSAGN or evidence of histone-like protein in their glomeruli have never been described [48].

Endostreptosin, a 40 to 50 kDa protein derived from streptococcal cell cytoplasm, has been detected in the glomeruli early in the clinical course of PSAGN, but not later in the disease [82, 83]. Antibodies directed against endostreptosin associate well with the course of the pathologic disease process [84]. These antibodies may represent a diagnostic marker for PSAGN, since they are elevated in patients with PSAGN as compared to healthy and disease (other types of glomerulonephritis and streptococcal infection) controls [85]. Perhaps endostreptosin was first studied in PSAGN by Treser [70], who showed that pre-incubating the serum with a fraction of streptococcus later determined to contain endostreptosin abolished staining of glomerular sections by serum IgG fractions from patients with PSAGN. Later, this was done with endostreptosin alone [86]. In a rat model, endostreptosin deposits along the GBM one day after injection but disappears in coincidence with the deposition of IgG and C3 at 8–12 days after injection [82]. This was explained by masking of the protein by bound antibody.

Yoshizawa et al. [87] isolated a 43 kDa protein called "pre-absorbing antigen" (PA-Ag) that others argue is identical to endostreptosin [48, 52]. PA-Ag was named for its ability to "pre-absorb" the antibody in convalescent PSAGN sera and prevent its glomerular deposition. PA-Ag activates the alternative complement pathway [87]. Antibody to PA-Ag was demonstrated in sera from 30 of 31 patients with PSAGN [87]. However, Rodriguez-Iturbe and Batsford [48] suggested that a subsequent study showed that sera of convalescent PSAGN patients had anti-IgG reactivity, which could result in the positive staining for endostreptosin in renal biopsies [76]. They also noted that injection of PA-Ag into rabbits resulted in findings that were inconsistent with PSAGN: mild proliferative (mesangial, endocapillary, or both) changes on biopsy and only mild hematuria and proteinuria [88]. In addition, Nordstrand et al. [89] found pre-absorbing antigen in non-nephritogenic strains of streptococci in their tissue cage mouse model of PSAGN.

Villareal et al. [90] isolated nephritis strain-associated protein (NSAP), a 46 to 47 kDa protein unique to the extracellular products of nephritogenic streptococci. NSAP was demonstrated in glomerular deposits for 14 of 21 patients with PSAGN, but none for control biopsies from five patients with acute renal failure (ARF) and 11 with nonstreptococcal glomerulonephritis. NSAP was also present in serum from 96% of PSAGN patients compared to 15–20% of patients with either ARF or impetigo [91]. NSAP has structural and biochemical properties identical to streptokinase. However, streptokinase cannot be demonstrated in glomerular deposits for patients with PSAGN [92], and serum levels of purified group A streptokinase were similar in patients with PSAGN and ARF. While NSAP and streptokinase may have similarities, they appear to be two distinct proteins [92]. Since a 43 kDa cleaved product of NSAP conserving NSAP's epitope [93] shares the same isoelectric point and molecular weight as PA-Ag, it was suggested that PA-Ag and the cleaved product of NSAP were the same molecule [92].

Cunningham attributed the inability to detect glomerular deposition of streptokinase by immunofluorescence to the insensitivity of the method [24]. Streptokinase was demonstrated by immunogold-silver staining in the glomeruli of mice infected with the nephritogenic streptococcal strain NZ131, and rendered the strain non-nephritogenic through deletion of the *ska1* gene responsible for production of streptokinase [94]. Reconstitution of the *ska1* gene into the NZ131 strain via a plasmid vector restored its nephritogenic properties [95]. Earlier work in rabbits had shown that deletion of a streptokinase gene from a type 49 strain eliminated its nephritogenic properties [96].

Holm et al. [97–99] suggested that NSAP contributed to the pathogenesis of PSAGN via its ability to convert plasminogen to plasmin, which cleaves C3, thus activating the alternative complement pathway and contributing to glomerular inflammation. Others suggested that active plasmin could induce PSAGN via degradation of extracellular matrix proteins and activation of matrix metalloproteinases [52, 100]. This has led to the investigation of other plasminogen-converting streptococcal components as possible nephritogenic antigens. Poon-King et al. [100] found a protein matching previous descriptions of NSAP that had plasmin binding properties and was identical to a precursor of streptococcal pyrogenic exotoxin B (speB). SpeB is a cationic extracellular cysteine proteinase with super antigenic properties produced by all group A streptococci strains [24]. Certain strains produce very high amounts of speB [101–103]. However, Poon-King et al. did not know if their protein was identical to the previously described NSAP, since antiserum prepared against NSAP was not available for direct comparison.

