

Extrarenal immune-mediated disorders linked with acute poststreptococcal glomerulonephritis: a systematic review

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Abbreviations: acute poststreptococcal glomerulonephritis = APSGN

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Abstract

BACKGROUND: Streptococcus A infections have been associated with immune-mediated sequelae including acute glomerulonephritis, acute rheumatic fever, thrombocytopenia, hemolytic anemia, Henoch-Schönlein purpura, arthritis, uveitis, guttate psoriasis and erythema nodosum. Available reviews do not report the occurrence of acute poststreptococcal glomerulonephritis in association with one of the mentioned conditions.

METHODS: We performed a systematic review of the literature on extrarenal immune-mediated disorders associated with acute poststreptococcal glomerulonephritis. The principles recommended by the Economic and Social Research Council guidance on the conduct of narrative synthesis and on the Preferred Reporting Items for Meta-Analyses and Systematic Reviews were used.

RESULTS: We identified 41 original articles, published after 1965, which reported on 52 patients (34 males and 18 females aged from 1.7 to 57 years, median 9) affected by acute poststreptococcal glomerulonephritis associated with a further post-streptococcal disease: 29 cases with rheumatic fever (17 males and 12 females aged 3.0 to 57, median 17 years), 16 with hematologic diseases such as thrombocytopenia or hemolytic anemia (13 males and 3 females aged 1.8 to 13, median 6.0 years) and seven with Henoch-Schönlein syndrome, reactive arthritis or uveitis (4 males and 3 females aged 1.7 to 14, median 7.0 years). Patients affected by acute poststreptococcal glomerulonephritis associated with acute rheumatic fever were on the average older ($P < 0.05$) than patients with acute poststreptococcal glomerulonephritis associated with thrombocytopenia, hemolytic anemia, Henoch-Schönlein syndrome, reactive arthritis or uveitis. Five large case series describing 2058 patients affected by acute poststreptococcal glomerulonephritis did not mention its occurrence in association with further immune-mediated disorders.

CONCLUSION: This review points out that acute poststreptococcal glomerulonephritis can be associated, albeit rarely, with rheumatic fever, thrombocytopenia, hemolytic anemia, Henoch-Schönlein syndrome, reactive arthritis or uveitis.

Keywords: acute poststreptococcal glomerulonephritis • acute rheumatic fever • hemolytic anemia • Henoch-Schönlein like purpura • reactive arthritis • thrombocytopenia • uveitis

INTRODUCTION

Throat or skin infections caused by A Streptococcus are occasionally followed by an acute glomerulonephritic syndrome termed acute poststreptococcal glomerulonephritis (APSGN). Of the estimated 500,000 new annual cases worldwide, the vast majority occurs in countries with poor socioeconomic status, where skin infections are still very frequent. The risk of APSGN is age-dependent, being high in subjects older than 60 years and highest in children aged between four and 12 years. APSGN is characterized histologically by endocapillary hypercellularity with frequent neutrophils and immunohistologically by distinctive deposits of immunoglobulin G and especially complement C3 distributed in a diffuse granular pattern within the mesangium and glomerular capillary walls. Most patients with APSGN, particularly children, have an excellent outcome, even those who present with acute kidney injury and crescents on renal biopsy [1, 2].

In addition to APSGN, Streptococcus A infections may be followed by further immune-mediated disorders [1, 2] including acute rheumatic fever and, less frequently, thrombocytopenia, hemolytic anemia, Henoch-Schönlein purpura, arthritis, uveitis, guttate psoriasis and erythema nodosum.

It has been assumed that APSGN and rheumatic fever, the most recognized immune-mediated complications of Streptococcus A infections, do not affect the same subject [1, 2]. However, the coexistence of these conditions has been a matter of debate since approximately 1840, when the term "rheumatic nephritis" [3] was coined in France by Pierre Rayer (1793-1867). Hence, we decided to perform a systematic review of the literature on extrarenal immune-mediated disorders associated with APSGN.

METHODS

Literature search strategy

Between March and April 2019, we searched the Medical Subject Headings terms (poststreptococcal glomerulonephritis OR postinfectious glomerulonephritis) AND (erythema nodosum OR guttate psoriasis OR psoriasis guttata OR h[a]emolytic an[a]emia OR PANDAS OR Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal

Infections OR rheumatic fever OR thrombocytopenia OR uveitis OR vasculitis) in the United States National Library of Medicine and in Excerpta Medica Database. The bibliography of each identified report and personal files were also screened. We used the principles recommended by the Economic and Social Research Council guidance on the conduct of narrative synthesis and on the Preferred Reporting Items for Meta-Analyses and Systematic Reviews [4]. The literature search was performed independently by two investigators. If results were incongruent, conflicts were resolved by reaching a consensus. To estimate the prevalence of extrarenal immune-mediated disorders in patients with APSGN, we also searched case series including each at least 100 unselected patients with this condition.

