

Arthritis associated with *Salmonella* infections

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Infection should always be considered as a possible cause in a patient presenting with arthritis. The diagnosis can be difficult to make because the arthritis may appear without evidence of infection elsewhere, and it may mimic other arthritides. Moreover, aspiration of the joint may only reveal a sterile serous effusion. Many organisms can cause arthritis. One of the rarer causes of such an arthritis is salmonellosis.

This paper presents seven cases of arthritis associated with *Salmonella* infections. Four of the patients were seen by the author and the other three had attended the same hospital in the previous 5 years. Six of the patients were adults.

Case reports

CASE 1

A woman aged 77 years was admitted to hospital on June 9, 1967, with a history of diarrhoea for 36 hours. She had ischaemic heart disease and osteo-arthritis of the knees and had been treated with steroids for giant cell arteritis for the previous year.

Examination

Both stool and blood cultures yielded *Salmonella typhimurium* Type U 163. She was treated with ampicillin 500 mg. 6-hrly from June 15 to 25, but her condition remained poor and diarrhoea persisted. Her temperature occasionally rose to 99° F. On July 13 the right knee became swollen and tender. At this time the haemoglobin was 10.3 g. per cent., W.B.C. 12,700 per cu.mm., neutrophil count 9,900 per cu.mm., and erythrocyte sedimentation rate 45 mm./1st hr (Wintrobe).

Treatment

The knee was aspirated and 150 ml. cloudy fluid were removed. The fluid contained many polymorphs, and *S. typhi-murium* was cultured from it. Intra-articular ampicillin 500 mg. twice daily was given from July 14 to 28, and treatment was then continued with oral ampicillin 500 mg. 6-hrly until August 19.

Result

Her knee and general condition were much improved, and she was allowed home on September 19 with slight stiffness of the knee.

She died of heart failure 3 months later and no *post mortem* examination was performed. There had been no recurrence of arthritis.

CASE 2

A housewife aged 37 years was admitted to hospital on August 28, 1968, with painful swelling of both knees and conjunctivitis of the right eye. On August 18 she had had diarrhoea which had lasted until August 25.

Examination

The body temperature was 101° F., and she had conjunctivitis and inflamed knees swollen with effusions. The haemoglobin was 14.5 g. per cent., W.B.C. 17,200 per cu.mm., neutrophil count 13,600 per cu.mm., and erythrocyte sedimentation rate 35 mm./1st hr (Wintrobe). The latex-fixation test for rheumatoid factor and the Brucella complement fixation test were negative. The anti-streptolysin-O (ASO) titre and serum uric acid were normal.

X rays of the knees showed only effusions; 20 ml. sterile serous fluid containing a few polymorphs were aspirated from the left knee. Blood cultures were sterile but cultures of the stools yielded *S. enteritidis* Type 11.

Treatment

On August 29 treatment was started with ampicillin 1 g. 6-hrly, but on September 6 the patient developed a rash and cephaloridine 1 g. 6-hrly was substituted. Bactericidal blood levels of this drug were obtained but fever and positive stool cultures persisted until October 17. During this period of treatment she had arthritis of the left ankle from October 3 to 17 and of the left elbow from October 9 to 17. On October 23 she had stiffness of both knees but was otherwise well and the cephaloridine was stopped. She was given methylprednisolone 4 mg. nightly and the joint stiffness disappeared. This drug was continued for one month and then stopped.

Result

She was well 6 months later.

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CASE 3

A male apprentice aged 18 years developed diarrhoea on June 29, 1968. On July 3 he improved but 2 days later he developed painful swellings of both wrists, the left knee, and the right ankle. On July 10 he developed conjunctivitis of both eyes. He had no history of urethritis. His doctor gave him penicillin and erythromycin 250 mg. of each 6-hrly. On July 13 he was admitted to hospital.