Further support for speB as the nephritogenic antigen is the finding that anti-speB antibodies are elevated in patients with PSAGN as compared to patients with ARF or scarlet fever or healthy individuals [104]. SpeB was found in the glomerular deposits in 67% of patients with PSAGN compared to 16% of patients with other glomerular diseases [104]. SpeB not only co-localized with C3 and IgG in the glomeruli of patients with PSAGN but was also demonstrated via immunogold-labeling of speB within the classic subepithelial hump [105]. A multicenter study showed that antibody to the zymogen of speB in South American patients with PSAGN was better than anti-streptolysin O and anti-DNAse B titers for demonstrating prior infection with nephritogenic streptococci [106].

Nordstrand et al. [52] felt that the role of speB in the pathogenesis of PSAGN was controversial, since sera from Ethiopian children showed no significant differences in reactivity against speB for patients with PSAGN and ARF. SpeB and its zymogen precursor were present during infection with both nephritic and non-nephritic streptococcal strains in a mouse tissue cage model of PSAGN [52]. In addition, sequencing of the genome of the group C *Streptococcus zooepidemicus* strain responsible for the PSAGN epidemic in Nova Serrana, Brazil revealed a lack of the gene encoding for speB, bringing into question its role as the sole nephritogenic antigen [71, 107].

Nephritis-associated plasmin receptor (NAPlr) was described by Yamakami et al. [108]. This 43 kDa glycolytic enzyme demonstrated plasmin binding and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) activity and was identical to a previously described plasmin receptor protein on group A streptococci [109]. Anti-NAPlr antibodies were detected in 92% of patients with PSAGN patients compared to 60% of patients with group A streptococcal pharyngitis patients without nephritis [110]. NAPlr was found in the

glomerular deposits of 100% of patients biopsied early in the course of PSAGN [110]. The glomerular distribution of NAPlr deposition and plasmin activity determined by in situ zymography was identical [111]. The fact that NAPlr did not co-localize with C3 in glomerular deposits was said to suggest that (1) complement was activated by NAPlr in the circulation rather than in situ, and (2) NAPlr induced PSAGN independently of complement activation by binding to the GBM and mesangial matrix via its adhesive character [110], and subsequently trapping and activating plasmin, causing in situ glomerular damage by degrading the GBM or activating latent matrix metalloproteases [111]. While speB was not expressed by the group C streptococcal strain responsible for the Nova Serrana, Brazil epidemic, NAPlr expression has been demonstrated in streptococcal groups A, C, and G [112]. However, Batsford et al. [105] failed to demonstrate either anti-NAPlr antibodies in serum from PSAGN patients or glomerular deposition of NAPlr. They suggested that the difference might have been due to the homogeneous Japanese population in the initial study [110] as compared to the diverse population from Venezuela in their study.

Since there is considerable evidence both for and against most putative nephritogenic antigens, collaborative efforts toward genomic sequencing of nephritogenic strains of streptococci have been initiated [107]. Discovery of new nephritogenic antigen candidates may be achieved by examination of conserved and differing regions of the genome. Such efforts will surely improve our understanding of the pathogenetic mechanism(s) underlying PSAGN.

Complement activation

Evidence from both serum complement profiles and immunofluorescence patterns for glomerular deposits indicates that C3 activation in PSAGN is predominately via the alternative pathway [113–115]. The immune deposits typically are made up of IgG, C3, properdin, and C5 [115]. These deposits virtually never contain the classical pathway components C1q and C4 [115]. C5b-9 (membrane attack complex) and its regulatory protein, the S protein, (vitronectin) localize in the same distribution as C3, indicating complete activation of the terminal complement pathway, which probably occurs in situ rather than in the circulation prior to deposition in the glomerulus [115, 116]. A recent study shows evidence for activation of the lectin-binding pathway from deposition of MBL in some patients with PSAGN [117].

Initially, some patients may have classical pathway activation, as evidenced by transient depression of serum C1q, C2, and/or C4 concentrations [118–120] and the presence of circulating C1-inhibitor-C1r-C1s complexes [120] or C4d fragments [114] during the first two weeks after onset. These findings of classical complement pathway activation could reflect the presence of circulating immune complexes in the acute stage that are distinct from the glomerular immune deposits.

The depression of serum levels of properdin, C5, C6, and the MAC (C5b-9) corresponds temporally to the persistent depression of serum C3 [114, 121]. Serum levels of the alternative pathway regulatory proteins, H and I, remain normal throughout the clinical course of PSAGN [114].