Selection criteria

We selected original articles reporting cases of APSGN associated with one of the aforementioned immune-mediated disorders. Reports published after 1965 in Spanish, Portuguese, Italian, German, French, English or Dutch were eligible.

The diagnosis of APSGN, rheumatic fever, poststreptococcal reactive arthritis, thrombocytopenia, hemolytic anemia, Henoch-Schönlein and PANDAS made in the original reports was reviewed using predefined criteria [1, 2].

The diagnosis of APSGN was retained in patients with acute onset of hematuria and proteinuria associated with decreased circulating complement C3 levels early in the course of the disease that returned to normal within 16 weeks, increasing titers of antibodies to extracellular streptococcal products or characteristic findings on a renal biopsy [1, 2]. Acute kidney injury was classified as stage I (increase in circulating creatinine to 1.5-1.9 times baseline, or increase by ≥ 27 $\mu\text{mol/l}$ above the upper limit of normal for age), stage II (increase in creatinine to 2.0-2.9 times baseline) and stage III (increase in creatinine to ≥ 3.0 times baseline, increase in creatinine by ≥ 354 $\mu\text{mol/l}$ or initiation of dialysis).

For children < 13 years of age, the diagnosis of clinically relevant arterial hypertension was retained if systolic or diastolic blood was $\geq 99^{\text{th}}$ percentile + 5 mm Hg [5]. For older subjects, the diagnosis was retained if blood pressure was $\geq 160/100$ mmHg [5].

The 2015 Jones criteria, which include, in addition to evidence of a

prior streptococcal infection, five major manifestations (arthritis, carditis, Sydenham chorea, erythema marginatum and subcutaneous nodules) and four minor manifestations (fever, arthralgia, elevated erythrocyte sedimentation rate and C-reactive protein, and prolonged electrocardiographic PR interval) were used for the diagnosis of rheumatic fever [6]. The diagnosis was made in cases with one major plus two minor manifestations or two major manifestations [6]. Patients with mitral valve regurgitation due to acute hypertensive cardiomyopathy were not included. The diagnosis of poststreptococcal reactive arthritis was made in patients with arthritis but insufficient Jones criteria [2].

The diagnosis of thrombocytopenia was made if platelet count was $\leq 150 \times 10^9/l$, that of hemolytic anemia if anemia was associated with at least two of the following: jaundice, increased reticulocyte count, increased circulating lactate dehydrogenase level, decreased haptoglobin or positive direct antiglobulin test [7]. The diagnosis of Henoch-Schönlein purpura was established using the European League Against Rheumatism consensus criteria [8], that of guttate psoriasis in subjects with rapid development of multiple small papules of psoriasis, mainly on the trunk, after a streptococcal infection [9] and that of erythema nodosum in subjects with acute onset of tender erythematous nodules on the bilateral shins temporally related to a streptococcal infection [10].

Data abstraction - analysis

From each published case, data were sorted using a predefined form. Attempts were also made to contact authors of original articles to confirm the accuracy of reported data and provide additional missing data. Results are given either as median and interquartile range (which includes half of the data points) or frequency, as appropriate. The kappa index was used to assess the agreement between investigators, the Kruskal-Wallis test (with the Dunn post-test) to compare continuous variables and the Fisher exact test to compare dichotomous variables. Significance was assigned at $P < 0.05$.

RESULTS

Search results

The initial search returned 498 articles. After the removal of 123 duplicate articles, 375 abstracts were screened. Upon completion of dual

screening, the full text of 75 articles was assessed and 29 were excluded. The chance-adjusted agreement between the two investigators on the application of the inclusion and exclusion criteria was 0.85. Ultimately, we retained 41 reports (Figure 1) describing patients with both APSGN and a further post-streptococcal disease [11-51]. We also retained five large case series describing patients affected by APSGN [52-56]. The 46 articles had been published between 1969 and 2018 in English (N=45) and French (N=1). They had been reported from the following continents: 20 from America (United States of America, N=14; Canada, N=3; Chile, N=1; Mexico, N=1; Venezuela N=1), 19 from Asia (Turkey, N=4; Japan, N=4; Saudi Arabia, N=3; Israel, N=2; China, N=2; India, N=1; Jordan, N=1; South Korea, N=1; Taiwan, N=1) and seven from Europe (Armenia, N=1; France, N=1; Italy, N=1; Lithuania, N=1; Macedonia, N=1; Slovenia, N=1; Switzerland, N=1).

