Review

Poststreptococcal reactive arthritis: what is it and how do we know?

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Objective. To find out whether poststreptococcal reactive arthritis (PSRA) is a discrete, homogeneous clinical syndrome.

Method. Literature review from case reports and case series.

Results. One hundred and eighty-eight cases were identified. The age distribution was bimodal, with one peak in childhood and one peak in adulthood. Eighty-three per cent of streptococcal isolates were group A. The clinical presentation was heterogeneous but appeared different both from that of acute rheumatic fever (ARF) and from that of HLA B27-associated reactive arthritis. Carditis was rare.

Conclusions. The term PSRA encompasses significant heterogeneity. The link between the arthritis and the streptococcal infection is unproven.

Key words: Poststreptococcal reactive arthritis, Streptococcal infection, Reactive arthritis.

Since the 18th century, various clinical syndromes associated with scarlet fever have been recognized [1]. In this tradition, Crea and Mortimer described ‘scarlatinal arthritis’: arthritis associated with scarlet fever in children, many of whom either were diagnosed with acute rheumatic fever (ARF) at the onset or developed clinical evidence of rheumatic heart disease many years later [2]. ‘Scarlatinal arthritis’ was therefore placed firmly within the spectrum of ARF.

In the same year [3], Friedburg observed that ARF after streptococcal infection in adults over 25 yr of age presented with arthritis far more often than with chorea, nodules or erythema marginatum. Friedburg proposed that rheumatic fever in the adult differs from that in the child in that it is rarely associated with carditis. He defined adult poststreptococcal arthritis as a non-deforming febrile polyarthritis without carditis after group A streptococcal infection. Response to salicylate therapy was a defining criterion.

McDanald and Weisman described the pattern of joint involvement in six adults with ARF, one of whom had active carditis [4]. In this group, arthritis was described as acute, polyarticular, symmetrical, additive, and predominantly affecting the large joints of the lower limbs, with or without tenosynovitis. Symptoms were considered to be disproportionate to the clinical findings. A dramatic response of fever and arthritis to aspirin therapy occurred within 48 h, which was seen to differentiate it from the recently established syndrome of ‘enteritis-associated reactive arthritis’.

Subsequent reports, however, emphasized similarities with enteritis-associated reactive arthritis. In 1982 Goldsmith and Long described a poststreptococcal syndrome in children, characterized by symmetrical arthritis followed by intense arthralgia that was poorly responsive to aspirin therapy [5]; an adult was described with sacroiliitis similar to that seen in HLA-B27-related reactive arthritis [6]. The term ‘poststreptococcal reactive arthritis’ (PSRA) was originally applied to children [7]. Partly because of the prognostic implications, a diagnosis of ARF based on the modified Jones criteria [8] would automatically trump that of PSRA.

A supposedly characteristic picture of PSRA has emerged, with significant differences from ARF. Deighton [9] proposed the following as distinguishing features of PSRA: onset within 10 days of group A streptococcal infection, prolonged or recurrent arthritis and poor symptomatic response to aspirin. Ayoub and Ahmed added that the arthritis was typically non-migratory, with a peak incidence in middle-aged women and with a low (quoted at 8%) risk of developing carditis. Diagnostic criteria have been proposed, based on these clinical features [10].

Before considering diagnostic criteria for PSRA, however, we felt it important to examine the basis on which this entity stands by reviewing the available literature.

