Post-streptococcal reactive arthritis: a clinical and serological description, revealing its distinction from acute rheumatic fever

T. L. Th. A. JANSEN*, M. JANSSEN, A. J. L. de JONG & M. E. C. JEURISSEN.
From the Department of Rheumatology, Rijnstate Hospital, Arnhem, the Netherlands


Objective. To follow-up prospectively patients with arthritis after infection with β-haemolytic streptococci of Lancefield group A (βHSA), with emphasis on clinical characteristics and serological features. We additionally investigated whether these patients, though often fulfilling the Jones’ criteria for acute rheumatic fever (ARF), had a disease with clinical characteristics different from ARF.

Design. We performed a systematic prospective observational study of consecutive patients at a Dutch Outpatient Clinic and Department of Rheumatology, with arthritis after throat infection with βHSA presenting to rheumatologist or internist from September 1992 until September 1996. Main outcome measures were clinical and biochemical characteristics with special reference to carditis.

Results. A total of 23 patients (21 Dutch, two Turkish; female/male ratio 15/8; mean (SD) age 42 (14) years) with predominantly non-migratory arthritis were included. A positive throat swab culture was obtained in 17%. All patients showed a significant rise of antistreptolysine-O (ASO; normal <200 IU mL⁻¹) and antideoxyribonuclease-B (anti-DNase-B; normal <200 IU mL⁻¹) titre. The mean (SEM) maximal ASO was 1305 (195) IU mL⁻¹, and anti-DNase-B titre 980 (115) IU mL⁻¹. Arthritis was present in mean (SEM) 5.4 (0.9) joints: 2.2 (0.7) small, 3.2 (0.4) larger joints. The arthritis was monarticular in 23% of the patients, oligoarticular in 35%, and polyarticular in 43%. Skin abnormalities were present in 12 patients: erythema nodosum in seven patients (30%), and erythema multiforme in five patients (22%). A transient cholestatic hepatitis was found in four patients (17%). In two patients a transient first-degree conduction block was found; however, neither echocardiography nor clinical course supported carditis. All patients were advised to receive monthly penicillin prophylaxis during a period of 2 years. Two patients refused to follow medical advice; in one a non-migratory arthritis recurred 15 months after the first episode of arthritis.

Conclusion. Commonly, arthritis secondary to βHSA infection in the Netherlands, a prosperous Western European country with State Welfare, is not accompanied by carditis, contrary to literature on classical ARF. Other factors discriminating it from ARF are the age of onset, the non-migratory character of the arthritis, the high frequency of erythema nodosum and multiforme, as well as the presence of transient hepatitis. As arthritis is the hallmark of this syndrome, post-streptococcal reactive arthritis (PSRA) is the most proper name for this disease entity. Whether penicillin prophylaxis is needed in PSRA, as it is in ARF, warrants further prospective investigation.

Keywords: post-streptococcal reactive arthritis, rheumatic fever, streptococci.

*Present address: Department of Rheumatology, Medical Centre Leeuwarden, POB 888, NL-8901 BR Leeuwarden, the Netherlands.

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Introduction

The last few decades have witnessed a striking resurgence of sequelae to infections with β-haemolytic streptococci of Lancefield group A (βHSA). Classically, arthritis following throat infection with βHSA is attributed to acute rheumatic fever (ARF) [1]. A reactive arthritis is defined as a sterile inflammatory arthritis occurring in association with a primary infection at a distant site [2]. Arthritis following primary throat infection with βHSA applies to this definition. Recent papers suggest that a spectrum of reactive post-streptococcal diseases may become manifest secondary to βHSA infection [3–9].

Though arthritis may be very painful in post-streptococcal disease, the complication which is most feared in ARF is a devastating carditis. First attacks of classical ARF in children are accompanied by carditis in 30–90% [10–13]. The incidence of carditis, however, declines markedly with advancing age [14, 15].

At present, there is an ongoing discussion whether post-streptococcal reactive arthritis (PSRA) is a forme fruste of ARF or whether it is a separate sequel to βHSA infection with a very low or possibly even absent risk of carditis [9, 16–19]. Long-term antibiotic prophylaxis in ARF is currently advocated in order to reduce a progressively increasing risk of carditis in subsequent episodes of ARF [1]. Whether a similar antibiotic regimen is needed in PSRA, however, is not clear. The literature lacks detailed data on clinical manifestations which would enable differentiation between ARF and PSRA. In a prospective study of consecutive patients we studied the clinical manifestations of a group of newly diagnosed patients with arthritis following infection with βHSA, and we compared our findings with well-known manifestations of ARF.