PSAGN with typical renal pathologic findings on light microscopy, immunofluorescence, and electron microscopy may occur in patients with no evidence of complement activation, as manifested by depression of serum C3 concentration [122, 123]. A study from Cincinnati Children's Hospital showed that 10% of children with PSAGN had normal serum C3 concentration at clinical onset [122]. The diagnosis of PSAGN in these normocomplementemic patients was confirmed by demonstration of typical findings for PSAGN on renal biopsy. Hypocomplementemic patients differ from normocomplementemic patients by virtue of the presence of factor B in the glomerular deposits [115]. This finding, along with the absence of the alternative pathway regulatory protein factor H, may indicate that C3bBb convertase is present in the glomerular immune deposits and that the ongoing complement activation in PSAGN may be in situ rather than systemic.

Crescentic PSAGN may have an increased association with normocomplementemia. Five of the 10 crescentic PSAGN patients from Memphis [124] and four of 11 from New Zealand [125] had normal or near-normal serum C3 levels; however, none of the four reported by Lewy et al. [126] had normal or near-normal serum C3 levels. The reason for this possible association of normocomplementemia with crescent formation in PSAGN is not clear.

Serum immunoglobulin levels

Serum IgG levels were elevated in 44% of 75 children hospitalized with PSAGN [127]. Twenty of those with elevated serum IgG levels were biopsied and over half had no IgG in their glomerular deposits [127]. Also, patients with an elevated IgG level were more likely to have anti-streptolysin O titers ≥833 Todd units ($p<0.001$). Elevated serum IgG concentration did not correlate with severity of disease, age of the patient, or the serum albumin or C3 level. There appears to be a subset of patients with elevated serum IgG levels who with high frequency have IgG absent from their glomerular deposits. Thus, failure to form antibody to a glomerular-bound protein produced by the nephritogenic streptococcus, widely assumed to be the origin of the IgG in the glomerular deposits, is in some way

significantly associated with elevated serum levels of IgG and antibody to streptolysin O.

Clinical manifestations—typical course, atypical features

The median age at presentation for PSAGN in childhood is between 6 and 8 years old [126, 128, 129]; the condition rarely occurs prior to age 2 [126, 130, 131]. The rarity of PSAGN in very young children was attributed to the low rate of streptococcal pharyngitis in this age group and an immature immune (or antibody) response [130]. Twice as many males are diagnosed with PSAGN as females [126, 130, 131]; the reason for this is unknown. There appears to be no difference in gender ratio whether PSAGN follows pharyngitis or pyoderma.

Children with PSAGN most often seek medical attention for edema or gross hematuria; occasionally symptoms or signs of hypertension will be the initial presenting feature leading to the diagnosis. The triad of edema, hematuria and hypertension is classic for PSAGN. Three phases of the disease can be identified: the latent phase, the acute phase, and the recovery phase. The general course is represented in Fig. 1. A preceding infection of the respiratory tract (usually pharyngitis) or of the skin is identified in the majority of cases. However, sub-clinical cases do occur, many of which are identified based upon the knowledge of an affected family member/contact. One report suggested that PSAGN occurs in about 20% of asymptomatic family members of patients with the condition [84]. The latency period between the streptococcal infection and the onset of the clinical syndrome ranges from 3–33 days [132] but on average is 7–14 days. The prevalence of clinical features during the acute phase of PSAGN differs somewhat among the various case series depending upon the era of publication and the method of patient selection. In fact, some of the earliest descriptions of cases of acute GN may have included patients that actually had conditions other than PSAGN.

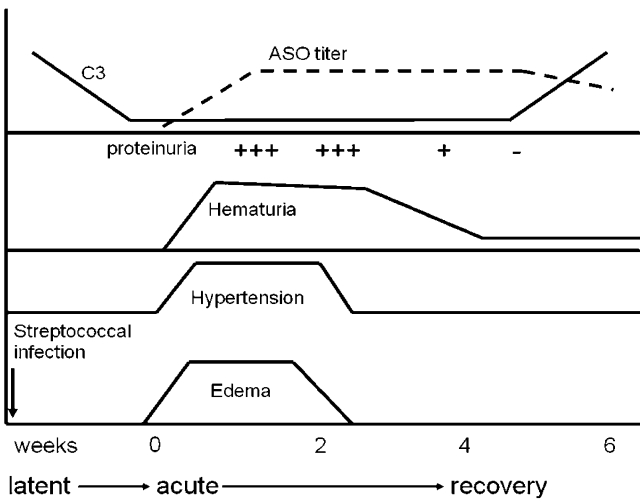

Fig. 1 Summary of the typical clinical course of post-streptococcal acute glomerulonephritis (PSAGN)

