Lesson of the week

Difficulties in diagnosing acute rheumatic fever—arthritis may be short lived and carditis silent

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Think of rheumatic fever in all cases of acute childhood arthritis

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The incidence of acute rheumatic fever has increased in the developed world.[1–4] Although the criteria for diagnosis are well known, the clinical symptoms needed to make a diagnosis do not always arise concurrently and the initial illness may be mild and short lived. Isolated arthritis is the presenting symptom in 14-42% of patients.[3–5] There may be no history of sore throat, or this symptom may not be mentioned by the patient,[5] and the carditis may be silent.[6 7] The diagnosis will be missed if appropriate investigations are not carried out during the acute illness. These patients are susceptible to recurrent attacks of rheumatic fever, and damage to heart valves becomes increasingly severe with each subsequent attack.[8 9] Children are affected more than adults and may present to their general practitioners or to accident and emergency, orthopaedic, rheumatology, or paediatric departments. To highlight potential diagnostic problems, we describe three cases of rheumatic fever in young people who presented to one musculoskeletal centre in a six month period.

Case reports

Case 1

A 3 year old girl was taken to an accident and emergency department with a painful swelling of her right knee that came on quickly. She had had a mild cough, sore throat, and low grade temperature for 10 days. There was no history of trauma. No fracture was seen on a radiograph, and the girl was sent home. Two days later the girl's right wrist swelled. She was admitted to the Nuffield Orthopaedic Centre for assessment. When she was examined her temperature was 37.4°C and her pulse was regular (80 beats per minute). She had large infected tonsils, posterior cervical lymphadenopathy, and a grade 2/6 basal ejection systolic murmur. Her wrist and knee were warm, red, swollen, and tender, but she had no rashes or subcutaneous nodules. By the following morning she was afebrile and her joint swelling had resolved spontaneously. A provisional diagnosis of viral arthritis was made and she was discharged home. Her general practitioner prescribed a course of amoxicillin for her cough and at follow up two weeks later she was completely well.

The heart murmur persisted, however, and as it had not been noted previously she was referred for paediatric cardiological assessment. Her electrocardiogram was normal. An echocardiogram showed a small posterior pericardial effusion with thickening of the mitral valve leaflets and shortening of the chordae tendinae. Blood samples taken two weeks after the initial presentation were strongly positive for the antistreptolysin O test (800 Todd units) but were negative for antinuclear antibodies and viral serology. A family history of rheumatic fever in both maternal grandparents was elicited. A diagnosis of acute rheumatic fever was made, based on the presence of migratory polyarthritis, carditis, and serological evidence of streptococcal infection. She was treated with anti-inflammatory doses of aspirin for six weeks, until her inflammatory markers and antistreptolysin O test results returned to normal. Repeat echocardiography showed resolution of the pericardial effusion but residual thickening of the mitral valve and slightly shortened chordae tendinae. The murmur at presentation was a pulmonary flow murmur, not related to her carditis. We plan for her to continue prophylactic treatment with penicillin at least until she leaves school.

Case 2

A 10 year old boy was referred with a one week history of sore throat and headache and a one day history of irritable left hip. The hip looked normal on radiography. An ultrasound scan showed an effusion from which 3 ml of clear, sterile fluid was aspirated. The boy's symptoms improved immediately after aspiration and although markers of inflammation were raised (erythrocyte sedimentation rate, 60 mm in first hour; C reactive protein, 77 mg/l), he was discharged home with a probable diagnosis of viral related arthritis.

The boy returned to school and was completely well for three days. He then developed bilateral ankle pain and was readmitted to hospital. At the time of physical examination he was fractious and had a low grade temperature, bilateral ankle synovitis, and an erythematous serpiginous rash over his trunk and upper thighs. His pulse was 84 beats per minute and regular. He had a grade 2/6 basal ejection systolic murmur, but his electrocardiogram was normal. His echocardiogram showed a small pericardial effusion, but was otherwise normal. Markers of inflammation remained high (erythrocyte sedimentation rate, 85 mm in first hour; C reactive protein, 77 mg/l), and an echocardiogram repeated one week later showed some mitral valve thickening and shortening of the chordae tendinae as well as the pericardial effusion.

