Poststreptococcal reactive arthritis

M H ARNOLD AND A TYNDALL

From the Florance and Cope Professorial Department of Rheumatology, The Royal North Shore Hospital of Sydney, St Leonards, New South Wales 2065, Australia

SUMMARY Five cases (three children and two young women) of sterile inflammatory arthritis are described, each preceded by a streptococcal infection. A throat swab from one patient grew group A, β haemolytic streptococci, and in each case unequivocal evidence of seroreaction to streptococcal antigens was present. The long term outcome in all cases was excellent, though one patient (female, 24 years of age) required prophylactic penicillin for three months. The diagnosis of a definite recent streptococcal infection is sometimes difficult as throat swabs may be negative and the diagnostic serological reaction missed unless antibodies to multiple antigens (particularly antistreptolysin O and DNAase B) are tested. These cases may represent a reactive arthritis and should be distinguished from rheumatic fever, streptococcal septic arthritis, viral arthritides, acute rheumatic diseases such as juvenile chronic arthritis, and a monoarticular presentation of seronegative spondyloarthropathy.

A reactive arthritis is defined as a sterile inflammatory arthritis occurring in association with an infection at a distant site.¹ Group A β haemolytic streptococci have long been known to induce such an arthropathy as part of the syndrome of rheumatic fever. This arthritis is migratory, transient, and usually responds to salicylates.²

This paper describes five cases of poststreptococcal arthritis which did not follow the typical pattern of rheumatic fever, were non-carditic, with an apparently benign outcome. The problem of under-interpretation or overinterpretation of streptococcal serological results is also discussed.

Case reports

PATIENT 1

An eight year old boy was transferred from a country hospital with a six week history of polyarthritides affecting proximal interphalangeal joints, both wrists, shoulders, knees, and ankles. A fever was present, without a specific pattern. A non-specific rash (not typical of Still's disease, or erythema marginatum) and cervical and inguinal lymphadenopathy were evident. He was systemically unwell. This illness had been preceded by a mild

upper respiratory tract infection, including a sore throat. Investigations showed an erythrocyte sedimentation rate of 30 mm/h, antistreptolysin O titre of >800 units (normal for age <200). Throat swab grew rhinovirus and herpes simplex virus. Neutralising antibodies to these viruses were not detected. All other investigations, including electrocardiogram, antinuclear antibodies, rheumatoid factor, and immunoglobulins, were normal or negative. He was treated with aloxiprin, and within 11 weeks there was complete resolution of the illness. Review at three months was normal, and the antistreptolysin O titre was <200 units.

PATIENT 2

A 14 year old boy developed a mild sore throat, pleuritic central chest pain, a maculopapular truncal rash, and low grade fever. Two days later a fixed progressive symmetric, and very painful polyarthritides ensued. Most joints excluding the axial skeleton were involved during the three week course of the illness. He was reviewed at three months and was perfectly well. DNAase B was 1280 units (normal for age <160 units) at presentation, and two weeks later was 1920 units. Antistreptolysin O titre remained normal at 160 units throughout the illness and convalescence. Throat swab was sterile. Electrocardiogram, chest x ray, antinuclear antibodies, rheumatoid factor, and viral serology (rubella, adenovirus, Coxsackie B, Ross River, and Epstein-Barr viral capsid antigen) were normal or negative.

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Correspondence to Dr A Tyndall, c/o The Florance and Cope Professorial Department of Rheumatology, The Royal North Shore Hospital of Sydney, St Leonards, New South Wales 2065, Australia.

PATIENT 3

A 31 year old woman was referred two weeks after her third episode of acute right hip pain in three months. Each episode had been preceded by an upper respiratory tract infection. During the first episode hip aspiration yielded sterile inflammatory fluid, with a total white cell count of $38 \times 10^9/l$, 80% of which were neutrophils. She was treated with parenteral flucloxacillin and recovered fully within two weeks. The second and third episodes of hip pain were treated with oral erythromycin and non-steroidal anti-inflammatory drugs, to which she responded fully. Investigations three months after the third episode showed an antistreptolysin O titre >800 units, which declined to <200 units three months later. At all times rheumatoid factor, antinuclear antibodies, electrocardiograph, and biochemistry remained normal. HLA-B27 was not detected, and plain x rays of the sacroiliac joints were normal.

PATIENT 4

This 24 year old woman presented with her fourth episode of painful left knee swelling. Synovial fluid was sterile with a white cell count of $4 \times 10^9/l$, 75% of which were neutrophils. There was no evidence of psoriasis or history or findings suggestive of a seronegative spondyloarthropathy. Throat swab grew group A β haemolytic streptococci, and antistreptolysin O titre was raised to 1/640 on this occasion. In view of her recurrent arthropathy, and failure to respond to non-steroidal anti-inflammatory drugs, prophylactic oral penicillin was administered. No further episodes had occurred at follow up three months later. On review 12 months after referral she remained well.

PATIENT 5

This three year old girl presented five days after the onset of a sore throat with a painful, swollen right knee. She refused to walk. Physical examination was notable for facial erythema and a right knee effusion. Erythrocyte sedimentation rate was 30 mm/h, antistreptolysin O titre was <200 units, and DNAase B was >2560 units on presentation. Antinuclear antibodies, rheumatoid factor, immunoglobulins, and complement profile were all normal. Antibodies to Ross River virus, rubella, Epstein-Barr viral capsid antigen, and parvovirus were not detected. As she remained clinically well, and her physical signs were resolving within 24 hours without antibiotics, joint aspiration was not performed. Five days later there was complete resolution. Convalescent serology showed an antistreptolysin O titre of 125 units and DNAase B of 1280.