With the exception of rare cases with atypical presentation, hematuria is present in essentially all patients. The classic description of tea- or cola-colored urine occurs in approximately 25–60% of patients. Proteinuria is also typically present, but nephrotic syndrome is rare in most case series. While a single series [133] reported 10% with nephrotic syndrome, most have reported only 2–4% [126, 134]. Hypertension occurs in approximately 80–90% of cases [40, 135, 136]. Cerebral complications of hypertension including headaches, seizures, mental status changes, and visual changes occur in 30–35% of children [40, 135]. The mechanism for hypertension is most likely retention of sodium and water with resulting expansion of the extracellular space [134]. As with other causes of glomerulonephritis, fractional excretion of sodium is generally less than 1%, similar to pre-renal azotemia [137, 138]. Renin levels (plasma renin activity) are typically low at presentation [139, 140]. Fluid retention correlates with suppression of the plasma renin activity [140]. Diastolic blood pressure significantly correlates with the degree of fluid overload as assessed by weight change pre- and post-spontaneous diuresis [139]. Patients may sometimes present with clinical and radiologic signs of pulmonary edema. While dyspnea is a presenting complaint in only 5% of patients, evidence for congestive heart failure was found in half of the children in one early series [135].

Atypical presentations of PSAGN include those individuals with sub-clinical disease and those presenting with acute illness, usually related to hypertension or edema in the absence of overtly abnormal urine [141]. There are numerous case reports of children who present with extreme manifestations, usually from hypertensive crises, who do not display the typical urinary findings at presentation [141.] Serial examination of the urine after presentation may eventually confirm the suspicion of acute glomerulonephritis.

Another atypical feature at presentation is the presence of a typical Henoch-Schönlein purpura rash [142–144]. The diagnosis of PSAGN was confirmed by renal biopsy in those cases.

Examination of the urine sediment confirms acute glomerular involvement with the presence of dysmorphic red blood cells and leukocytes; red blood cell and white blood cell casts are usually identified. In the early part of the acute phase, urinary leukocytes may predominate over red blood cells.

The glomerular filtration rate (GFR) is often decreased during the acute phase of the disease. Increased blood urea nitrogen (BUN) was noted in 60–65% of patients [40, 135],

with decreased estimated creatinine clearance less than 90 ml/min/1.73 m^2 present in 20% [40]. Quantitation of urinary protein excretion in 78 cases of PSAGN between 1979–1988 revealed nephrotic range proteinuria (defined as >40 mg/m^2/h) in 27 (34.6%) and normal urinary protein excretion (defined as <5 mg/m^2/h) in 20 (25.6%) [17]. Hypoalbuminemia is quite common: in one large study of PSAGN serum albumin was lower than 3.0 g/dl in 46% and less than 2.5 g/dl in 15% [145].

Decreased blood hemoglobin is common in PSAGN. One large series showed that only 10% of 155 patients had a hemoglobin level of ±12 g/dl, and over 50% were below 10 g/dl [145]. In extreme cases, severe anemia may occur [145]. While traditionally the drop in hemoglobin has been attributed via clinical observation solely to volume overload [146], there could be other factors at work. In two instances, autoimmune hemolytic anemia was documented in the early stages of PSAGN [147, 148].

The serological markers most commonly used by the clinician are anti-streptolysin O (ASO) titer and depression of serum C3 level. Increased antibody levels to anti-streptococcal antigens [ASO, anti-hyaluronidase (A-H) and anti-DNAase] are documented less often than low levels of C3. ASO titers are higher in pharyngitis-associated PSAGN than pyoderma-associated PSAGN [9, 128, 149, 150]. In an early study, the sensitivity of an elevated ASO titer was extremely high (97%), but the specificity was only 80%, presumably due to the fact that up to 20% of unaffected controls show evidence of streptococcal exposure with a significantly elevated titer [151]. Early descriptions of the time course for increasing ASO and A-H titers show that in a group of patients with typical (previously known as type A) acute glomerulonephritis, ASO was increased above normal in 72% [135]. In Roy's series of biopsy-proven cases from Memphis, 60% had ASO titer elevation as defined by Todd units >333 [40]. Cases following pyoderma are more likely to demonstrate elevated anti-DNAase B titer than an elevated ASO titer [118, 128].

In children whose initial ASO titer is normal, subsequent measurements may be elevated, thus supporting the suspected diagnosis. This is demonstrated by Longcope [9] and Dodge et al. [128], who found that the ASO titer continued to increase over the four weeks after presentation in some cases [9] and the mean titer peaked at three weeks [128]. In addition, performance of more than one streptococcal antibody test increased the number of individuals with "positive" titers from 80 to 95% [151]. Travis et al. tested for ASO, AH, and anti-DNAse in 60 patients and often found ASO to be negative while anti-DNAse and/or AH were positive [136].

The acute reduction of serum C3 concentration in PSAGN with the typical return to normal levels within six weeks of onset is of foremost diagnostic importance when renal biopsy is not performed [10, 114, 118, 152]. Depression of serum C3 level in PSAGN has been shown to precede the onset of hematuria [118, 120].