Clinical data

General information

Forty-one articles reported on 52 patients (34 male and 18 female subjects aged from 1.7 to 57 years, median 9 years) affected by APSGN associated with a further post-streptococcal disease: 29 cases with acute rheumatic fever (17 males and 12 females aged 3.0 to 57, median 17 years), 16 cases with hematologic disease such as thrombocytopenia and hemolytic anemia (13 males and 3 females aged 1.8 to 13, median 6.0 years) and 7 cases with Henoch-Schönlein syndrome, reactive arthritis or uveitis (4 males and 3 females aged 1.7 to 14, median 7.0 years). Patients affected by APSGN associated with acute rheumatic fever were on the average older ($P < 0.05$) than patients with APSGN associated with thrombocytopenia, hemolytic anemia, Henoch-Schönlein syndrome, reactive arthritis or uveitis. The diagnosis of glomerulonephritis was confirmed by means of a biopsy in 32 (62%) out of the 52 cases [11-51].

The literature search did not detect any well documented case of glomerulonephritis associated with guttate psoriasis or erythema nodosum. Finally, we did not identify any APSGN case affected by more than one extrarenal disorder.

In 44 (85%) of the 52 cases, the renal disease and the non-renal diseases presented almost concomitantly. The renal disease presented with relevant arterial hypertension in 31 (60%) cases. Acute kidney injury was stage I in 29 (56%), stage II in 10 (19%) and stage III in 12

(23%) cases (this information was not available in one case). The severity of kidney injury was similar in patients affected by APSGN associated with acute rheumatic fever, hematological diseases and in those with further immune-mediated complications. The renal disease fully recovered in 44 cases (this information was not available for the remaining cases).

Rheumatic fever

The characteristics of the 29 cases of APSGN associated with rheumatic fever [11-33] are depicted in Table 1. Four patients had a history of rheumatic fever in the past. More than three-quarter of the patients presented with both a cardiac (mostly an isolated or a combined mitral regurgitation) and an articular involvement. A cutaneous or a central nervous system involvement was less frequently observed. Interestingly, a cutaneous Henoch-Schönlein like purpura was also observed in one case [33]. A persistent valvular disease was noticed in 10 (34%) cases.

Thrombocytopenia - hemolytic anemia

A hematological disease (Table 2) was observed in 13 male and three female subjects aged 18 years or less [34-45]. Isolated thrombocytopenia was observed in eight patients, isolated hemolytic anemia in six patients and both hemolytic anemia and thrombocytopenia in two patients.

Further associations

In the reminder seven cases [46-51], glomerulonephritis was associated with a reactive arthritis (N=1), a uveitis (N=1) or a Henoch-Schönlein syndrome (N=5), as given in Table 3. The diagnosis of APSGN associated with Henoch-Schönlein syndrome was made on the basis of characteristic APSGN renal biopsy findings in all five cases [46-49]. In two cases, a skin biopsy revealed a small-vessel leukocytoclastic vasculitis. Immunofluorescent studies disclosed deposits of immunoglobulin A in one of the two skin specimens [46].

Prevalence of extrarenal immune-mediated disorders

We found five large case series describing a total of 2058 patients affected by APSGN [52-56]. These articles did not mention the occurrence of APSGN associated with further immune-mediated disorders.

DISCUSSION

This careful review of the literature documents 29 patients concurrently affected by APSGN and rheumatic fever. We also found 23 cases of APSGN associated with thrombocytopenia, hemolytic anemia, Henoch-Schönlein syndrome, reactive arthritis or uveitis. Erythema nodosum and guttate psoriasis have been occasionally associated with an acute glomerulonephritic syndrome, which was regrettably poorly documented [57, 58].

APSGN mainly affects children from four to 12 years (with a peak age of 7-9 years) and is almost twice more frequent in males than in females [1, 2]. Similar figures (with a male to female ratio of 2.8) were noted in our 23 cases of APSGN associated with thrombocytopenia, hemolytic anemia, Henoch-Schönlein syndrome, reactive arthritis or uveitis. While the association of APSGN with rheumatic fever was still more prevalent in males, the male to female ratio was only 1.4 and the peak age was 17 years, possibly reflecting that rheumatic fever is slightly more common in females than males and occurs in slightly older subjects, i.e. from five to 20 years of age [6].

