Department of Medicine,
Hammersmith Hospital,
London W12 0HS

Case presented by:
T Vyse, MRCP, medical
registrar

Chairman:
S R Bloom, FRCP, professor of
endocrinology

Discussion group:
A So, MRCP, senior lecturer,
rheumatology unit
J Cleland, MRCP, senior
lecturer, clinical cardiology
D N S Kerr, FRCP, dean of
Royal Postgraduate Medical
School
A J Rees, FRCP, professor of
nephrology
J H Baron, FRCP, senior
lecturer, gastroenterology unit

Series edited by:
Dr Robert Winter.

BMJ 1991;302:518-20

Rheumatic fever: changes in its incidence and presentation

Tests for streptococcal antigens needed in young people with polyarthritis

When a young patient presents with polyarthritis the differential diagnosis includes rheumatic fever. Our case shows clinical features that have occurred in several outbreaks and that suggest that the incidence and presentation of rheumatic fever may be changing.

Case history

A 14 year old girl presented with polyarthritis. She had been in good health until one month before admission when she had sustained abrasions above both ankles while ice skating in a pair of new boots. The lesions had not healed immediately and had become secondarily infected. Ten days before admission she presented to her local casualty department with ulcers above each lateral malleolus; a swab was taken for bacterial culture and amoxycillin and flucloxacillin were prescribed. Within three days she developed fever and chills associated with pain and swelling around both ankles. Pain and swelling around the left knee and, later, the wrist and metacarpophalangeal joints of the right hand developed over the next few days, and she was unable to walk because of pain. She did not have a sore throat and had no ocular or gastrointestinal symptoms. She had not recently been abroad, and she lived with her parents and five siblings, all of whom were well; there was no family history of joint disease.

On examination she was feverish but had no rash, lymphadenopathy, or pharyngitis. She had a sinus tachycardia of 96 per minute, and her blood pressure was 120/60 mm Hg. There was an added third heart sound, but she had no cardiac murmurs. Neither her liver nor her spleen was enlarged. Asymmetrical polyarthritis affected her left knee, both ankles, the right wrist, the fourth and fifth metacarpophalangeal joints, and all proximal interphalangeal joints of the right hand. All metatarsophalangeal joints of the left foot were affected as were the lateral two metatarso-

phalangeal joints of the right foot. Healing ulcers were present above each lateral malleolus (fig 1).

Investigations showed her to have normochromic, normocytic anaemia with a haemoglobin concentration of 97 g/l, and her peripheral blood leucocyte count was $10 \times 10^9/l$ with a normal differential count. Electrophoresis of her haemoglobin gave normal results as did an automated biochemical profile. Her random glucose concentration was 5.3 mmol/l. Urine analysis showed trace proteinuria on dipstick testing, but microscopy showed no cells or casts.

Her erythrocyte sedimentation rate was elevated at 134 mm in the first hour and her C reactive protein concentration was 213 mg/l (normal less than 10 mg/l). Latex agglutination assay for rheumatoid factor and an autoantibody screen gave negative results. Immunoglobulin concentrations were: IgG 25.2 g/l, IgA 3.14 g/l, and IgM 1.12 g/l (normal ranges IgG 5.0-16.0 g/l, IgA 1.25-4.25 g/l, IgM 0.5-1.8 g/l); the electrophoretic strip showed raised concentrations of α_1 , α_2 , and γ globulins. She had normal values for the third and fourth complement components and total haemolytic complement.

Repeated blood cultures from samples taken on admission were sterile, but the swabs of the leg ulcers, taken before antibiotic therapy 10 days earlier, grew *Staphylococcus aureus* and a group A β haemolytic streptococcus. Her midstream specimen of urine was sterile, and a throat swab showed only normal respiratory flora. Aspiration of her left knee joint provided 20 ml of yellow, non-viscous fluid containing 2.9×10^6 cells/l (mostly neutrophils). The fluid was sterile on bacterial and mycobacterial culture. A Paul-Bunnell test for infectious mononucleosis and a test for hepatitis B surface antigen gave negative results. Her serum titre of streptolysin O antibodies was appreciably raised at 600 IU (normal less than 200 IU).

Radiographs of her chest and both ankles appeared normal. An electrocardiogram showed sinus tachycardia (100 beats per minute) with a PR interval of 0.20 seconds but no other abnormalities.

