

# Polyarthritis associated with *Yersinia enterocolitica* infection

## Clinical features and laboratory findings in nine cases with severe joint symptoms

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During the last few years it has become apparent that human infections due to *Yersinia enterocolitica* (formerly Pasteurella X) are relatively common in several countries (Niléhn, 1969; Simond, 1970; Von Noyen, Vandepitte, and Isebaert, 1970). Patients with this bacterial infection have shown various symptoms, such as fever, diarrhoea, abdominal pain, colic, headache, backache, arthralgia, and erythema nodosum (see also Winblad, 1969; Hannuksela and Ahvonen, 1969). Recently, nonpurulent arthritis has been added to the list of clinical symptoms of *Yersinia* infection (Ahvonen, Sievers, and Aho, 1969a; Ahvonen and Rossi, 1970). The frequency of arthritis is probably higher than in enteric infections with other bacterial pathogens (Ahvonen and others, 1969a). Accordingly, *Yersinia* arthritis seems to be an important addition to the list of causes of non-purulent arthritis. Our series of nine patients, who have been treated and followed up during the years 1969–1970 in one hospital, yields new information on the clinical features and laboratory findings of arthritis associated with *Y. enterocolitica* infection.

### Patients and methods

From January, 1969, to September, 1970, nine patients with *Y. enterocolitica* infection were treated in the department for rheumatic diseases at Kivelä Hospital, Helsinki. Their ages ranged from 22 to 49 years (mean 32). There were seven female and two male patients. In addition to these nine patients, three with similar clinical histories and symptoms showed low agglutination titres of 1:40 against *Y. enterocolitica* during their stay in hospital. Since laboratory investigations revealed no other causes, the arthritis in these patients was probably also due to *Y. enterocolitica* infection.

*Yersinia* agglutinins were determined as described previously (Ahvonen and others, 1969a). *Yersinia* culture of the stool specimens was performed according to the method of Niléhn and Sjöström (1967).

After hospitalization, the patients were seen at about 2 weeks' intervals in the out-patient department, 5 to 18 months later, a detailed follow-up study was performed, which included the physical examination and the relevant electrocardiographic, radiological, and laboratory investigations.

### Results

#### JOINT SYMPTOMS

The affected joints, and the main arthritic symptoms and signs in the nine patients are recorded in Table I. In a typical case, several joints were involved in quick succession, in a period of time varying from a few days to about 2 weeks. In general, no further joints were affected thereafter. The duration of the acute joint symptoms ranged from 36 days to 4 months in all cases but in Case 7, who has had acute inflammatory signs in several joints during the whole observation period of 17 months. The joints most usually affected were the weight-bearing joints of the lower extremities. In order of frequency, the affected joints were the ankles (7 cases), knees (6), toes (5), fingers (5), wrists (5), elbows (3), and shoulders (2). If the finger joints in one hand or the toe joints in one foot are considered as a single joint, the mean number of joints with arthritis (defined as definite swelling and tenderness) was 3 joints, and the mean number of joints with arthralgia (pain on motion or tenderness without apparent swelling) 6.6 joints. Bilateral involvement seemed to be the rule, although the intensity of the arthropathy in the bilaterally involved joints varied greatly. The onset of the joint symptoms was in several cases 'migratory', in the sense that the onset of arthritic symptoms 'migrated' from joint to joint within a few days, as at the onset of arthritis due to rheumatic fever. The pain and swelling did not subside in one joint when another became involved, but later on the inflammatory reaction subsided more

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**Table I** Joint symptoms and signs and cell count of synovial fluid in nine patients with *Yersinia enterocolitica* infection