The mechanisms that lead to the development of an immune-mediated disorder after a streptococcal infection remain incompletely understood [1, 2, 59]. It is generally assumed that APSGN develops after an infection caused by a "nephritogenic" strain and rheumatic fever after an infection caused by a "rheumatogenic" strain [1, 2]. While exotoxin B and nephritis-associated plasmin receptor are considered the streptococcal antigens associated with APSGN [1, 2], it has been postulated that particular M serotypes of group A streptococci have rheumatogenic potential [1, 2]. Such serotypes are heavily encapsulated and form large, mucoid colonies rich in M-protein. These characteristics might enhance the ability of the bacteria to adhere to tissues and to resist phagocytosis in the human host [1, 2]. Yet, data supporting the hypothesis of "selective streptococcal rheumatogenicity" appear anecdotal. It is now widely accepted that a permissive genetic background is necessary for the development of an acute poststreptococcal autoimmune disease such as APSGN, rheumatic fever or Henoch-Schönlein syndrome [59-61].

Patients with a chronic autoimmune disease are at increased risk of developing further autoimmune diseases [59]. However, attempts to identify the "genetic smoking guns" explaining the tendency of chronic

autoimmune diseases to cluster are so far inconclusive [62]. The results of the present analysis support the assumption that also acute autoimmune diseases such as APSGN and acute rheumatic can occur in the same subject close in time, often triggered by an infectious agent.

APSGN (like poststreptococcal reactive arthritis) is deemed to occur early and rheumatic fever rather late after a noninvasive streptococcal infection. Nonetheless, in this study, the renal and the non-renal disease presented concomitantly in the vast majority of the cases. The literature, however, suggests the existence of a large overlap: the latent period between infection and the immune-mediated complication ranges from one to three weeks for APSGN and from one to five weeks for rheumatic fever [1, 2]. A further possible explanation is that arterial hypertension and peripheral edema, which are typical in glomerulonephritis, are recognized and referred later than joint swelling and rash, which are typical in rheumatic fever.

There are limitations and strengths that should be noted when reading this review. The major limitation relates to the fact that it integrates data from a small number of cases reported since 1969 that were sometimes poorly documented. Furthermore, available data do not allow to exactly estimate the prevalence of the reported associated conditions. Finally, no attempt was made to investigate the uniqueness of isolated group A streptococci or the genetic background of affected patients. The most important strength of the study relates to the comprehensive and exhaustive literature search, aiming at surveying the entire literature on this topic (as documented by the fact that two reports were found neither in the United States National Library of Medicine nor in Excerpta Medica Database but exclusively in our files).

The term Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococci, usually termed PANDAS, refers to a group of neuropsychiatric disorders that are proposed to have an autoimmune basis and to be related to infections caused by A Streptococcus. Since the relationship between A Streptococcus and PANDAS remains elusive, the association of APSGN and PANDAS was not addressed in this review of the literature [63].

In clinical practice, the diagnosis of acute poststreptococcal glomerulonephritis associated with an extrarenal immune-mediated disorder may be tricky and a high level of suspicion must be kept. For

example, an acute glomerulonephritic syndrome associated with palpable purpuric skin lesions is usually caused by Henoch-Schönlein syndrome [8], an acute glomerulonephritic syndrome associated with hemolytic anemia or thrombocytopenia is mostly due to hemolytic uremic syndrome [64], while a glomerulonephritis complicated by volume overload and severe arterial hypertension may result, per se, in mitral valve regurgitation. Finally, the presenting manifestations of systemic lupus erythematosus are diverse, and any organ system may be involved [65].

In conclusion, this review supports the hypothesis suggested about 180 years ago by Pierre Rayer [3]. On average, one case a year of glomerulonephritis associated with rheumatic fever, thrombocytopenia, hemolytic anemia, Henoch-Schönlein like syndrome, reactive arthritis or uveitis has been reported since 1969, pointing out that acute APSGN can be associated, albeit rarely, with a variety of extrarenal immune-mediated manifestations.

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FIGURE 1 - LEGEND

Extrarenal immune-mediated disorders in patients affected with poststreptococcal glomerulonephritis. Flowchart of the literature search process [11-51]. Two articles [42, 44] were found uniquely in our personal files.