Treatment with naproxen was started, and within 36 hours her fever resolved. Her joint symptoms also improved considerably, and after four days she was walking without difficulty and was discharged. At follow up four weeks later her ankle ulcers had healed. She described mild morning stiffness in the right wrist and left knee, which was worse when she did not take her non-steroidal anti-inflammatory drug. Her erythrocyte sedimentation rate was 123 mm in the first hour and her C reactive protein concentration 201 mg/l. For the first time an apical pansystolic murmur was heard, indicating mitral regurgitation. Doppler echocardiography showed good left ventricular function. Her mitral valve leaflets were thickened, and there was partial fusion of the two commissures, indicating mitral stenosis (figs 2 and 3). These echocardiographic abnormalities were consistent with a diagnosis of rheumatic heart disease.

On follow up six months later she was completely well with no arthritis, although the cardiac murmur persisted. Her erythrocyte sedimentation rate and C reactive protein had returned to normal ranges, and

FIG 1—Ulcer above right lateral malleolus

FIG 2—M mode echocardiogram across mitral valve showing mobile anterior leaflet but fixed posterior leaflet. Left ventricular cavity is normal and there is good function. (Right) Two-dimensional short axis view of left ventricle at mitral valve level showing mild commissural fusion

FIG 3—Continuous wave Doppler echocardiogram across mitral valve during diastole showing early and late filling of left ventricle. Pressure at half time was calculated at 100 ms, which gives estimated effective mitral orifice area of 2.2 cm² (normal >3.5 cm²)

her streptolysin O antibody titre was less than 200 IU. A repeat echocardiogram showed no new changes. She no longer required anti-inflammatory drugs but continued to take phenoxymethylpenicillin 250 mg twice daily as prophylaxis.

Comment

The diagnosis of rheumatic fever in this case was supported by microbiological and serological evidence of infection with a group A β haemolytic streptococcus; polyarthritides that responded rapidly to an anti-inflammatory drug; a persisting acute phase response; and cardiac disease with the development of a cardiac murmur and with reversible prolongation of the PR interval on electrocardiography and compatible electrocardiographic abnormalities.

These clinical features satisfy the revised Jones criteria for diagnosis of rheumatic fever,¹ but reactive polyarthritides has also been reported after streptococcal infection without evidence of the heart being affected.² This type of reactive arthritis has been reported mainly in children and young adults, and some of these cases may satisfy the Jones criteria, with one major and two minor criteria being present.

The incidence of rheumatic fever has fallen considerably this century, both in the United States and in western Europe. At the turn of the century the quoted incidence was 200 per 100 000 in Minnesota, which compares with current figures of less than one per 100 000.³ The decrease has been particularly noticeable since 1940, and a decrease in the severity of the cardiac lesions has been reported based on long term follow up of these patients. Although there has been a fall in Western countries, the World Health Organisation data show that the incidence of rheumatic fever has increased in non-industrialised countries. Several factors may have contributed to the fall in the incidence in the United States and western Europe: the introduction of penicillin, a general reduction in the frequency of streptococcal carriage in the community, better social and environmental conditions, and a reduction in the virulence of rheumatogenic strepto-

cocci.³ During 1985-8, however, four separate outbreaks of rheumatic fever occurred in the United States. About 100 cases were reported, representing a 20-fold increase over the expected incidence in the affected areas. Most cases were in white, middle class children and young adults aged 3 to 24 years.^{4,8}

On review several clinical features common to these outbreaks were found to differ from the classic descriptions of rheumatic fever. Less than half of the patients had a history of sore throat (also absent in our patient), and there was a low rate of isolation of streptococci by culture (in some reports this could be accounted for by previous treatment with antibiotics). These reports all emphasise the importance of serological diagnostic tests for recent infection, and in most cases a high streptolysin O antibody titre corroborated the diagnosis. Some authors also recommended routine measurement of antibodies against other streptococcal antigens such as DNase B antibodies.² Reports on the diagnostic sensitivity of DNase B antibodies, however, are conflicting.⁹

As the age of the patients increased there seemed to be a propensity towards additive polyarthritides as seen in our patient, rather than migratory polyarthritides, which is the classic description in rheumatic fever. A higher incidence of carditis was found in these four outbreaks than in earlier accounts, with almost 90% of patients being affected in one series,⁴ but this may reflect more sensitive means for its detection with Doppler echocardiography. In all recent outbreaks cutaneous and neurological manifestations were uncommon.

The reduced prescription of antibiotics as a routine treatment for sore throat may be a factor in these outbreaks. The increased incidence in most of the outbreaks was not explained by increased streptococcal carriage, but the M-18 serotype was common among those streptococci that were cultured. This serotype is known to be a potent rheumatogenic strain, suggesting that increased pathogenicity may account for the increased incidence in the areas where outbreaks occurred.