Method

We conducted a systematic search on Medline and Pubmed using the words ‘streptococcal’ and ‘arthritis’. We excluded non-English language articles and work published in abstract form. We included cases with evidence of recent streptococcal infection [anti-streptolysin O (ASO) titre ≥800, rising or falling ASO titres, antibodies to two streptococcal antigens above reference range, or streptococcus grown on culture]. Patients in whom ARF was actually diagnosed were excluded. Where the same authors had reported multiple series, only the most recently published series was analysed, unless the overlap was clearly specified. As reassigning diagnoses without access to the original case notes would not be justified, we did not revise the published diagnoses other than to exclude patients with arthritis but no arthritis, although some authors [11, 12] acknowledged that some patients diagnosed with PSRA also just fulfilled criteria for ARF (one major and two minor criteria). This approach is therefore a review of reports of patients diagnosed with PSRA. As explained above, the concept of PSRA as a discrete entity separate from ARF only emerged around 1982; therefore we excluded case reports prior to this, to avoid attaching implications to phrases like ‘poststrepto-
coccal arthritis’ [4] which were not originally intended by their authors.

Clinical features were extracted from available data and summarized. Arthritis was characterized as monoarthritis, oligoarthritis (two to four joints involved) or polyarthritis (five or more joints involved).

**Data from literature**

**Age and gender**

We identified 188 cases published in the literature between 1982 and 2002 using the above criteria [6, 11–36]. A hundred of these (53%) were adults (18 yr or over).

Of 180 cases in which this information was given, 91 (50.5%) were male. Forty-two (46%) of the adults were male and 49 (56%) of the children were male.

The age distribution of the reported cases (Fig. 1) appears bimodal, with a peak incidence of PSRA at ages 8–14 and a secondary peak at ages 21–37. This secondary peak contained 15 males and 22 females.

**Geographical origin**

Case reports derived mainly from developed countries (Fig. 2).

**HLA association**

Of 36 patients reported to have been HLA-typed, 6 (16.6%) were positive for HLA-B27. One patient had ‘prominent’ sacroiliitis [6]; one had sacroiliitis and subsequently developed erosions of both hip joints and ankylosing spondylitis [25]; and three came from a case series [26] which showed an unusual frequency (6 of 25 patients) of axial disease. Of the 153 cases not tested for HLA-B27, sacroiliitis was reported in 2 [22, 25].

In one case series [26] a higher prevalence of HLA DRB*01 was found in PSRA than in normal controls. A higher prevalence of HLA DRB*01 was observed in PSRA than in ARF. These findings were not replicated in a subsequent study [37].

**Infection**

The clinical history of streptococcal infection almost always consisted of self-reported symptoms of sore throat. In the 129 patients for whom the interval between onset of symptoms and onset of arthritis was known, there was a mean interval of 14 days (Fig. 3). Of the 91 adults and 38 children constituting this group, the mean interval was 15.6 and 11.6 days respectively.

In 69 patients a positive streptococcal culture was obtained. This was from a throat swab in 57 patients. Three cases were diagnosed from blood cultures and one from high vaginal and endocervical swabs (throat swab negative) in a patient with a history of a sore throat.
throat during childbirth followed by acute polyarthritis 9 days later [35].

Of these 69 streptococcal isolates, 57 were group A, two were group B, six were group C and four were group G.

In one patient, group A streptococcal infection was diagnosed clinically by the presence of toxic shock syndrome. In another patient, ‘physician-documented scarlet fever’ occurred 5 weeks before the onset of arthritis [11].

Information on streptococcal M-protein serotype was available in only two cases [29]: in these cases the M-protein serotypes were 9 and 28.

Kobayashi et al. [21] reported 13 patients who had recurrent episodes of tonsillitis, fever and arthritis over a period between 2 weeks and 10 yr. The arthritis occurred 7–10 days after tonsillitis. Seven of these cases are included in this analysis because Streptococcus was isolated on tonsillar swabs; throat swabs from four patients grew other organisms (Staphylococcus aureus with Peptostreptococcus, Pseudomonas aeruginosa, Klebsiella oxytoca and Staphylococcus) and in two patients no organism was isolated. Five patients underwent tonsillectomy, of whom three experienced a transient exacerbation of arthritis 10 days later. After this no further exacerbations were seen.

Clinical features: musculoskeletal

In most cases arthritis was non-migratory, involved one or a few joints, and resolved within weeks (Table 1).