Despite treatment with oral aspirin and penicillin, the patient developed accelerated diastolic flow velocity across the mitral valve and reduced leaflet excursion. Oral prednisolone was therefore added to his treatment regimen. Subsequent echocardiograms showed gradual improvement of the mitral valve excursion and reduction of the cusp thickening. Group A haemolytic streptococci were cultured from a throat swab taken at the time of admission to hospital. His antistreptolysin O titre was 1200 Todd units and his anti-DNase B titre was 1920 units—strongly supporting a recent streptococcal infection. Viral serology and antinuclear antibody values were negative.

A diagnosis of acute rheumatic fever was made, based on the carditis, arthritis, and the evidence of recent streptococcal infection. The rash was erythema marginatum. The systolic murmur noted at presentation was an innocent pulmonary flow murmur, which was not related to his subsequent carditis. The patient's mitral valve leaflets and chordae tendinae remain slightly thickened, but there is no mitral incompetence and no appreciable valve gradient. He has been slowly weaned off oral prednisolone and aspirin. We plan that he should have long term prophylactic treatment with penicillin.

Case 3

A 17 year old trainee nursery nurse was referred to the rheumatology service in early April with pain and swelling of her left elbow associated with overlying erythema nodosum. She had presented with similar symptoms in early April on the previous two years. On those occasions she had been woodland camping with cub scouts, but gave no history of insect bites or upper respiratory infections. Orthopaedic surgeons, paediatricians, and haematologists (as the resolving erythema nodosum looked like bruises) had investigated the patient. Results of investigation of joint aspirate, magnetic resonance imaging, inflammatory markers, and clotting screens were normal. On both previous occasions the patient had been treated empirically with flucloxacillin for two weeks, and her symptoms had resolved completely after four weeks. The third episode had started on 1 April 1998, but on this occasion she had not been camping. The patient noted a sore throat which she believed had developed two days after the elbow pain.

At the time of physical examination the patient's temperature was 37.2°C, her pulse rate was 80 beats per minute, she had purulent faeces, but no subcutaneous nodules were evident. A consultant cardiologist detected a grade 1/6 apical systolic murmur. The young woman's elbow was warm, swollen, and tender; the range of movement was reduced; and there was overlying erythema nodosum. Her erythrocyte sedimentation rate was 47 mm in first hour, the C reactive protein value was 130 mg/l, profuse group A streptococci were cultured from a throat swab, and antistreptolysin O titres rose from 200 to 400 Todd units in two weeks. The patient's electrocardiogram was normal. No synovitis or fluid was seen on magnetic resonance imaging and ultrasound scans of her elbow.

Echocardiograms four and eight weeks later showed a thickened mitral valve with shortened chordae tendinae and mild mitral regurgitation consistent with acute rheumatic damage. One maternal grandmother had had rheumatic fever. The patient was treated with oral penicillin and ibuprofen, and although her sore throat improved quickly, her joint problems took three months to settle completely. The valve leaflet thickening and mitral incompetence had resolved completely at nine month review. Rheumatic fever was diagnosed, based on the evidence of arthritis, carditis, and recent streptococcal infection. The previous episodes may also have been mild attacks of acute rheumatic fever. We have advised the patient to continue prophylactic treatment with penicillin for as long as she works with children.

Investigating acute childhood arthritis

The following investigations should be carried out:

- Full blood count and film
- Erythrocyte sedimentation rate and C reactive protein
- Throat swab
- Urine analysis
- Antinuclear antibody
- Antistreptolysin O test (serial titres)
- Serial anti-DNase B titres if antistreptolysin O titres are low/borderline and suspicion is high
- Viral titres (parvovirus, rubella, Epstein-Barr, cytomegalovirus, hepatitis)
- Blood cultures
- Arthrocentesis (if septic arthritis suspected)
- Plain radiographs (to exclude trauma, tumour, and infection)

If streptococcal infection or systemic juvenile chronic arthritis is suspected:

- Electrocardiograph (look for prolonged PR interval)
- Chest radiograph (look for cardiomegaly, heart failure, infection)
- Echocardiogram (if there are cardiac signs or evidence of group A streptococcal infection)

Discussion

It is important to make a clear diagnosis (box) of acute rheumatic fever so that valvular damage can be minimised during the initial attack and further episodes and long term sequelae prevented with prophylactic antibiotic treatment. However, it is also important not to overdiagnose the condition as this might lead to morbidity from unnecessary use of antibiotics and unwarranted anxiety in patients and their families. The future insurance and employment prospects of these patients may also be adversely affected by a diagnosis of rheumatic fever.