Hypertension usually resolves within 1–2 weeks, and rarely requires long-term treatment [135, 136]. Renal biopsy is indicated in cases in which the clinical diagnosis is not clear in order to confirm the diagnosis or in the presence of significant renal insufficiency to rule out crescentic glomerulonephritis.

The recovery phase occurs after resolution of fluid overload with diuresis—either spontaneous and/or pharmacologically induced—along with normalization of blood pressure and resolution of proteinuria and gross hematuria. Most case series note that the proteinuria disappears much earlier than the microscopic hematuria [40, 153] with the exception of Travis et al., who noted the opposite [136]. During this phase, the C3 level returns to normal in the majority of affected children. PSAGN has occurred in patients previously diagnosed (by biopsy) with IgA nephropathy [154–156]. Because IgA nephropathy is the most commonly occurring type of chronic glomerulonephritis and often goes undiagnosed, the association with PSAGN is most likely the chance occurrence of the two conditions in the same individual.

Second attacks of PSAGN have been reported but are rare [145, 157–160]. In the earlier reports, the PSAGN was pyoderma-associated for both attacks in most instances [145, 158, 159], while two case reports since 2000 were both pharyngitis-associated PSAGN [157, 160]. A recent case series reported two recurrences of PSAGN, but didn't specify the route of infection acquisition [161].

Renal biopsy findings

A renal biopsy is generally not indicated for diagnosis of PSAGN, but is usually performed when atypical clinical features occur. Such features that could lead to a biopsy are normocomplementemia [122], failure to document a recent streptococcal infection by a rise in ASO or streptozyme titer, and renal insufficiency, particularly when the GFR remains less than 30 ml/min/1.73 m^2 for more than one week [124].

In the past, some pediatric nephrologists recommended a renal biopsy for patients with presumed PSAGN whose C3 concentration remained depressed for more than eight weeks after clinical onset, mainly to exclude the diagnosis of membranoproliferative glomerulonephritis (MPGN). One study documented failure of C3 to become normal by eight weeks in five of 20 patients despite typical improvement in clinical features, including resolution of proteinuria and normal kidney function [162]. Renal biopsies that were performed in three of these patients showed typical findings of PSAGN. Thus, persistent hypocomplementemia with

resolving features of acute glomerulonephritis does not exclude the diagnosis of PSAGN, and the authors and others felt that the renal biopsy could be deferred. Subsequent studies have backed these findings [163, 164].

When a biopsy is performed, the typical light microscopy findings are diffuse hypercellularity of endothelial and mesangial cells and infiltration of the glomerular tuft with polymorphonuclear cells [165]. This endocapillary hypercellularity may lead to a reduction in the capillary lumen space that appears to associate with the initial severity of renal insufficiency [126]. Using a cell-proliferation marker, Ki-67, Chung and Kim [166] provided evidence that most of this hypercellularity is due to infiltrating inflammatory cells. In most cases of PSAGN there is little or no evidence of tubular, interstitial or vascular injury [47].

In more severe cases, epithelial crescents may form during the course of PSAGN. Rarely, patients with PSAGN will have crescentic involvement in over 50% of glomeruli, leading to the clinical picture of rapidly progressive glomerulonephritis [36, 124, 125].

The immunofluorescence pattern typically seen in biopsies performed during the acute phase of PSAGN shows discrete granular deposits of IgG and C3 in a capillary loop and mesangial distribution [32, 167]. However, about 30% of PSAGN biopsies show C3 and the absence of IgG even when the biopsies are performed early in the clinical course [32, 127, 168–170]. Sorger et al. [171] described the immunofluorescence patterns in PSAGN using the term "starry sky" to represent a typical pattern and the term "garland pattern" to indicate the presence of heavy and sometimes confluent capillary loop deposits with the total absence of mesangial deposits. This garland pattern was associated with more numerous and larger subepithelial "humps" and higher degrees of proteinuria. However, this association with heavy proteinuria has not been confirmed by any case series in the two decades following the initial report.

The hallmark pathologic finding on electron microscopy is the subepithelial hump, which was first noted by Kimmelstiel and associates in 1962 [172]. However, electron dense deposits may also occur in subendothelial and intramembranous locations [168] and the presence of such deposits should not lead one to dismiss the diagnosis of PSAGN, since they were found in PSAGN patients as early as 1966 [168].

Lewy et al. [126] observed an association between the degree of polymorphonucleocyte infiltration of the glomerular tuft and the number of subepithelial humps; they also noted that higher degrees of endocapillary proliferation were associated with lower complement levels. West and McAdams [173] demonstrated a significant association between absence of paramesangial (the portion of the capillary loop in continuity with the mesangium) deposits and low serum albumin levels in children with PSAGN. These patients differed from those with paramesangial deposits in that they were more edematous, were less likely to have gross hematuria and tended to be normocomplementemic.