Examination

The body temperature was 100° F. and the pulse rate 112. The left knee and right ankle were swollen, painful, and inflamed and he had conjunctivitis. He also had a simple atrial septal defect confirmed by chest x ray and electrocardiogram. The haemoglobin was 11 g. per cent., W.B.C. 8,400 per cu.mm., neutrophil count 4,700 per cu.mm., and erythrocyte sedimentation rate 60 mm./1st hr (Wintrobe). Latex-fixation tests for rheumatoid factor and LE-cells were negative. ASO titre and serum uric acid were normal. X rays of the joints were normal. Blood cultures were sterile and stool culture yielded no pathogens. Sterile serous fluid containing a few polymorphs was aspirated from the knee. Serum agglutinins were found at 1 in 1280 to *S. typhi* Type 0 and at 1 in 160 to *S. enteritidis* H. antigens. He had not had T.A.B. vaccine and on this basis a diagnosis was made of arthritis associated with a *Salmonella* of the enteritidis group.

Treatment

On August 13 treatment was started with ampicillin 500 mg. 6-hrly and continued until August 26, by which day his fever and arthritis had settled. Stiffness in the joints persisted until October 30 but disappeared after he was given methylprednisolone 4 mg. nightly for one month.

Result

9 months later he was quite well.

CASE 4

A 25-year-old policeman developed fever and diarrhoea on February 21 and this lasted until February 25, 1968. On February 28 he developed persistent low back ache and on March 4 pain and swelling of the right fourth toe. Despite treatment with erythromycin 250 mg. 6-hrly the left knee swelled painfully on March 11 and he was admitted to hospital.

Examination

The body temperature was 101°F. and the pulse rate 100. The left knee was painful and swollen by an effusion and the right fourth toe was similarly affected at the metatarsophalangeal joint. The haemoglobin was 13.5 g. per cent., W.B.C. 10,400 per cu.mm., neutrophil count 6,500 per cu.mm., and erythrocyte sedimentation rate 42 mm./1st hr (Wintrobe). The latex-fixation tests for rheumatoid factor and antinuclear factor were negative. The serum Wasserman reaction, gonococcal complement-fixation test, and Brucella complement-fixation test were negative, and the serum uric acid and ASO titre were normal. X rays of the knee and toe showed osteoporosis consistent with infection. Blood cultures were sterile and stool culture yielded no pathogens. The knee was aspirated and yellow slightly turbid fluid was removed.

This fluid contained a few polymorphs and was sterile. Serum agglutinins were present at 1 in 320 to *Salmonella* phase 2H and at 1 in 20 to *S. typhi-murium* H phase I. 0 agglutinins were at first absent but after 2 weeks *S. paratyphi B* 0 antigens agglutinated at 1 in 80. The patient had not had T.A.B. vaccine.

A diagnosis of arthritis in association with *Salmonella* infection was made on the basis of the serological tests.

Treatment

On March 15 treatment was started with chloramphenicol 500 mg. 6-hrly and on March 28 ampicillin was substituted, at first in a dose of 500 mg. 6-hrly but subsequently at 2.5 g. 6-hrly. On May 2 the toe joint was biopsied and the synovial membrane showed non-specific inflammation. The ampicillin was stopped on May 13, by which date the fever had settled and the arthritis was much improved.

Result

By July 3 he had only stiffness in his knees and this did not disappear until October 2. He then returned to work and has had no recurrence in 9 months.

CASE 5

A 19-year-old girl was admitted to hospital in 1963 after one day's vomiting, diarrhoea, and colic. *S. typhi-murium* Type 1a was grown from her stools. She had no fever. After treatment for 10 days with chloramphenicol 500 mg. 6-hrly, she was free from symptoms although still excreting *S. typhi-murium*; 2 weeks after the start of the illness she developed arthritis in the knees, right ankle, and left acromio-clavicular joint.

Examination

The haemoglobin was 11 g. per cent., W.B.C. 9,400 per cu.mm., neutrophil count 6,400 per cu.mm., erythrocyte sedimentation rate 37 mm./1st hr (Wintrobe). The latex-fixation test and gonococcal complement-fixation test were negative and the ASO titre was normal. X rays of the joints were normal. A diagnosis of arthritis following *Salmonella* infection was made.

Treatment

She was started on prednisolone 5 mg. 8-hrly and improved slowly over the next 3 weeks. The erythrocyte sedimentation rate fell slightly. The swelling and stiffness of the knees continued for 3 months and gave her trouble for 2 years.

Result

She has now been well for 2 years.