Table 1. Characteristics of 29 patients 3.0 to 57 years of age presenting with both acute post-streptococcal glomerulonephritis and acute rheumatic fever. Results are given either as frequency (and percentage) or as median and interquartile range (which includes half of the data). Due to rounding effect, percentage total may sometimes slightly differ from 100%.

N	29
Males : Females, N (%)	17 (59) : 12 (41)
Age, years	10 [7.0-15]
≤18 years, N (%)	24 (83)
>18 years, N (%)	5 (17)
Preceding infection	
Streptococcal pharangitis, N (%)	23 (79)
Unknown, N (%)	6 (21)
Kidney disease	
Relevant arterial hypertension, N (%)	14 (48)
Acute kidney injury	
Stage I, N (%)	17 (59)
Stage II, N (%)	7 (24)
Stage III, N (%)	5 (17)
Rheumatic disease	
Past history of rheumatic fever, N (%)	4 (14)
Valvular heart disease, N (%)	24 (83)
Isolated mitral regurgitation, N (%)	13 (54)
Mitral and aortic regurgitation, N (%)	6 (25)
Mitral, aortic and tricuspid regurgitation, N (%)	2 (8)
Isolated aortic regurgitation, N (%)	2 (8)
Isolated tricuspid regurgitation, N (%)	1 (4)
Articular involvement, N (%)	22 (76)
Cutaneous involvement, N (%)	5 (17)
Sydenham chorea, N (%)	1 (3)
Latency kidney disease - rheumatic fever	
Concomitant kidney and rheumatic disease [◇] , N (%)	23 (80)
Kidney disease precedes rheumatic fever by 1-3 weeks, N (%)	4 (14)
Rheumatic fever precedes kidney disease by 1-3 weeks, N (%)	2 (7)

* carditis was not evaluated echocardiographically in 7 cases published before 1987; [◇] ≤1 week.

Table 2. Characteristics of 16 patients 1.8 to 13 years of age presenting with acute post-streptococcal glomerulonephritis and thrombocytopenia, hemolytic anemia or both and thrombocytopenia and hemolytic anemia. Results are given either as frequency (and percentage) or as median and interquartile range (which includes half of the data). Due to rounding effect, total percentage may slightly differ from 100%.

N	16
Males : Females, N (%)	13 (81) : 3 (19)
Age, years	6.0 [4.8-9.3]
Preceding infection	
Streptococcal pharyngitis, N (%)	8 (50)
Streptococcal skin infection, N (%)	2 (13)
Further infection, N (%)	3 (19)
Unknown, N (%)	3 (19)
Kidney disease	
Relevant arterial hypertension, N (%)	11 (69)
Acute kidney injury	
Stage I, N (%)	8 (50)
Stage II, N (%)	3 (19)
Stage III, N (%)	4 (25)
Stage unknown, N (%)	1 (6)
Hematologic diseases	
Isolated thrombocytopenia, N (%)	8 (50)
Isolated hemolytic anemia, N (%)	6* (38)
Thrombocytopenia and hemolytic anemia, N (%)	2* (13)
Latency kidney disease - hematologic disease	
Concomitant kidney and hematologic disease ^o , N (%)	14 (88)
Kidney disease precedes hematologic disease by 1-3 weeks, N (%)	2 (12)

^o <1 week; *direct antiglobulin test always positive; ^odirect antiglobulin test always negative.

Table 3. Characteristics of 7 patients 1.7 to 44 years of age presenting with acute post-streptococcal glomerulonephritis complicated by conditions other than rheumatic fever or a hematologic disease. The kidney disease and the non-renal diseases presented with a latency of one week or less in the 7 patients. Due to rounding effect, total percentage may slightly differ from 100%.

N	7
Males : Females, N (%)	4 (57) : 3 (43)
Age, years	7.0 [6.3-19]
≤18 years, N (%)	5 (71)
>18 years, N (%)	2 (29)
Preceding infection	
Streptococcal pharyngitis, N (%)	3 (43)
Unknown, N (%)	4 (57)
Kidney disease	
Relevant arterial hypertension, N (%)	6 (86)
Acute kidney injury	
Stage I, N (%)	4 (57)
Stage II, N (%)	0 (0)
Stage III, N (%)	3 (43)
Further disease	
Henoch-Schönlein like syndrome, N (%)	5* (71)
Reactive arthritis, N (%)	1 (14)
Uveitis, N (%)	1 (14)

*purpura associated with arthralgia-arthritis (N=2), purpura associated with abdominal involvement (N=1), purpura associated with both arthralgia-arthritis and abdominal involvement (N=2).