Various rheumatic syndromes in adult patients associated with high antistreptolysin O titres and their differential diagnosis with rheumatic fever

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Abstract

Objectives—The purpose of this study was to analyse retrospectively adult patients with acute joint or muscle symptoms and a high antistreptolysin O (ASO) titre to find out which syndromes of clinical arthritis are associated with serological evidence of streptococcal infection.

Methods—Seventy six adult patients with an acute arthritis syndrome or an exacerbation in their chronic rheumatic disease and simultaneously a high ASO titre (≥ 500 Todd units) were examined in two time periods in the 1980s.

Results—Twenty six patients had arthritis associated with a known rheumatic disease, 25 had non-specific arthralgia/myalgia, 20 had reactive arthritis, and five had septic arthritis. No case of classic rheumatic fever classified by two major criteria was found. Six patients fulfilled one major and at least two minor criteria. The frequency of HLA-B27 was significantly higher in the whole patient group than in the healthy Finnish population (30 v 14%).

Conclusions—It is concluded that classic rheumatic fever is now rare, even in patients with arthritis with a high ASO titre. These results support the suggestion that β haemolytic streptococci may trigger reactive arthritis as well as rheumatic fever.

associated with this kind of reactive arthritis^{19–25} and also in some HLA-B27 positive patients.^{26–29} Streptococcal infections have also been suspected to act as a triggering or exacerbating factor in various rheumatic and connective tissue diseases.^{30–40}

The purpose of this study was to analyse retrospectively adult patients with acute joint or muscle symptoms and a high antistreptolysin O (ASO) titre to find out which kinds of clinical arthritis syndromes are associated with serological evidence of infection due to β haemolytic streptococci A, C, and G, which are known to increase the ASO titre^{29–41} and to cause arthritis syndromes.⁴² In addition, we considered the incidence of classic rheumatic fever in these patients with high ASO titres according to the revised Jones' criteria.^{43–44}

Patients and methods

PATIENTS

All adult patients (aged ≥ 15 years) treated in Meilahti Hospital, Helsinki University Central Hospital during 1980–4 (series I) and 1987–90 (series II) were included in this study if they were admitted to the hospital because of acute joint or muscle symptoms or an acute exacerbation in their chronic rheumatic disease within three months before admission to hospital and they simultaneously had a high ASO titre (≥ 500 Todd units). Patients with suspected endoprosthetic infections were excluded. The ASO limit represents about the 98–99th centile value in the healthy Finnish population during the study period.⁴⁵

The first series consisted of 48 patients who fulfilled these criteria. All 48 patients were invited to a control examination one to five years after the onset of the acute phase. Five patients, one with septic arthritis, two with polymyalgia, and two with unclassified arthritis in the primary phase could not participate in the control examination. In total, 43 patients (mean age 42 years; range 18–85 years), 22 women and 21 men, formed the patient group in the first series. Twenty nine of 43 patients had acute disease defined as acute joint or muscle symptoms which began within three months of their admission and who had no previous rheumatic disease. Twelve patients had acute onset joint or muscle symptoms within three months but they had previously had rheumatic symptoms without any definite diagnosis of rheumatic disease, and two

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β Haemolytic streptococci can cause various clinical syndromes of arthritis of which septic arthritis^{1–4} and rheumatic fever⁵ are the best known. Rheumatic fever caused by pharyngeal infection by group A streptococcus is one form of reactive arthritis. A statistically significant association between rheumatic fever and certain HLA class II antigens (DR4 in white subjects and DR2 in black subjects) has been reported,^{6–8} but no association with HLA class I antigens, especially HLA-B27, has been found.⁹

Certain gastrointestinal and genitourinary tract pathogens, of which the best known are yersinia,¹⁰ salmonella,^{11–12} shigella,¹³ campylobacter^{14–15} and *Chlamydia trachomatis*^{16–17} can trigger another form of reactive arthritis, especially in subjects with the HLA-B27 antigen.¹⁸ β Haemolytic streptococci have been

patients had an acute exacerbation of their known chronic rheumatic disease. The control examination included, in addition to a clinical examination, laboratory tests (erythrocyte sedimentation rate, C reactive protein, ASO, rheumatoid factor, antinuclear antibodies, and HLA-B27 tissue typing), and radiological examinations were included when they were clinically indicated.

The second patient series from the years 1987–90 with the same diagnostic criteria as the first series were gathered retrospectively from the patients with high ASO titres. There were 33 patients in this second series (mean age 38 years; range 16–78 years), 11 women and 22 men. Twenty two (67%) of 33 patients had acute disease, five had acute onset disease but with previous rheumatic symptoms, and six patients had an acute exacerbation of their known chronic rheumatic disease. No systematic follow up or control study was arranged for the patients in the second series.