The particular joints affected were not specified in all patients. However, the frequency of reports of named swollen joints is shown in Fig. 4.

Adductor enthesis was described in one patient [17]. Tenosynovitis was also described, affecting the dorsum of the left foot in one case [12], the palmar flexor tendons in six cases [23] and the peroneal tendons of the right ankle in one case [35]; the Achilles tendons were tender bilaterally in at least two cases [21, 34]. In one case bilateral adductor enthesis and bilateral supraspinatus tendonitis was described [17]. One case [38] was not included in this analysis because dactylitis rather than arthritis was described.

One study [36] compared two cohorts of children with ARF and PSRA and found no significant difference in the clinical presentation of arthritis.

Response to aspirin or NSAID was variable, as was the dose used and criteria to define response. Systemic steroid therapy was used in a substantial minority of patients. Arthritis lasted 8 months or more in only four individuals, though in many others arthralgia was noted to persist for longer.

Seventeen adults and six children experienced recurrences of arthritis (rather than simply arthralgia), usually in association with streptococcal pharyngitis, but one recurrence was attributed to soft tissue infection [33]. These recurrences sometimes affected the same joint as the original episode of arthritis [13]. In some of these patients, treatment appeared to alter the course of the disease; one patient [13] was reported as experiencing a fourth episode, but no further episodes were seen after oral penicillin prophylaxis was started. Seven patients [21] had recurrent episodes which ceased after tonsillectomy.

![Fig. 3. Time in days between pharyngitis and arthritis in 129 patients.](image)

![Fig. 4. Frequency of patients with particular joints swollen.](image)

**TABLE 1. Characteristics of arthritis in those for whom data were available**

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Adults</th>
<th>Children</th>
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<tbody>
<tr>
<td>Non-migratory</td>
<td>129 of 158</td>
<td>68 of 84</td>
<td>61 of 74</td>
</tr>
<tr>
<td>Symmetrical</td>
<td>63 of 152</td>
<td>40 of 78</td>
<td>24 of 74</td>
</tr>
<tr>
<td>Monoarthritis</td>
<td>37 of 162</td>
<td>19 of 100</td>
<td>18 of 60</td>
</tr>
<tr>
<td>(1 swollen joint)</td>
<td>(23%)</td>
<td>(19%)</td>
<td>(30%)</td>
</tr>
<tr>
<td>Oligoarthritis</td>
<td>60 of 162</td>
<td>35 of 100</td>
<td>25 of 60</td>
</tr>
<tr>
<td>(2–4 swollen joints)</td>
<td>(37%)</td>
<td>(35%)</td>
<td>(42%)</td>
</tr>
<tr>
<td>Polyarthritis</td>
<td>65 of 162</td>
<td>46 of 100</td>
<td>17 of 60</td>
</tr>
<tr>
<td>(&gt;4 swollen joints)</td>
<td>(37%)</td>
<td>(46%)</td>
<td>(28%)</td>
</tr>
<tr>
<td>Resolved within 6 weeks</td>
<td>44 of 84</td>
<td>16 of 49</td>
<td>27 of 35</td>
</tr>
<tr>
<td></td>
<td>(52%)</td>
<td>(33%)</td>
<td>(77%)</td>
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</table>
Clinical features: extraskeletal

None of these cases had chorea or erythema marginatum: this would have put them in the diagnostic category for ARF. Carditis at onset was seen in one case (see below). Nodules were seen in two cases (see below).

Carditis. Four children developed carditis. In one case this was evident at the time of presentation of PSRA [18]; the others showed evidence of carditis 1, 9 and 18 [12, 26, 32] months from the onset of arthritis. One adult had pericarditis at day 9 but had no evidence of valvular disease over the 9-month follow-up [15].

Glomerulonephritis. Glomerulonephritis was noted in six adults and two children. The histology was reported in one case as ‘segmental glomerulonephritis’ [23].