Material and methods

Study design

The cohort consisted of consecutive patients with an arthritis secondary to infection with βHSA, presenting in our outpatient clinics or departments of rheumatology and internal medicine from September 1992 until September 1996. Patients were included when arthritis following βHSA infection was proven and other potential causes of arthritis were excluded. The excluded causes of arthritis were: septic arthritis, rheumatoid arthritis or connective tissue diseases, crystal deposition disease, reactive arthritis (Parvovirus B19, Salmonella, Shigella, Yersinia, esterocollitica Campylobacter fetus jejuniun, and Chlamydia), and arthritis associated with inflammatory bowel disease. All patients were regularly seen on an outpatient basis for follow-up. The following laboratory tests were obtained: full blood count, erythrocyte sedimentation rate, serum creatinine, alkaline phosphatase, gamma-glutamyltranspeptidase, aspartate-aminotranspeptidase, alanine-aminotranspeptidase, uric acid, immunoglobulin M rheumatoid factor, antinuclear antibodies, C-reactive protein and urine microscopy. An electrocardiogram was performed for all patients.

Literature on ARF was obtained from Medline and compared with our data.

Serological measurements in βHSA infection

In all patients antistreptolysine-O (ASO) and antideoxyribonuclease-B (anti-DNase-B) titres were simultaneously measured and sequentially monitored at 2, 3, 4, 6, 8, 12 weeks following the primary infection. In those continuing follow-up the same titres were measured at 16, 24, 52 and 104 weeks. The characteristics of the ASO and anti-DNase-B titres that were required prior to inclusion in the cohort were as follows. (i) ASO and anti-DNase-B must reach a supraphysiological level (ASO: >200 U L⁻¹ in adults, >300 U L⁻¹ in adolescents/children; anti-DNase-B >200 U L⁻¹). (ii) Both titres must show a significant rise: critical difference between consecutive ASO values, 26%, and between consecutive anti-DNase-B values, 14%. Serological titres were determined using a nephelometry kit from Behring (Marburg, Germany); according to Behring’s manual our laboratory used intra- and interassay coefficients of variation of ASO (range 175–850 U mL⁻¹) 9 and 13%, respectively; those of anti-DNase-B (range 145–1200 U mL⁻¹) were 3.5 and 7%, respectively.

Statistical analyses

Data from the literature, especially on the incidence of carditis, were compared with our findings using the chi-squared test including Yates’ continuity correction.

Results

During a period of 48 months 23 patients (female/
male ratio 15/8: mean (SD) age 42 (14) years) with arthritis secondary to βHSA infection presented in our outpatient clinics (17 patients) or at the departments of rheumatology or internal medicine (six patients) (Table 1). All cases were sporadic, and clustering of cases was not encountered. None of the patients had a history of ARF nor of a pre-existing cardiac condition. Other potential causes of acute arthritis, as mentioned above, were excluded (data not shown). All patients presented with arthritis, which is a Jones’ major criterion. All patients had at least two Jones’ minor criteria: elevated ESR: mean (SD) 67 (30) mm h$^{-1}$, elevated CRP 73 (52) mg L$^{-1}$; leucocytosis was observed in 11/23 patients with mean (SD) value of 12.7 (2.1). All patients presented with fever: 25% with an intermitting type and 75% with a remitting type during a mean (SD) period of 6.3 (2.6) days and a maximum temperature of 39.5°C.

Prior to the arthritis 14 patients (61%) complained of a painful throat. Throat culture was obtained in 17 patients (74%). Culture of the throat swab was positive for βHSA in 4 (17%). In a group of nine patients without prior antibiotic treatment, the throat culture was positive in 3 cases (33%). In a group of eight patients who had already been treated with antibi-

![Fig. 1 Time-course of antistreptolysin-O titre (ASO; mean ± SEM) and anti-DNase-B titre in 23 PSRA patients. Time-courses are not significantly different. (a, ASO; □, anti-DNase-B).](image-url)
otics, only one patient (12.5%) had a positive culture for βHISA.

In all patients the ASO titres and anti-DNase-B titres increased significantly during the first weeks following primary infection and decreased later during follow-up, Fig. 1. The time-courses of both titre curves were similar. The mean maximum ASO titre (SEM) was 1305 (195) U L\(^{-1}\), and occurred 6.5 (0.9) weeks after the initial throat infection. Mean maximum anti-DNase-B titre (SEM) 980 (115) U L\(^{-1}\) occurred 6.0 (0.7) weeks after the initial infection.