Discussion

SRB: Could you clarify the differential between post-streptococcal polyarthritides and rheumatic fever?

AS: Acute rheumatic fever was diagnosed on the basis of the revised Jones criteria¹ as the disease fulfilled two major and two minor criteria. At her initial presentation, however, when there was no evidence of cardiac disease, the differential was between post-streptococcal reactive arthritis and juvenile chronic arthritis. Reactive arthritis is a label for arthritis that follows an identified infection when the infectious agent is not isolated from the joint itself. The term post-streptococcal reactive arthritis was first used to describe cases of polyarthritides with a clinical pattern that differs from that seen in rheumatic fever.² In post-streptococcal reactive arthritis most cases fulfil one major (arthritis) and often one or two of the minor Jones criteria (a raised erythrocyte sedimentation rate and fever) and strictly would therefore have fulfilled the criteria for a diagnosis of rheumatic fever. Doctors are often reluctant to diagnose rheumatic fever in the absence of other substantive features and I therefore regard post-streptococcal reactive arthritis as lying within the same spectrum of disease as rheumatic fever. Arthritis is a common presenting feature of rheumatic fever, being present in 70% of cases. Typically it affects the larger joints, such as knees, ankles, and wrists, and is migratory. In a recent report from Australia of five patients with arthritis in association with a raised streptolysin O antibody titre and sometimes positive throat cultures for group A

streptococci the pattern of arthritis varied from monoarticular to symmetrical polyarticular disease.² In recent reports of rheumatic fever from North America polyarthritis often did not show the migratory pattern.¹ We must therefore be more alert to the possibility of rheumatic fever as a cause of polyarthritis in the young, and seek evidence of streptococcal infection either by direct culture or by serology.

Another interesting observation that has emerged from the North American outbreaks is that certain M types of group A streptococci are more prevalent, in particular the M-18 serotype, which has also been termed "rheumatogenic." Earlier studies had implicated another M type as rheumatogenic, although there is no clear explanation of how rheumatogenic strains lead to joint disease. Unfortunately, the serotype of the streptococcus isolated from our patient was not determined.

SRB: The point was made that this was a dermatological infection, does this matter when diagnosing the condition?

AS: All the classic descriptions are of rheumatic fever after pharyngitis or throat infection with β haemolytic streptococci. These accounts also state that rheumatic fever is not associated with skin infections, and our case would therefore have been considered unusual. In only half the cases of rheumatic fever is a streptococcal throat infection proved.⁹ None the less our patient may have been a chronic pharyngeal carrier of streptococci, and the leg ulcers could have been contaminated from the mouth source. She had been treated with antibiotics for leg ulcers, and when she was first admitted there had been no indication to perform a throat swab in the absence of symptoms, although in retrospect this would have shown if she was a chronic carrier of the streptococcus later isolated.

SRB: What is the pathophysiological basis of the prolonged conduction time? Why does the lesion persist? We saw the diseased mitral valve and the abnormalities shown on echocardiography.

JC: A prolonged PR interval is common during acute rheumatic fever, although it does not always indicate active carditis. It can readily be reversed by atropine.¹⁰ It seems unrelated to the subsequent development of chronic rheumatic heart disease.

There is cross reactivity between streptococcal antigens and antigens on the myocardial sarcolemma. The initial immune response might expose antigens on the myocardial surface, and patients with acute rheumatic fever show an increase in titres of various heart antibodies. Studies of the recent outbreaks of rheumatic fever in the United States have provided insights into the epidemiology of acute rheumatic fever but have not made appreciable progress in understanding the pathogenesis. As it is uncommon to see the acute stages of rheumatic carditis in western Europe there is little recent information on this topic. The factors controlling inflammation and its resolution as scarring in the myocardium are still poorly understood.

DNSK: Is it known why the nephritogenic strains of streptococcus cause rheumatic and skin disease but the rheumatogenic strains seem not to be associated with renal disease?

AS: Differences in the mucopolysaccharide or some of the other cell wall antigens may be important in accounting for the differing clinical pictures, and the antigen that has been most studied is the M protein. Thus in the rheumatogenic strains M-18 is present, but in the nephritogenic strains M-12, M-14, and M-49 are commonly implicated. The second possibility is that there are host factors that determine disease expression. Some investigators have found that nearly all patients with rheumatic fever possess a B lymphocyte allo-antigen, defined by a monoclonal antibody D8/17, whereas the antigen is found in only a fifth of normal

subjects.¹¹ This alloantigen is not an HLA antigen. Weak HLA associations have also been reported.

SRB: How does that fit with nephritic varieties and also with chorea?