Eyes. Conjunctivitis was described in three cases [15, 25] and uveitis in one [25]. Kobayashi et al. [21] described sicca symptoms in a patient with anti-nuclear antibodies, anti-Ro antibodies and anti-cardiolipin antibodies. The same authors [34] reported anterior uveitis in association with two cases of poststreptococcal reactive arthritis; one of these patients, who had previously had a tonsilllectomy, went on to develop posterior uveitis and impaired visual acuity.

Abdomen. Abdominal pain [21] and splenomegaly [15, 21] have been reported. A transient cholestatic hepatitis was noted in four of a series of 23 patients [29]. Epididymo-orchitis was noted in one case [14].

Lung. In a single case [27], a pulmonary infiltrate was reported on the chest radiograph. In another [16] rales were heard in the lung bases and the chest radiograph showed a small left pleural effusion and left basal atelectasis.

Skin. Erythema nodosum was noted in one patient from the UK [14] and three from The Netherlands [27, 31]; one series of 41 patients from The Netherlands reported erythema nodusum and/or multiforme in 19 individuals [29]. Vasculitic lesions were also observed: biopsy showed leucocytoclastic changes in five cases [23] and necrotizing vasculitis in one case. Madhuri et al. [25] reported three cases with pustular skin lesions. Another patient [27] had livedo reticularis and cutaneous nodules, biopsy of which revealed a necrotizing vasculitis ‘similar to that seen in polyarteritis nodosa’, with normal appearance on immunofluorescence. Non-specific rash appeared common [13, 21, 26, 30].

One patient had a penile ulcer and palpable purpuric lesions on both aspects of the hands and dorsal aspect of the feet, with ‘mild perivascular inflammation’ on biopsy [16]. Lymphadenopathy was noted in two cases [13, 28].

Discussion

Poststreptococcal reactive arthritis has been proposed as a homogeneous clinical entity distinct from acute rheumatic fever and from other forms of reactive arthritis. The primary aim of this paper is to consider whether the available data provide a clear or reasonable foundation for this concept; the pooling of the case reports in this analysis should not be taken to imply an assumption that this is the case. The analysis of the data contained in the individual case reports and case series of PSRA is severely limited, both by the heterogeneity of the source data and by difficult questions relating to the establishment of causality. So what conclusions can be drawn?

Amongst patients said to have PSRA, males and females are affected equally, both as adults and children. The age distribution of PSRA appears to be bimodal, with a peak at ages 8–14 and another at age 21–37. This contrasts with ARF, which has a single peak incidence in childhood at around 12 yr [39], and with reactive arthritis, which has a single peak incidence at 27–34 yr [40, 41]. The geographical distribution of case reports of PSRA probably reflects reporting bias rather than true prevalence. There are very few data on association with HLA. The data support the possibility, however, that there may be a subset of patients with PSRA who are HLA-B27-positive and are more likely to develop sacroiliitis. A tentative association with HLA DRB*01 [26] needs clarification in larger studies.

Cases were defined by the association with streptococcal infection. Eighty-three per cent of isolates were group A streptococcus, although a significant number were groups B, C or G. Even for the group A streptococcus, the M-protein serotype was ‘non-rheumatogenic’ in the two cases in which this serotype was determined. ARF is classically defined as occurring only in relation to group A streptococcal infection, although this has recently been questioned [42]. This may be compared with the findings of a survey of throat cultures in children with acute pharyngitis, in which 83% of isolates were group A and most of the remainder were group C or G [43]. It should be noted that healthy children frequently carry β-haemo-

<table>
<thead>
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<th>Table 2. Antibiotic treatment (short course for acute episode) and outcome</th>
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<tr>
<td>Treatment given</td>
</tr>
<tr>
<td>Number of patients</td>
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<tr>
<td>Number with recurrence of joint disease</td>
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<tr>
<td>Number developing carditis</td>
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<th>Table 3. Antibiotic treatment (prophylaxis) and outcome</th>
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<tr>
<td>Prophylaxis given</td>
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<tr>
<td>Number of patients</td>
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<tr>
<td>Number with recurrence of joint disease</td>
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<td>Number developing carditis</td>
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Analysis has not been done because of the heterogeneity in the data. In particular it should be noted that the length of follow-up varied between 1 and 46 months, and that echocardiography was seldom done either at baseline or at follow-up.
lytic streptococci in the throat, whereas such carriage in the adult is rare [44].