Treatment

Treatment remains largely supportive and usually addresses the most urgent problem of hypertension. No modern studies are available to guide the first choice of anti-hypertensive agent. However, salt restriction and loop diuretics are the first-line treatment for fluid overload and hypertension; thereafter, hypertensive therapy is often transitioned to vasodilators. Although successful treatment with ACE inhibition has been reported [106], ACE inhibitors are generally not used during the acute phase due to the potential for decrease in GFR and hyperkalemia. In those individuals with hypertensive emergencies, continuous infusion of anti-hypertensive medication is the preferred initial approach.

One difficult question that has yet to be definitively answered is whether prompt treatment of group A streptococcal pharyngitis or pyoderma will prevent or attenuate the subsequent development of PSAGN. In 1970, Dillon stated, "In spite of vigorous efforts to do so, we have not been able to prove unequivocally that we can prevent cases of AGN by prompt treatment of streptococcal skin infection" [34]. While more recent studies have not disputed this assertion, treating communities in which PSAGN is epidemic with benzathine penicillin G may reduce carriage of nephritogenic strains and thus lower the incidence of PSAGN [174].

Immunosuppression has not been proven to be effective, although it is often used in the clinical setting of rapidly progressive glomerulonephritis or when crescents are seen on biopsy. However, there is considerable debate as to whether immunosuppressive treatment is effective in this setting. Roy et al. [124], in a study of 10 patients, reported no difference in outcome between patients receiving quintuple therapy (prednisone, azathioprine, cyclophosphamide, dipyridamole, and anticoagulation) and those receiving supportive care. More recently, Wong et al. [125] reported the clinical course of 27 patients biopsied for difficult clinical course, 11 of whom had >50% crescents on biopsy, and found no benefit of immunosuppression.

Long-term outcome

A major problem with the attempts of older studies to make prognostic associations for PSAGN is that the statistical methodologies employed were non-existent or inadequate by today's standards. Thus, many of the stated conclusions

reflect the bias of albeit excellent clinical observers. Since the current standard of clinical practice is to forego renal biopsy in typical cases of suspected PSAGN [134], it is important to note that 10–15% of clinical diagnoses of PSAGN were not supported after a renal biopsy was performed [128]. In a series of 47 patients, those erroneously diagnosed with PSAGN had a significantly worse prognosis than patients who had PSAGN. Clinical and histologic evidence of non-healing was observed in 50% of patients whose biopsies revealed exacerbation of other underlying renal disease, as opposed to only 5% of patients with PSAGN [128].

Published studies on the prognosis of PSAGN in children are comprised only of cases that are clinically apparent [134]. Sagel et al. [175] found that all biopsies of children with transient hypocomplementemia and microscopic hematuria following streptococcal infection demonstrated histologic evidence of glomerulonephritis. Published estimates of the ratio of subclinical to clinical cases of PSAGN are from 1.5:1 to 19:1 [31, 134, 175–177].

Reports on clinicopathologic correlations in PSAGN have sometimes described surprising disparities. A report published in 1969 found normalization of urinalysis in the presence of progressive post-streptococcal glomerular lesions, and, conversely, histopathologic healing with persistent urinary abnormalities [178]. In that study, the duration and degree of hypocomplementemia correlation did not associate with subsequent histologic healing.

Certain histologic findings may predict a poor prognosis. In a series of 23 patients with PSAGN, the single patient who died secondary to renal disease had more extensive subepithelial hump deposition than the other cases [136]. The garland pattern of immunofluorescence has been associated with heavy proteinuria and poor outcome [171]. While higher degrees of endocapillary hypercellularity appear to associate with the initial severity of renal insufficiency, this finding has not been shown to associate with progression to end stage renal disease (ESRD) [126].

Extracapillary crescent formation is the most ominous histologic finding in PSAGN. The patient who died in the case series of Travis et al. [136] had crescentic disease. In Lewy's case series of 46 patients with PSAGN published in 1971 [126], three of the four patients who died had crescents with glomerular sclerosis on biopsy, and well-developed epithelial crescents were present in three of four patients with a persistent course. In PSAGN patients studied between 1962 and 1970, two died from rapidly progressive glomerulonephritis during the acute phase of illness [179]. In a series of 36 children who were biopsied, the two who had many large crescents were uremic at onset and never remitted [133]. A recent study by Wong et al. [125] examined 27 renal biopsies diagnostic of PSAGN in children over a 12-year period. They showed that progression to ESRD was more prevalent with crescentic PSAGN, occurring in two of 11 patients as opposed to none of the 16 children with PSAGN without crescents. Indications for biopsy in this study were anuric renal failure, acute severe glomerulonephritis, or unexpected delay in recovery from acute glomerulonephritis. These investigators estimated that only 2% of cases of PSAGN were severe enough to warrant biopsy, supporting earlier claims of good prognosis in children with PSAGN.