The mean (SEM) incubation period from throat infection to arthritis was 16.5 (2.1) days. The arthritis was non-migratory in 22 patients (96%), and asymmetrical in 19 patients (83%). The knee joint was affected in 61% of patients, followed by the ankle 57%, wrist 39%, elbow 35%, metacarpophalangeal joints 22%, proximal interphalangeal joints 13% and metatarsalphalangeal joints 9%. The mean (SEM) number of arthritic joints per patient was 5.4 (0.9): 2.2 (0.7) small joints and 3.2 (0.4) greater joints. It presented as monarthritis in 22%, as oligoarthritis in 35% and as polyarthritis in 43%. All patients responded well to NSAID treatment (diclofenac 50 mg t.i.d., ibuprofen 400 mg t.i.d. or naproxen 500 mg twice daily), which was given during a period of 7.6 (1.0) weeks, ranging from 1 to 20 weeks. There was a full recovery in all patients after a mean (SD) period of 5.6 (4.6) weeks.

Skin abnormalities were present in 12 patients: seven (30%) had erythema nodosum (Fig. 2), five (22%) had erythema multiforme (Fig. 3); 11 (48%) had no skin abnormalities.

None of the patients had features of acute glomerulonephritis.

In a group of four patients (14%) a transient cholestatic hepatitis was seen: mean (SEM) alkaline phosphatase 246 (36) U L\(^{-1}\) (normal: 30–105 U L\(^{-1}\)); gamma-glutamyltranspeptidase 193 (32) U L\(^{-1}\) (normal: 9–50 U L\(^{-1}\)); aspartate-aminotranspeptidase 71 (36) U L\(^{-1}\) (normal: 5–30 U L\(^{-1}\)); alanine-aminotranspeptidase 111 (23) U L\(^{-1}\) (normal 5–30 U L\(^{-1}\)).
In a 68-year-old female with a transient cholestatic hepatitis a liver biopsy was obtained. Histology revealed severe inflammation of Kiernan’s triangle with perforation of membrana limitans and piecemeal necrosis (Fig. 4).

A 2-year period of monthly penicillin prophylaxis was advised. Two patients refused to follow medical advice. In one of them arthritis secondary to HSA infection recurred 15 months after the first attack. In the 21 patients who were compliant with penicillin prophylaxis no recurrence was observed during a mean (SD) observation period of 19 (13) months: range 3–48 months. Six patients have already completed the 2-year period of prophylaxis. The total follow-up after prophylaxis in these six patients is 76 months. During this follow-up period no recurrences were observed of arthritis secondary to HSA infection.

Carditis could not be detected in our group of patients with arthritis secondary to HSA infection. A search in our hospital diagnosis registration system revealed that during the study period of 48 months no patients with ARF were referred to other specialists like cardiologists and paediatricians. Generally, a frequency of >30% of carditis in first attacks of ARF [10–13, 20] is accepted. The absence of carditis in our patient group is significantly different from the historically expected frequency of the aforementioned figure of >30% (chi-squared test >8.5 at d.f. = 1: two-sided P < 0.005).

Discussion

After several decades of a steadily declining frequency of ARF the last decennium has witnessed a striking resurgence in post-streptococcal diseases [21]. The aim of this study was to define the clinical picture of reactive arthritis in adult patients following β-haemolytic streptococcal of Lancefield group A (βHSA) infection, as the literature lacks detailed description of the clinical characteristics.

According to the literature the first attacks of ARF in children are accompanied by carditis in 30–90% [10–13]. The incidence of carditis is probably low in adult patients [15, 21]. Generally, a frequency of >30% of carditis in first attacks of ARF is accepted [10–13, 20]. Assuming a theoretical risk of 30% developing carditis in ARF, one might expect to observe seven patients with carditis in our group of 23 patients. This was obviously not the case. Explanatory factors for this discrepancy might be a declining incidence of carditis in adult patients [14, 15], possibly due to concurrent alterations in the immune response. The discrepancy might possibly be explained by differences in pathogenicity of the organism, alterations within the infected host or possibly bias due to changing study methods over time. Whatever the cause might be, the clinical discrepancies between classical ARF, predominantly in children, and current PSRA in adults suggest that the patients we describe here suffer from a syndrome distinct from ARF. The use of historical controls might be risky, especially so because ARF is very rarely described in adult patients [22]. In one paper concerning patients over 45 years of age carditis was found in eight of 23 patients [15]. However, seven of the eight patients with carditis had already had a previous attack of ARF or had pre-existing valvular lesions. In our group none of the patients had such a history. Recently, Feuer & Spiera [20] also found a significant incidence of carditis in a group of Hasidic Jewish adults, with ages varying from 21 to 50 years. Our study underscores the suggestion previously made by others [4–9, 23, 24] that there exists a disease clinically distinctive from ARF which is also secondary to HSA throat infection with a low or absent risk of carditis in adulthood. As the patients presented here satisfy the definition for reactive arthritis [2], post-streptococcal reactive arthritis (PSRA) seems to be the most suitable name for this entity [23].