CASE 6

A 54-year-old Polish lady, who had spent the war in a concentration camp, developed pain in the limb girdles. X-ray examination of the shoulders and pelvis showed calcification in the muscles consistent with cysticercosis. Because of mild diarrhoea the stools were cultured and grew *S. typhi-murium* U 163 for which she was given neomycin 1 g. 6-hrly for 10 days. She developed painful swelling of the wrists and metacarpophalangeal joints 3

months later with the appearance of mild rheumatoid arthritis.

Examination

The haemoglobin was 13·8 g. per cent., W.B.C. 6,500 per cu.mm., neutrophil count 3,000 per cu.mm., and erythrocyte sedimentation rate 7 mm./1st hr (Wintrobe). Latex-fixation tests for rheumatoid factor and L.E.-cells were negative, as were the Wasserman reaction and gonococcal complement-fixation test. X rays of the hands were normal. Stool culture yielded no pathogens.

Treatment

She was treated with paracetamol and the arthritis improved after 5 months; the latex-fixation test remained negative.

Result

She had no recurrence for 3 years.

CASE 7

A girl aged 2 years was admitted to hospital with a painful swelling of the left knee which had been present for over 12 hours. She had no history of diarrhoea.

Examination

She had an occasional rise in temperature to 100° F. The haemoglobin was 11·9 g. per cent., W.B.C. 10,200 per cu.mm., neutrophil count 5,200 per cu.mm. A latex-fixation test for rheumatoid factor was positive but three subsequent tests were negative. X rays of the knee were normal. Blood cultures were sterile. After 12 days the knee was aspirated and green sterile fluid containing a moderate number of polymorphs was obtained. Stools were cultured and *S. enteritidis* was grown. Serum agglutinins were present at 1 in 80 to *S. typhi* 0, at 1 in 160 to *S. para B* 0, and at 1 in 40 to *S. enteritidis* H.

Result

No treatment was given and 2 months later the knee was normal again. She was still excreting *S. enteritidis* 3 months after admission.

Discussion

David and Black (1960) reviewed the literature on *Salmonella* arthritis, reported one personal case, and collected histories of 83 others. Full details were not given in each case. The organism was cultured from the joint fluid in 52 cases and this fluid was reported as purulent in 21 cases. In only one case was the joint fluid recorded as sterile and serous.

Berglöf (1963) reported seven patients with arthritis following diarrhoea, of whom six had salmonellosis. The joint fluid was sterile in the four patients in whom it was examined.

Vartiainen and Hurri (1964) reported twelve cases of arthritis associated with *S. typhi-murium* infection. The cases they reported were different and the disease resembled rheumatic fever with sterile serous effusions.

AGE

The ages of our seven patients ranged from 2 to 77 years, an age span comparable to that of the 84 cases collected by David and Black. The distribution by age was not similar for only sixteen of their cases were adults and eleven of these were in one series. The patients described by Vartiainen and Hurri were all adults, and those described by Berglöf were aged from 9 to 43 years.

INCIDENCE

David and Black (1960) considered arthritis to be a rare complication of *Salmonella* infections. Saphra and Wassermann (1954) reported an incidence of arthritis in *S. cholerae-suis* infections of 2·4 per cent. but Saphra and Winter (1957) reported an incidence of 0·24 per cent. for all *Salmonella* infections. (The former figure was obtained from a retrospective study of cases from several continents.)

Vartiainen and Hurri (1964) studied patients who had been admitted to two Finnish hospitals during 1961 and 1962. They found an incidence of arthritis in all *Salmonella* infections of 1·9 per cent. and in *S. typhi-murium* of 2·4 per cent. Arthritis had been seen only in infections with *S. typhi-murium*. Berglöf (1963) saw his patients in 1960–62 at Lund and gives no clear incidence of the arthritis.

The seven patients described here were seen in the years 1963–1969 at the Royal Hampshire County Hospital, Winchester. During this period 22 patients with *Salmonella* infection were admitted to the hospital and 295 cases were detected in the district by the Public Health Laboratory. Assuming that patients without complications were not admitted, the incidence of arthritis in diagnosed *Salmonella* infections was 2·4 per cent. A figure of 2·5 per cent. was found for *S. typhi-murium* and of 9·5 per cent. for *S. enteritidis*. The last figure seems very high and is probably not a true incidence.