Joint involvement is typically non-migratory and affects the large joints, particularly those of the lower limb. Mono-, oligo- and polyarthritis are equally represented. This differs from the polyarthritis of ARF, and the relatively high prevalence of upper limb involvement would be atypical for sexually acquired or enteric reactive arthritis.

Carditis was recorded in only 4 of 180 (2%) cases, all of whom were children. This would seem to imply that PSRA in adults does not lead to carditis; however, in most of the case reports the follow-up was short, evidence of carditis was not always sought assiduously, and few cases of recurrent disease were reported.

There seems little consensus on acute treatment. The effect of antibiotics during the acute episode is unclear (Table 2). Antibiotic prophylaxis was given to 105 patients, and these patients had a lower incidence of recurrence of arthritis (Table 3). However, there are likely to be confounding factors, such as variability in the duration of follow-up and in the use of echocardiography; without a controlled epidemiological study, no clear conclusion as to the value of antibiotic prophylaxis can be drawn.

Glomerulonephritis was recorded in eight cases of PSRA. This is a well-recognized complication of streptococcal infection but is rarely reported in association with ARF [45, 46].

Association with pharyngitis was usual, but there are no reports of association with impetigo, a common streptococcal skin infection. In a group of Japanese patients [21, 34], arthritis recurred after repeated episodes of tonsillitis, and tonsillectomy appeared to alter the course of the disease; a similar pattern of arthritis was observed by the same authors after non-streptococcal tonsillar infection. In one patient with established rheumatoid arthritis, the joint disease repeatedly flared in association with non-streptococcal tonsillitis, and improved after tonsillectomy and knee synovectomy [47].

Several factors limit the conclusions that can be drawn from this analysis. The heterogeneity of reports and the small number of cases reported are particularly important in this respect. Reporting of selected cases lends itself particularly well to Procrustean methods of making each case neatly fit within pre-existing concepts, whereas in the larger series data relating to individual cases is sometimes limited.

Despite these limitations, the available literature at present supports the idea that PSRA is in reality a heterogeneous group of clinical entities, some of which share features with ARF and others with HLA B27-related spondyloarthropathies. The assumed causal role of streptococcal infection is far from proven. No specific microorganism has been implicated, the range of streptococci identified resembles that found in normal children with uncomplicated pharyngitis, and a clinical syndrome similar to PSRA may also be associated with non-streptococcal tonsillitis [22, 47]. It is worth asking whether pharyngitis or tonsillitis itself, rather than the microbial agent discovered by culture or serology, may be the crucial precursor to arthritis in this group of patients.

These two crucial questions—do sore throats cause arthritis? and does streptococcal sore throat cause arthritis?—need answering. Two approaches might be productive. A large prospective study of people presenting with sore throats in primary care might yield answers if appropriate microbiology, serology and follow-up were included. Additional useful data may also be obtained from early arthritis clinics and registries.

Furthermore, if there is truly clinical equipoise over the value of antibiotic prophylaxis [48], then proceeding to a randomized placebo-controlled trial of antimicrobial prophylaxis following PSRA may be the only satisfactory method of resolving some of the uncertainties regarding the management of this condition.

**Key messages**
- PSRA is probably a heterogeneous group of disorders.
- The assumed causal role of streptococcal infection remains unproven.
- This subject requires clarification by prospective study of streptococcal infection or sore throat.

The authors have declared no conflicts of interest.

### References