It is important to note that post-streptococcal crescentic glomerulonephritis may carry a better prognosis than crescent formation of other etiology. The Southwest Pediatric Nephrology Study Group found that of 50 children with crescent formation, five with PSAGN had normal GFR, compared to progression to ESRD for 23 of 42 patients with crescent formation of other etiology [180]. However, this concept was challenged by experience from northern India that suggested that the prognosis for post-streptococcal crescentic glomerulonephritis is equally as poor as that for other types of crescentic glomerulonephritis [181].

Studies on the outcome of sporadic PSAGN are summarized in Table 1. On the surface, with the notable exception of Baldwin's group in New York City [182], virtually all studies report good prognosis for the vast majority of children with PSAGN. The Baldwin group studies include a 1979 report that asserted that irreversible renal disease, as evidenced by hypertension, proteinuria, decreased renal function or glomerulosclerosis, occurred in at least 40% of children following sporadic PSAGN [133]. They even argued that their data were similar to those of earlier reports [126, 128, 136] and took issue with the criteria for favorable outcome in those reports [133]. Lewy et al. [126] reported normal creatinine clearance of >77 ml/min/1.73 m^2 in 25 of 26 patients with over three years follow-up, while the Baldwin group reported normal creatinine clearances of >105 ml/min/1.73 m^2 in 20 of 26 children and considered proteinuria of 200 to 500 mg per 24 h to represent irreversible glomerular damage [133]. They also chose to interpret the presence of sclerosis as chronicity rather than healing, as Travis et al. [136] had done.

The poor prognosis implied by the Baldwin group may also be due to insufficient length of time for follow-up, for although they followed some patients for up to 17 years, 46 out of 83 patients were followed for only two years. Selection bias related to the patients with recovery being lost to follow-up early surely applies to their work [182]. Roy et al. showed that recovery from PSAGN can be protracted. In their study, histologic healing occurred in 20% at two years, in 94% at 10 years, and in 97% at 12 years after disease onset [40].

Roy et al. [40] also argued that light microscopy more accurately determines healing than clinical indices of blood

Table 1 Outcome of sporadic cases of pediatric post-streptococcal acute glomerulonephritis

Study	No. of patients	Antecedent pyoderma	Antecedent URI/pharyngitis	Patient ages	Sex ratio M:F	Time of follow-up	Histologic healing	No. of renal-related deaths	Proteinuria at follow-up	Hypertension at follow-up	Decrease in GFR at follow-up	Hematuria at follow-up
Lewy et al. [126]	46	5/46	35/46 (6/46 with other)	≤7 (*n*=6) 8–14 (*n*=20) 15–21 (*n*=9) ≤22 (*n*=5) unknown (*n*=6)	29:17	6 months–9 years	34/46	4/46	3/21 (2–4 years) 2/13 (4–6 years) 2/5 (6–8 years) 1/1 (8–10 years)[e]	1/14 (2–4 years) 3/14 (4–6 years) 1/3 (6–8 years) 1/2 (8–10 years)[b]	2/19 (2–4 years) 3/14 (4–6 years) 2/6 (6–8 years) 0/1 (8–10 years)[g]	4/20 (2–4 years) 1/15 (4–6 years) 1/4 (6–8 years) 0/1 (8–10 years)[f]
Travis et al. [136]	60	25/60	26/60	2.5–24.5 years	39:21	3–10 years	49/54	1/60	31/54 (>1 year) 17/52 (≥2 years)	2/40 (2–4 years)[h] 1/8 (4–6 years)[b,i]	6/22 (2–8 years)[d]	5/53 (6–12 months) None after 1 year
Roy et al. [40]	35	24/35	11/35	3.6–12.8 years	16:19	4–12 years	34/35	0/35	2/21 (2–4 years) 5/32 (4–6 years) 1/22 (6–12 years)[e]	0/22 (2–4 years) 0/34 (4–6 years) 1/25 (6–12 years)[b]	1/20 (2–4 years) 2/30 (4–6 years) 4/24 (6–12 years)[g]	6/21 (2–4 years) 9/21 (4–6 years) 9/22 (6–12 years)[f]
Sanjad et al. [192]	153	100/153	45/153	14 months–13 years	1.6:1	6 months–11 years		2/153	0/103	0/103	0/48	0/103
Schacht et al. [133]	83	6%	79% (4% both; 11% unknown)	2–16 years	43:40	≤17 years	10/12 at 2 years follow-up	0/54	24% (≥2 years) 16% (≥5 years) 18% (≥10 years)[a]	16% (≥2 years) 25% (≥5 years) 33% (≥10 years)[b]	16% (≥2 years) 26% (≥5 years) 35% (≥10 years)[c]	–
Clark et al. [179]	36	0/36	34/36 URI 4/36 tonsillitis 2/36 OM	1.9–14.3 years	21:15	5–12 years (*n*=32) 15–22 years (*n*=30)		2/36	3/30–34 (one biopsied type II MPGN)	1/30–34	0/33 (SCr <1.5 in males, <1.25 in females)	3/30–34 (≥10 RBC/μl)
Popovic-Rolovic et al. [193]	104	88.5%	11.5%	2–16 years	61.9:38.1	5–9 years (*n*=40) 10–17 years (*n*=88)		0/104	2/40 (5–9 years) 2/88 (10–17 years)	2/40 (5–9 years) 3/88 (10–17 years)	0/104	0/40 (5–9 years) 2/88 (10–17 years)
Herthelius and Berg [194]	33	?	?	2–16 years	25:8	2–11 months		0/22			2/22 (=92 ml/min/1.73 m^2)	
Kasahara et al. [195]	138	?none (either +ASO or +throat cx or latex agglut.)	?all	3–14 years	84:54	≤4 years		0/138	2.2% (1–2 years) 0.7% (2–3 years) 0% (3 years)	0/138		5.8% (2–3 years) 2.9% (3–4 years) 0% (4 years)