At follow up three months later she remained perfectly well.

Discussion

These five unusual cases suggest that a reactive arthritis may have been precipitated by a streptococcal infection. None of these patients can be considered to satisfy the Jones criteria for rheumatic fever.³ The non-migratory nature of the arthritis, the lack of cardiac involvement, and the absence of subcutaneous nodules, erythema marginatum, and chorea make a diagnosis of rheumatic fever untenable. Clearly there has been a decline in the incidence and severity of the non-suppurative complications of streptococcal disease in this century, even before the introduction of antibiotic treatment. Scarlet fever is no longer a fatal infection of children, and clinical rheumatic fever is now rarely seen in developed countries.⁴ This probably represents a host resistance change as all the various serological subtypes of group A streptococcus have to some degree an interdependent existence, and all would need to undergo similar modification to account for the change in disease expression. Certainly, true rheumatic fever is now less often preceded by the once familiar acute exudative tonsillitis. In addition, true rheumatic fever in adults is less likely to be carditic but more likely to produce arthritis in adults as opposed to children.

Three patients presented with an inflammatory monoarthritis, septic arthritis being excluded by joint aspiration in two cases and spontaneous resolution before diagnostic aspiration could be performed in patient No 5. Streptococci of various Lancefield groups may cause an oligoarticular or polyarticular septic arthritis in association with bacteraemia.^{5,6} This is usually asymmetric with a slow response to appropriate antibiotic treatment and a generally poor outcome.^{5,6} Monoarticular or oligoarticular arthritis in conjunction with other distant infections such as bacterial meningitis is seen in 2–3% of cases.^{7–11} A diphasic presentation has been noted, with an early septic arthritis, and later sterile monoarthritis or oligoarthritis, with a benign outcome. It is possible that these cases may represent treated, 'culture negative' septic arthritis, particularly in the case of bacteraemic patients. Late 'reactive' arthritis has been noted in children after *Haemophilus influenzae* meningitis,⁷ and after meningococcal^{8,9} and pneumococcal meningitis,¹⁰ and it has been postulated that immune complexes may in part be responsible for the development of a benign monoarthritis or oligoarthritis.^{8–11} Viral arthritides, such as that associated with parvovirus B-19 infection, may produce a symmetric polyarthritis, and rarely a

monoarthritis or oligoarthritis.^{12 13} Patient 5 presented with an inflammatory monoarthritis and facial erythema consistent with the 'slapped cheek' appearance seen in erythema infectiosum. Definite serological evidence of a recent streptococcal infection was present, however, and seroconversion to parvovirus B-19 did not occur. Similarly, there was no evidence to substantiate recent or intercurrent viral infection in the other patients.

Reactive arthritis after streptococcal infection has been reported by two groups.^{13 14} Hubbard and Hughes and Gerster *et al* described HLA-B27 positive patients who developed lower limb large joint oligoarthritis,^{14 15} sacroiliac joint pain,¹⁴ dactylitis, and calcaneal erosions¹⁵ after a streptococcal sore throat¹⁴ or a typical case of rheumatic fever.¹⁵ Interestingly, none of our patients developed dactylitis, enthesitis, or other extra-articular accompaniments of a reactive arthritis. Psoriasis, spondyloarthritis, or inflammatory bowel disease could not be implicated as the cause of the arthropathy in our patients. HLA-B27 was not detected in patient No 3, the only patient in whom HLA studies were performed.

Streptolysin O is produced by most group A streptococci, and also groups C and G. Antistreptolysin antibodies rise between one and four weeks after infection and fall after a period of three to six months. Laboratory reference ranges fluctuate according to the age of the patient and the time of year. Normal values in Sydney are currently quoted as <150 units for children under five years of age and <300 in older individuals. A prospective study of 19 children conducted over a 12 month period in the United Kingdom, however, showed sustained antistreptolysin O titres of 400–800 units in three children without clinical correlation.¹⁶ This emphasises the need to show changing, unequivocally raised titres before a positive diagnosis can be made.

Most group A streptococci produce significant amounts of the exoenzyme DNAase B. Apart from groups C and G, no other streptococci produce DNAase B in significant quantities. Levels are considered to be raised if >80 units in a child under 5 years of age, >320 units between 5 and 19 years of age, and >160 in individuals over the age of 20. DNAase B antibodies are raised after cutaneous and upper respiratory tract infections, whereas the antistreptolysin O titre is often not raised after cutaneous infections. DNAase B antibodies have the added diagnostic advantage of not being subject to the false positives which are encountered in the antistreptolysin O titre test as a result of liver disease, bacterial growth in the specimen, and oxidation of the streptolysin O molecule.

It is recommended that at least the antistreptoly-

sin O titre and DNAase B antibodies are always tested in suspected streptococcal infection. Multiple simultaneous antigen testing using combined reagents may be falsely raised and are subject to batch variability. Unequivocally high levels are a useful finding, but intermediate titres do not, in themselves, confirm a recent streptococcal infection (Dr J Tapsall, personal communication).

In summary, these cases suggest a streptococcal cause for the development of a benign reactive arthritis in five patients, on the basis of definite serological evidence of a recent streptococcal infection. The possibility of a reactive arthritis should be considered in arthritides after infectious diseases of sites other than the gastrointestinal and genitourinary tracts.

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