AS: Antigenic mimicry has been invoked to explain the associations of particular strains with different clinical patterns of disease, and cross reactive antibodies have been shown for renal glomeruli and neurones. Whether these cross reactive antibodies are pathogenic is still disputed.¹²

JHB: Thirty years ago a child presenting with rheumatic carditis would have been treated with aspirin and bed rest. Are these treatments now obsolete?

AS: Treatment with non-steroidal anti-inflammatory drugs is probably as effective as aspirin, though aspirin is the conventional treatment. We started treatment with naproxen before rheumatic fever was definitely diagnosed and were impressed by the speed of resolution of her joint and systemic symptoms; she was therefore maintained on naproxen. To my knowledge there is no evidence that non-steroidal anti-inflammatory drugs are better than aspirin in treating this condition. Our patient was resting both as an inpatient and after she was discharged home, yet she still developed carditis.

AJR: Turning to the question of pathogenesis, there have been some elegant studies apparently defining autoantibodies to glomerular basement membrane antigens in patients who have post-streptococcal nephritis¹³ and localising those particular motifs of autoantigenic amino acids on the surface of nephritogenic streptococci.¹⁴ These studies have also shown that binding of autoantibodies to normal human kidney can be prevented with these. Have similar observations been made in patients with arthritis or carditis after streptococcal infection?

AS: No.

SRB: Given the evidence of carditis based on prolonged conduction time and the generally poor long term prognosis after carditis, should the initial management have been different? For example should corticosteroids have been given after antibiotics. As I understand it the valvitis or myocarditis can continue, can these be halted?

AS: There is no evidence that steroids are better than aspirin in reducing the severity of the carditis.

We thank Miss J Joshi for performing the echocardiography.

- 1 American Heart Association. Jones criteria (revised) for guidance in the diagnosis of rheumatic fever. *Circulation* 1984;69:204-8A.
- 2 Arnold MH, Tyndall A. Post-streptococcal reactive arthritis. *Ann Rheum Dis* 1989;48:686-8.
- 3 Gordis L. The virtual disappearance of rheumatic fever in the United States: lessons on the rise and fall of disease. *Circulation* 1985;72:1155-62.
- 4 Veasy LG, Wiedmeier SE, Orsmond GS, et al. Resurgence of acute rheumatic fever in the inter-mountain area of the United States. *N Engl J Med* 1987;316:421-7.
- 5 Congeni B, Rizzo C, Congeni J, Sneevivasan VV. Outbreak of acute fever in north east Ohio. *J Pediatr* 1987;111:176-9.
- 6 Wald ER, Dashefsky B, Feidt C, Chiporis D, Byers C. Acute rheumatic fever in western Pennsylvania and the tri-state area. *Pediatrics* 1987;80:371-4.
- 7 Hosier DM, Craenen JM, Teske DW, Wheller JJ. Resurgence of acute rheumatic fever. *Am J Dis Child* 1987;141:730-3.
- 8 Wallace MR, Garst PD, Papadimos TJ, Oldfield EC. The return of acute rheumatic fever in young adults. *JAMA* 1989;262:2557-61.
- 9 Ayoub EM. Acute rheumatic fever. In: Adams FH, Emmanouilides GC, Riemenschneider TA, eds. *Moss's heart diseases in infants, children and adolescents*. 3rd ed. Baltimore: Williams and Wilkins, 1989:692-704.
- 10 Robinson RW. Effect of atropine upon the prolongation of the PR interval found in acute rheumatic fever and certain vagotonic persons. *Am Heart J* 1945;29:378.
- 11 Khanna AK, Buskirk DR, Williams RC Jr, et al. Presence of non-HLA B cell antigen in rheumatic fever patients and their families as defined by a monoclonal antibody. *J Clin Invest* 1989;83:1710-6.
- 12 Zabriskie JB. Streptococcal diseases and their relationship to antigenic mimicry in the group A streptococcus. In: Lachmann P, Peters DK, eds. *Clinical aspects of immunology*. 4th ed. Oxford: Blackwell, 1982:1428-44.
- 13 Kefalides NA, Pegg MT, Ohno N, Poon-King T, Zabriskie N, Fillit H. Antibodies to basement membrane collagen and laminin are present in sera from patients with post-streptococcal glomerulonephritis. *J Exp Med* 1986;163:588-602.
- 14 Kraus W, Beachey EM. Renal autoimmune epitope of group A streptococci specified by M protein tetrapeptide Ile-Arg-Leu-Arg. *Proc Natl Acad Sci USA* 1988;85:4516-20.