There were 76 patients (mean age 40 years; range 16–85 years) in total, 33 women and 43 men. Fifty one patients had acute disease, 17 had an acute disease with previous rheumatic symptoms, and eight had an exacerbation of a known chronic rheumatic disease.

STATISTICAL METHODS

Fischer’s exact test or the χ^2 test with Yates’s correction were used.

Results

Table 1 gives the clinical diagnosis of the 76 patients in the acute phase. There was no case of classic rheumatic fever if this was defined as the presence of at least two major diagnostic criteria such as polyarthritis, carditis, erythema marginatum, or chorea as required in the revised Jones’ criteria for the diagnosis of rheumatic fever. Possible rheumatic fever with one major and two minor criteria was found in six patients. One of the patients with possible rheumatic fever had carditis and arthralgia, but no arthritis. The other five patients had polyarthritis with fever.

The most common clinical arthritis syndrome of the whole patient group was arthritis

associated with some known rheumatic disease or syndrome (26 patients) followed by unspecific arthralgia/myalgia (25 patients) and reactive arthritis (20 patients). None of the patients in the group with reactive arthritis had any clinical, cultural, or serological evidence of salmonella, yersinia, or chlamydia infection in the acute phase. Five patients had septic arthritis, three of which were due to β haemolytic streptococci, one due to gonococcus, and one due to *Staphylococcus aureus*.

Thirty per cent of the patients were HLA-B27 positive (36% of typed patients) compared with 14%^{46–48} of the healthy Finnish population ($p<0.001$). Fourteen (33%) of 43 patients typed in series I were HLA-B27 positive and nine (27%) of 33 patients in series II. Only 20 patients in series II had been typed, however, which means that 45% of the typed patients were HLA-B27 positive.

Clinical evidence of preceding infection within one month before the onset of joint or muscle symptoms based on the patients’ history was obtained in 50 patients in the acute phase (table 2). Only two patients had clinical, cultural, or serological evidence of gastrointestinal or genitourinary tract infections. One patient had gonococcal urethritis proved by culture and one patient with ankylosing spondylitis had a high stable antibody titre against *Chlamydia trachomatis*. In the HLA-B27 positive patients respiratory infections preceded muscle or joint symptoms more often than gastrointestinal or urogenital infections (11 v 1; $p<0.01$).

A follow up examination was carried out in 43 patients in series I at one to five years after the acute phase. One patient, with post-infectious arthritis in the acute phase but with an earlier history of Reiter’s disease was diagnosed as having ankylosing spondylitis at follow up. No other new cases of chronic rheumatic disease were diagnosed at follow up. Thirty two (74%) of 43 patients were healthy in the control examination.

At follow up 12 (28%) of 43 patients still had a high ASO titre (≥ 500 Todd units) in the control examination. Four (33%) of these 12 patients still had rheumatic symptoms compared with eight (38%) of the 21 patients whose ASO titre had decreased to less than 500 Todd units during follow up. Two of the four patients with a high ASO titre and rheumatic symptoms had ankylosing spondylitis without acute respiratory infections within one month before the control examination and three of these were HLA-B27 positive.

Table 1 Clinical diagnosis of the 76 patients in the acute phase with high ASO titre and simultaneous joint or muscle symptoms in relation to HLA-B27 tissue type

Clinical diagnosis	No (%) of patients			
	HLA-B27+	HLA-B27–	Not typed	Total
Septic arthritis	1(1)	4(5)	0(0)	5(7)
Reactive arthritis	7(9)	12(16)	1(1)	20(26)
Classic rheumatic fever	0(0)	0(0)	0(0)	0(0)
Possible rheumatic fever	2(3)	4(5)	0(0)	6(8)
Post-infectious arthritis	5(7)	8(11)	1(1)	14(18)
Arthritis associated with a known rheumatic disease	10(13)	12(16)	4(5)	26(34)
Ankylosing spondylitis	6(8)	0(0)	0(0)	6(8)
Rheumatoid arthritis ⁵⁰				
Definite	0(0)	3(4)	3(4)	6(8)
Possible	1(1)	1(1)	0(0)	2(3)
Psoriatic arthritis	1(1)	2(3)	0(0)	3(4)
Sarcoidosis	0(0)	3(4)	0(0)	3(4)
Still’s disease	1(1)	1(1)	0(0)	2(3)
Vasculitis	1(1)	2(3)	1(1)	4(5)
Arthralgia/myalgia/tendinitis	5(7)	12(16)	8(11)	25(33)
Total	23(30)	40(53)	13(17)	76(100)