Two of our cases show that the arthritis associated with acute rheumatic fever may be migratory and short lived. If appropriate tests to establish group A streptococcal infection are not taken at presentation, the opportunity may be missed. There may be no history of sore throat,[6] especially in younger children, who are poor at localising sites of illness. Examination of the fauces and throat swab should therefore be routine for all children presenting with arthritis. Current tools used for diagnosing streptococcal illness are imperfect. The throat swab will be positive in only a third of patients infected with group A streptococcus before antibiotic treatment, and in only a tenth of patients afterwards.[10] In addition, a positive culture may show a chronic carrier state and not recent infection. Ideally, a positive throat culture plus a sequential rise in titres shown by serological tests will confirm recent group A streptococcal infection. Since antistreptolysin O titres remain negative in 20% of patients with acute rheumatic fever, a second streptococcal serum antibody test such as the anti-DNase B titre should also be used. When the two tests are combined, the sensitivity rises to over 90%.[1 11] The anti-DNase B test detects antibodies against the deoxyribonuclease B enzyme produced by most group A streptococci.[12] It is more time consuming and expensive than the

antistreptolysin O test, and should be used if clinical suspicion is high, throat cultures are negative, and the antistreptolysin O test result is borderline or low.

Suspicions of diagnosis

All three patients presented with acute arthritis. In communities where rheumatic fever is rare, the arthritis is difficult to distinguish from that associated with a viral infection (see box). It occurs early in the illness, at a time when anti-streptococcal antibody titres should be rising, underlying the need to take timely laboratory samples. The arthritis is non-erosive, rarely lasts more than four weeks, and responds well to aspirin and non-steroidal anti-inflammatory drugs. Patients who have isolated persistent (rather than migratory) arthritis and group A streptococcal infection are usually classed as having post-streptococcal reactive arthritis. The relation between post-streptococcal reactive arthritis and acute rheumatic fever is debated, but as these patients are prone to subsequent attacks of acute rheumatic fever and carditis they are usually given the same advice about antibiotic prophylaxis patients with acute rheumatic fever.[10 13–15]

Two of our patients had easily audible heart murmurs, which raised our suspicions about the diagnosis of acute rheumatic fever. In both cases the murmur was innocent and the rheumatic lesions (trivial mitral stenosis and pericardial effusion) were clinically silent. In the third case, the mitral murmur was very quiet. The reported incidence of silent carditis varies between 7% and 47%, depending on the phase the disease has reached when the echocardiography is performed.[3–7] Echocardiography with colour Doppler flow is the most sensitive technique for detecting cardiac involvement. Progressive mitral valve thickening and progressive chordal shortening or a combination of aortic and mitral incompetence with cusp thickening are changes specific for acute rheumatic fever. Pericardial effusion or reduced ejection fraction are non-specific, but establish that the heart has been affected. These findings should lead to repeated echocardiograms over the next three weeks, as valvular involvement may follow. Thickening of the mitral valve together with chordal elongation and valve incompetence can be difficult to distinguish from a congenitally myxomatous valve. However, if these findings are associated with a reduced ejection fraction or serial scans show an evolving picture, the combined changes are also specific for rheumatic fever. In the three patients described here, the diagnosis of acute rheumatic fever was established only after echocardiography.

It is pertinent that two of our patients had a family history of rheumatic fever. Some HLA types are more susceptible to this disease than others.[16]

Guidelines for diagnosing the initial attack of rheumatic fever

If supported by evidence of preceding group A streptococcal infection, two major manifestations or of one major and two minor manifestations indicate a high probability of acute rheumatic fever:[1]

Major manifestations

- Carditis
- Polyarthritis
- Chorea
- Erythema marginatum
- Subcutaneous nodules

Minor manifestations

Clinical findings

- Arthralgia
- Fever

Laboratory findings

- Raised acute phase reactants (erythrocyte sedimentation rate, C reactive protein)
- Prolonged PR interval
- Supporting evidence of antecedent group A streptococcal infection
- Positive throat culture or rapid streptococcal antigen test
- Raised or rising streptococcal antibody test