CLINICAL PICTURE

Transitory diarrhoea occurred in the six adults and preceded the arthritis by between 6 days and 3 months. The delay between the diarrhoea and the arthritis was 0 to 8 weeks for Vartiainen and Hurri, 0 to 7 weeks for David and Black, and 5 to 14 days for Berglöf. Fever accompanied the arthritis in five patients. In our patients 2, 3, and 4 it was intermittent, reaching 101° F. and lasting 3 to 7 weeks, while in patients 1 and 7 there were occasional rises in temperature to 99° F. Vartiainen and Hurri found fever averaging 101·6° F. for 1 to 5 weeks and Berglöf found fever lasting a few weeks to 3 months and reaching 102·2° F. in three patients. Several joints were involved in five patients while patients 1 and 7 had a monoarticular arthritis. In the seven patients the joints affected were the knees (eight),

ankles (three), wrists (four), and elbow, toe, and acromio-clavicular joint (once each). This distribution is similar to that in the other series.

Conjunctivitis was seen in two patients and none gave a history of urethritis. One of Vartiainen and Hurri's patients had conjunctivitis and iritis, and two of Berglöf's patients had conjunctivitis, one of whom had urethritis.

LABORATORY FINDINGS

The haemoglobin was low in three cases but not below 10.3 g. per cent. The cells were normocytic normochromic. The white cell count ranged from 6,500 to 17,200 per cu.mm., the neutrophil count from 3,000 to 13,600 per cu.mm., and the erythrocyte sedimentation rate from 7 to 60 mm./1st hr (Wintrobe). These findings are comparable to the other series; except that Vartiainen and Hurri reported that the erythrocyte sedimentation rate averaged 75 mm. and was as high as 131 mm. Berglöf reported anaemia in each patient, leucocytosis in two, and an erythrocyte sedimentation rate over 75 mm. in six.

Haemoglobinopathy was not sought in our seven patients, but there was no reason to suspect it. *Salmonella* osteomyelitis is commoner in patients with haemoglobinopathy (*Brit. med. J.*, 1957), but David and Black found only one case of *Salmonella* arthritis secondary to osteomyelitis who had a haemoglobinopathy.

The x-ray films were normal in four patients, and showed an effusion in two, and osteoporosis in one. No osteomyelitis was seen, but it was found in nine of the cases collected by David and Black.

BACTERIOLOGY AND SEROLOGY

The responsible organism was *S. typhi-murium* in four patients and *S. enteritidis* in three. David and Black found *S. cholerae-suis* in 70 per cent. of patients, *S. typhi-murium* in three and *S. enteritidis* in one. Vartiainen and Hurri and also Berglöf found arthritis only with *S. typhi-murium*. The organism was grown from the stools, blood, and joint fluid in one patient and from the stools in four. In the other two patients the diagnosis was made from the serum agglutination tests. David and Black reported culture of the organism from the joint fluid in 52 cases and from the stools and blood in five, and relied on serology in the remainder. Vartiainen and Hurri and Berglöf obtained the diagnosis from stool cultures in all their patients.

TREATMENT

Various antibiotics were used in these patients with no apparent clinical improvement in the arthritis, fever, or stool cultures. The other authors came to no conclusions on treatment, although David and

Black pointed out that the three deaths dated from the pre-antibiotic era.

Steroids were used in three patients and seemed to give improvement. They were also given by Berglöf and Vartiainen and Hurri.

NATURE OF THE ARTHRITIS

David and Black reported that the joint contained pus in all but one of the 22 patients in whom the nature of the joint fluid was recorded. Their own patient had a cell count in the fluid of 45,000 per cu.mm. of polymorphonuclear cells. The organism was cultured from the joint in 52 patients. One patient had sterile joint fluid. 45 patients had monoarticular arthritis and five had two or three joints involved (details were not given in the remainder). They regarded *Salmonella* arthritis as a condition in which the organisms entered the joint and caused a suppurative reaction.

Berglöf aspirated the joint in four patients and found serous fluid in three and thick yellow fluid containing many polymorphonuclear cells in the fourth. The fluid was sterile, but three of the patients were being treated with antibiotics. One patient had monoarticular arthritis and the others polyarthritis. He considered *Salmonella* arthritis to be an aseptic asymmetrical polyarthritis.