URI upper respiratory infection, *OM* otitis media, *cx* culture, *latex agglut* latex agglutination

[a] Proteinuria defined as ≥200–500 mg/24 h

[b] Hypertension defined as >140/90 mmHg

[c] GFR of 105 ml/min/1.73 m^2 defined as lower limit of normal

[d] GFR of <60 ml/min/m^2 (<104 ml/min/1.73 m^2) defined as lower limit of normal

[e] Proteinuria defined as >50 mg/12 h

[f] Hematuria defined as Addis count of $>1\times10^6$ red blood cell (RBC)

[g] Creatinine clearance of 90 ml/min/1.73 m^2 defined as lower limit of normal

[h] Familial hypertension, 2nd attack PSAGN

[i] Familial hypertension

pressure elevation, proteinuria, and hematuria. Although six of 35 patients in their study were labeled "non-healed" by these clinical criteria at 49 to 135 months from onset of PSAGN, all had healed histologically, as indicated by light microscopy.

It is generally accepted that epidemic cases of PSAGN carry a better prognosis than sporadic cases, with some asserting that healing occurs in all cases [136]. This may be secondary to sporadic cases often presenting in a hospital setting, while the increased index of suspicion inherent in epidemics leads to the presentation of a greater number of mild cases [133]. Other factors may be the portal of entry and the strain of streptococci. Drachman et al. [183], citing studies originating from Trinidad [184, 185], Maracaibo [37], and New York (Baldwin group) [182, 186, 187], as well as their own [188, 189], noted that the prognosis was more favorable in pyoderma-associated than pharyngitis-associated PSAGN, and that glomerulonephritis following infection with the M55 strain had a favorable prognosis. However, Roy et al. [40] showed that initial histologic changes were more severe in the pyoderma-associated than pharyngitis-associated PSAGN, but that there was no difference in subsequent healing rates.

The future of PSAGN

The availability of a vaccine for group A streptococci is highly desirable and anticipated, both in terms of preventing invasive disease and nonsuppurative complications [190]. Presumably, a vaccine that eradicated all group A streptococci would eliminate PSAGN. There are two approaches for the development of a vaccine against group A streptococci. The most difficult and costly approach target a protein common to all group A streptococci. Alternatively, since antibodies to M proteins are generally protective against the strain from which the M protein comes, a multivalent vaccine could be designed. The current thrust of group A streptococcal vaccine research has been to target M proteins [191]. Because invasive disease and acute rheumatic fever are the most important preventable complications of group A streptococcal infection in the industrialized world, the vaccine currently in development is a 26-valent vaccine that targets the variable region of the M proteins of the most common rheumatogenic streptococci [191]. This vaccine appears to be well tolerated in adults and immune sera have been successful in preventing invasive disease in rabbits. Unfortunately, no M proteins from nephritogenic streptococci were included in the vaccine. In addition, because the most common M protein types differ geographically, this vaccine may be of limited efficacy in the developing world, which would presumably continue to bear the majority of the world burden of PSAGN and ARF.

Thus, prevention of PSAGN in the developing world continues to be based upon public health measures such as improved hygiene and better housing conditions. The elimination of epidemic pyoderma, as occurred in the southern United States over the past 25 years, offers the best hope for control.

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