Changing pattern of acute rheumatic fever

The incidence of rheumatic fever has risen, but the experience of most doctors in this country in recognising and treating the condition is limited. Patients and doctors are currently discouraged from investigating and treating sore throats.[17] Debate continues on optimal primary prevention, acute treatment, and secondary prophylaxis regimens as the risk of recurrent acute rheumatic fever varies between populations.[18 19 20] It is estimated that without antibiotic prophylaxis patients with acute rheumatic fever but no clinical evidence of carditis and those with post-streptococcal reactive arthritis have an 8-10% risk of developing acute rheumatic heart disease over the subsequent five years.[14 21] In general, the risk of recurrent acute rheumatic fever increases with the number and severity of previous attacks, continued exposure to group A streptococcal infection, and economic disadvantage. The risk falls with age and increasing interval since most recent attack. Until specific risk factors (either host or bacterial characteristics) for the development of subsequent carditis are better delineated, antibiotic prophylaxis should be given to both groups of patients. Intramuscular benzathine penicillin (1.2 million units every 3 or 4 weeks) or oral penicillin (250-500 mg twice daily) is usually given until the end of full time education or five years after the last acute attack. Some doctors argue that lifetime prophylaxis should be given.[16 18 19]

Our cases illustrate the changing pattern of acute rheumatic fever. All three patients were from white, middle class families, and had atypical features. Case 1 was a preschool child whose arthritis lasted a short time only. In case 2 the interval between the onset of the sore throat and other symptoms was only one week, although a gap of two or three weeks would usually be expected. Case 3 had prolonged involvement of one joint, which was also affected by erythema nodosum. These atypical features lead us to emphasise that evidence of recent group A streptococcal infection should be sought in all young patients who present with acute arthritis. This should include not only history and examination but also throat swabs and sequential serological tests. All patients who have evidence of group A streptococcal infection together with acute arthritis should be referred for echocardiographic assessment. If the initial echocardiogram is normal and clinical suspicion remains high, the study should be repeated.

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A memorable patient

For want of a bag of blood

I had been working in sub-Saharan Africa for a month, and it was the height of the malaria season. When I first arrived I asked what the transfusion threshold was, and was told, "A haemoglobin of 5 if they are sick; otherwise 3.5." An otherwise perfectly normal little girl was admitted with a haemoglobin of 2.6 and malaria. Like any toddler, she was able to sit, look around, and resist examination. I tried to give her oxygen but, like most toddlers, she would not keep the mask on. However, she had the respiratory distress and metabolic acidosis of severe malaria, and needed blood urgently.

Most children with this life threatening syndrome did well with simple treatments: antimalarials, fluid, and blood. It was the blood that enabled the patient to meet the high oxygen demand from fever and respiratory distress in the face of severe parasite induced anaemia. Many had anaemia even before they had malaria, from a combination of iron deficiency and worms. Despite all the difficulties in running a hospital in a developing country, the blood bank normally did a remarkably good job. Blood was obtained from the relatives of patients, who were not discharged until the blood they used was replaced. Volunteer donors were uncommon. Blood was available, screened, and cross matched at all hours of the day.

The little girl waited over four hours for the blood to arrive. It never did, due to an unusual shortage at the blood bank. She had a fit, arrested, and it was not possible to resuscitate her. Her mother was understandably distraught. I kept thinking how avoidable the whole thing was, for want of a bag of blood.

The girl's death had two consequences for me. Firstly, I gave blood for the first time in my life, overcoming a life long needle phobia. I almost fainted in the hot, humid, dingy room, despite using local anaesthetic cream and being given a drink by the bemused technician. All the local donors just lined up, gave blood, and walked away. Secondly, I learnt the value of blood in severe anaemia. I had never seen anyone die of anaemia without blood loss before, and I realised what a medical emergency it can be.

Not long afterwards a little boy with malaria, anaemia, and respiratory distress arrived grunting and rapidly became unconscious, only to be jeopardised by the absence of a blood bank technician. After one nerve racking hour we were forced to ask our own laboratory technician to group the blood (AB+), and raided the blood bank with the key for a suitable bag—it turned out to be 0+. The emergency transfusion saved his life.

Before going to Africa I was mindful of the risks of blood transfusion where HIV is prevalent. We estimated a prevalence of 4% in the local children. In the West we try to use blood sparingly, but we seldom see patients with such profound anaemia. That child, and many others, taught me that, despite its risks, blood can be a life saving treatment in severe anaemia.

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We welcome articles of up to 600 words on topics such as *A memorable patient, A paper that changed my practice, My most unfortunate mistake,* or any other piece conveying instruction, pathos, or humour. If possible the article should be supplied on a disk. Permission is needed from the patient or a relative if an identifiable patient is referred to. We also welcome contributions for "Endpieces," consisting of quotations of up to 80 words (but most are considerably shorter) from any source, ancient or modern, which have appealed to the reader.