In addition to the absence of carditis in our patient group, there were other clinical characteristics differentiating this entity from ARF. The arthritis is characterized by an occurrence predominantly in females, whereas ARF predominates in males [18]. The latency period of 16.5 days in the present patient group was shorter than the expected 3–4 weeks described for ARF [8], but similar to the 18.6 days in ARF mentioned by Rammelkamp & Stolzer [25]. ARF is almost invariably found between 5 and 20 years of age, with a peak incidence at 8 years old [10], contrary to the present patient group, which was considerably older. We also found differences with respect to the type of arthritis. ARF is known for its migratory type of arthritis occurring in 50–100% [10, 18, 22, 24] whereas we found predominantly a non-migratory type of arthritis. However, PSRA was similar to classical ARF in that the knee and ankle were the joints most commonly...
affected, and arthritis always led to full recovery [10]. In our series, however, monarthritis was accepted as a Jones’ criterion. In classical ARF a migratory oligo- or polyarthritis is needed in order to fulfil this criterion [1]. Therefore the monarthritic presentation of PSRA may be another distinction from ARF. Subgroup analysis comparing the monoarticular group with the oligo- or polyarticular group did not reveal differences concerning the other clinical manifestations (data not shown).

Erythema nodosum, has been only very rarely reported in ARF patients [14, 15, 20, 26, 27, 28]. It occurred in only two sporadic cases in a series of 369 ARF patients [26]. Ben-Dov & Berry’s review [15] reports that erythema nodosum in ARF occurs somewhere between 4 and 7%. In the present patient group, erythema nodosum and erythema multiforme both were frequently found. The cause for this discrepancy in frequency of erythema nodosum in classical ARF and in PSRA remains speculative.

In addition to the reactive arthritis, we observed in some patients a transient hepatitis with piecemeal necrosis, which is only sporadically described in ARF [14, 22, 29].

Further studies are warranted to investigate which factors are responsible for the development of the differences in clinical manifestations between PSRA and ARF. Adults may be prone to developing PSRA instead of ARF, possibly due to age-dependent host factors, as it is known that the incidence of carditis declines markedly with age [14]. Another explanatory factor may be found in the different types of streptococcal virulence factors in PSRA when compared to ARF. The prevalence of specific M-serotypes has possibly changed during the last few decades; the currently prevalent M-serotypes in Western Europe may be responsible for a more benign type of presentation of PSRA in which carditis is less likely. Also, several human host factors, especially age-and sex-related differences in the immune response are candidate factors to explain clinical differences between PSRA and ARF.

Another interesting point was that all clinical findings had subsided before the ASO titre and anti-DNase-B titre reached their maximum values. This underscores the idea that these antibody responses played no significant role in the pathogenesis of disease manifestations, but are probably epiphenomena.

Recommendations for antibiotic prophylaxis following ARF are undisputable but it is unclear whether prophylactic treatment with penicillin is needed in PSRA. Deighton recommended penicillin prophylaxis only for adult PSRA patients with certain characteristics, i.e. mitral or aortic valve disease, extra-articular symptoms, more than one episode of PSRA and a first-degree relative with a history of ARF [5]. In our patient group we are now performing a study investigating whether a 2-year period of monthly penicillin prophylaxis (benzylpenicillin 1.2 million units) is a safe policy. Until now we have found no relapses in the treated group of patients.

In conclusion, PSRA is a disease entity following throat infection with βHSA after a short delay. A typical patient is a middle-aged female presenting with fever and arthritis; about 50% of patients simultaneously have erythema nodosum or erythema multiforme; a minority of patients have signs of cholestatic hepatitis. On average the patient fully recovers in about 6 weeks, even before the ASO and anti-DNase-B titres reach their maximum values. In contrast to ARF, carditis is not a manifestation of PSRA in adult patients.

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Correspondence: Dr Matthijs Janssen MD, Department of Rheumatology, Ziekenhuis Rijnstate, Postbus 9555, NL-6800 TA Arnhem, the Netherlands (fax: +31 26 3786612; e-mail: mjaassen@rijnstate.nl).