Table 2 Preceding clinical infections and HLA-B27 in patients with high ASO titre and various rheumatic symptoms

Preceding infection	No (%) of patients		
	HLA-B27+	HLA-B27–	Not typed
Respiratory tract infection	11(14)	21(28)	8(11)
Urogenital infection	1(1)	1(1)	0(0)
Gastrointestinal infection	0(0)	0(0)	0(0)
Dental infection	1(1)	0(0)	1(1)
Skin infection	0(0)	3(4)	1(1)
Bacteraemia	0(0)	1(1)	1(1)
No known infection	10(13)	14(18)	2(3)
Total	23(30)	40(53)	13(17)

If the 43 patients in series I are divided into HLA-B27 positive and negative groups independent of the clinical diagnosis, it seems that the HLA-B27 positive patients had a longer duration of rheumatic symptoms than the HLA-B27 negative patients. Ten (71%) of 14 HLA-B27 positive patients had joint or muscle symptoms lasting for over six months compared with 11 (38%) of 29 of the HLA-B27 negative patients ($p < 0.10$).

Discussion

The present study shows that acute joint or muscle symptoms, or both, associated with a high ASO titre in adults are now seldom due to classical rheumatic fever in Finland. None of the 76 patients fulfilled two major criteria for definite rheumatic fever and only six patients fulfilled the revised Jones' criteria for possible rheumatic fever.

It is customary in Finland to determine the ASO titre of all patients suspected to have rheumatic fever or post-infectious arthritis. It is therefore probable that these subjects represent almost all the cases of rheumatic fever seen in our hospital during the study period. Some patients with lower ASO titres or other evidence of recent streptococcal infection might have been lost as we used a high ASO titre as the diagnostic criteria. It is evident, however, that classical rheumatic fever with two major manifestations is now a rare disease in Finland. Differential diagnosis between rheumatic fever and other rheumatic diseases with a high ASO titre may become increasingly difficult in spite of the revised form of Jones' criteria. For instance, the differential diagnosis between possible rheumatic fever and post-infectious arthritis in our study is partly arbitrary. The most important differences between these patient groups were only one joint affected and fever less than 37.5°C in the post-infectious arthritis syndrome compared with febrile polyarthritis in the patients with possible rheumatic fever.

HLA-B27, which is associated with ankylosing spondylitis and reactive arthritis triggered by various bacterial species, was significantly overrepresented (30 v 14%) in these patients compared with the healthy Finnish population.⁴⁶⁻⁴⁸ The frequency of HLA-B27 in the reactive arthritis group also was higher (35%) than in the overall population. There are some reports which suggest that β haemolytic streptococci may trigger reactive arthritis in HLA-B27 positive patients.²⁶⁻²⁹

From a retrospective study such as this it is difficult to draw any firm conclusions about the role of streptococcal infection as a triggering factor in various arthritis syndromes. Some cases may have been coincidental streptococcal infections in patients with rheumatic disease. However, the present data support the theory that β haemolytic streptococci may trigger other forms of reactive arthritis in addition to rheumatic fever. One form of reactive arthritis could be associated with HLA-B27. Seven patients in the reactive arthritis group had a

high ASO titre and HLA-B27 positivity, with no evidence of gastrointestinal or urogenital pathogens such as salmonella, yersinia, or chlamydia, which are currently the most common triggering infections in Finland in patients with reactive arthritis.²⁹ In addition, most of these patients had some preceding respiratory infection, further supporting the role of streptococci as a triggering infection in these patients. It must be remembered, however, that not only group A but also groups C and G β haemolytic streptococci may raise the ASO titre^{29 41} and groups C and G have also been associated with post-infectious rheumatic syndromes.⁴² In adult patients 20% of the cases of tonsillitis may be caused by groups C and G streptococci.⁴⁹ It is therefore possible that groups C and G instead of group A streptococci may have been the causative agents in these patients.

The present data are compatible with the findings that high ASO titres or other evidence of streptococcal infection are also found in patients with known rheumatic or connective tissue disease.³⁰⁻⁴⁰ It is difficult to judge the possible role of streptococcal infections in these patients and it is possible that streptococcal infections are only coincidental events in these patients. We cannot exclude the possible role of streptococcal infections in the aetiopathogenesis of some known rheumatic syndromes, however.

As a summary, we conclude that at least the classic form of rheumatic fever is a rare disease in Finland in adult patients with acute rheumatic symptoms and a high ASO titre and that positivity for HLA-B27 in these patients is overrepresented compared with the general population.

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