Vartiainen and Hurri aspirated the joints in two patients and found normal sterile fluid. One patient had monoarticular arthritis and the others polyarthritis. The polyarthritis resembled rheumatic fever in that it flitted from joint to joint with rapid recovery and recurrence. The antistreptolysin 0 titre was normal in all their patients.

Our Patient 1 had a purulent monoarticular arthritis from which the organism was grown. She had osteoarthritis and was being treated with steroids, both of which predispose to the development of septic arthritis (Willkens, Healey, and Decker, 1960). She had been treated with ampicillin and yet developed a purulent arthritis similar to that in the cases described by David and Black.

In our other six patients the nature of the arthritis was not so clear. Joints were aspirated in four of them and sterile serous fluid containing few or a moderate number of polymorphonuclear cells was obtained. Two of these patients had not been treated with antibiotics and the other two had had short courses of antibiotics ineffective against *Salmonella*. Antibiotics were not the cause of the sterile joint fluid although a low-grade infection may have been present with failure to culture the organism. The arthritis was probably a sympathetic serous reaction to *Salmonella* infection of the intestine. The patients' disease resembled that described by Berglöf. There was little resemblance to the clinical picture seen by Vartiainen and Hurri for only Patient 2 developed further joint involvement after the initial onset and

she did not have a fitting arthritis. Patient 6 developed arthritis some time after her attack of gastroenteritis and clinically had definite rheumatoid arthritis (ARA, 1959). Her latex-fixation test for rheumatoid factor was negative. It is quite possible that rheumatoid arthritis developed coincidentally after the *Salmonella* infection, but the latter may have been a factor in its development.

Arthritis is seen as a manifestation of other bowel disease. Chaudhuri, Chakravarti, and Rai-Chaudhuri (1951) described a boy who developed a sterile polyarthritis after mild shigella dysentery diagnosed from agglutination titres. Rappaport, Rossien, and Rosenblum (1951) described four patients with 'arthritis' (three of whom were considered to have 'definite' rheumatoid arthritis) with *Entamoeba histolytica* infection of the colon. The arthritis disappeared with treatment of the amoebiasis. Arthritis may occur with ulcerative colitis (Bywaters and Ansell, 1958), Crohn's disease (Ansell and Wigley, 1964), idiopathic steatorrhoea (Cook, Peeney, and Hawkins, 1953), and Whipple's disease (Caughey and Bywaters, 1963).

The association of bowel and joint disease is also seen in Reiter's disease. Reiter (1916) described the case of an officer who developed conjunctivitis and urethritis one week after an attack of bloody diarrhoea, followed a few days later by inflammation of the knees. In the United Kingdom and North America, Reiter's disease is attributed to sexual contact and urethritis or dysuria are the presenting symptoms. In Scandinavia and the Middle East the disease is associated with dysentery. Paronen (1948) described an outbreak of Reiter's disease following a large epidemic of *Shigella flexner* dysentery in Finland. The arthritis appeared from 11 days to 3 months after the dysentery and the

knees were most commonly affected. Urethritis was not seen in all cases. 17 per cent. had conjunctivitis and arthritis without urethritis. Two of the patients described here had conjunctivitis, one of Berglöf's patients had conjunctivitis and urethritis, and one of Vartiainen and Hurri's patients had conjunctivitis and iritis. Iritis is seen only in chronic Reiter's disease. One quarter of Paronen's patients had balanitis circinata and a few had keratoderma blennorrhagica. Neither lesion had been described with *Salmonella* arthritis. Reiter's disease following non-specific dysentery (Jacobs, 1961) and *Shigella sonnei* dysentery (Corner, 1950) has been described in children. The connection between the bowel infection and Reiter's disease is not clear and it is likely that the infection precipitates, rather than causes, the disease. Patients 2 and 3 might have been diagnosed as cases of Reiter's disease if the preceding *Salmonella* infection had not been discovered. Perhaps Reiter's disease may be induced by *Salmonella* as well as by *Shigella* infection in the susceptible individual.

Summary

Seven patients with arthritis following *Salmonella* infections are described. In one patient a purulent monoarticular arthritis developed while the others had nonbacterial arthritides. Two patients had conjunctivitis. It is suggested that a *Salmonella* infection should be considered as a possible cause in unusual cases of arthritis and in Reiter's disease without evidence of urethritis.

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