Case no.	Sex	Age (yrs)	Affected joints	Tenderness*	Swelling*	Effusion*	Synovial fluid	
							Cell WBC/mm. <sup>3</sup>	Per cent. polymorphonuclears
1	F	30	Knees, ankles, left MTP I-III, right MCP I, left MCP I	++	++	++	9,600	68
2	F	40	Knees, wrists, left MPT II-III	+	+	+	12,500	59
3	F	22	Right MTP II-IV, left MPT II-III	+	+			
4	F	22	Right knee, ankles, left wrist, shoulders	++	++	++	29,000	84
5	M	29	Right ankle and wrist, right MTP I, left MCP II and III, left PIP III	+	+			
6	F	49	Knees, ankles, left elbow, right PIP III-IV, left PIP IV	+	+	++	58,000	95
7	F	24	Knees, left wrist, right MPT I	++	++			
8	F	29	Ankles, wrists, right MCP I-II	+	+			
9	M	40	Knees, right elbow, left MPT III and PIP III	+	++	++		

The most severely affected joints have been mentioned. Abbreviations: metacarpophalangeal joints = MCP; metatarsophalangeal joints = MTP; proximal interphalangeal joints = PIP.

\* The degree of activity of a symptom or sign has been recorded as ++ in severe cases and as + in moderate cases.

or less simultaneously in all the inflamed joints. During the acute phase the pain was in some cases (Cases 4 and 7) so intense that narcotics were repeatedly needed.

In the follow-up study 5 to 18 months after hospitalization, only three of the patients were symptom-free (Cases 1, 6, and 9). Case 2 still felt slight arthralgic pains and stiffness in the knees. In Case 3, the patient felt slight tenderness in the right metatarsophalangeal II-IV joints on palpation. In Case 4, the patient had pronounced crepitation on motion in her knees even 18 months after hospitalization. In Case 5, the patient stated 6 months after discharge from hospital that since his illness he felt arthralgic pain in the affected joints every time he took beer or other alcoholic drinks but was otherwise symptomfree. Patient 8 still had some discomfort in her knees 4 months after the onset of the arthritis and she too had characteristic alcohol-induced arthritic and muscular pains. Case 7 has run a course of prolonged chronic joint disease resembling rheumatoid arthritis. She has twice subsequently been hospitalized because of relapsing hydrops in her knees, arthralgic pains, and periarticular swellings in several joints. At the follow-up study in August, 1969, 17 months after the initial symptoms, she still had slight periarticular swelling in the right ankle. Besides this sign of active disease, she had very distinct crepitations on movement in

both knees and these crepitations still persist. Since the clinical picture has been very like that of rheumatoid arthritis, laboratory tests for rheumatoid factors have been repeatedly taken, but the results have been consistently negative.

#### SYNOVIAL FLUID

Yellow to greenish-yellow synovial fluid was aspirated from four patients with effusion in the knee joints. The amount of fluid aspirated varied from 18 to 80 ml. In Cases 4 and 7, recurrence of the hydrops necessitated repeated aspiration. The number of white cells varied from 9,600 to 58,000, of which 59 to 95 per cent. were polymorphonuclears. In Case 7 aspiration of the synovial fluid from the right knee was performed six times and from the left knee three times during 8 months. The maximum and minimum amounts of fluid aspirated were the same as in the whole series (from 18 to 80 ml.) and the proportion of polymorphonuclear leucocytes ranged from 76 to 95 per cent. Bacterial culture of the synovial fluid was negative in every case.

#### GENERAL SYMPTOMS

Fever, diarrhoea, abdominal pain, headache, tiredness, and a feeling of weakness were the most common symptoms preceding the arthritis (Table II, overleaf). Except in Cases 3 and 9, at least two of these symptoms

**Table II** *Main symptoms of nine patients with Yersinia enterocolitica infection*

Case no.	Joint* symptoms	Fever	Diarrhoea	Abdominal pain	Headache	Sense of weakness	Muscular pains	Signs of upper respiratory infection	Cardiac† symptoms
1	9-68	1-54	1-7	—	1-7	+	—	—	—
2	2-36	2-31	1-9	—	—	+	+	—	+
3	1-47	—	—	—	—	+	—	—	+
4	4-120	1-40	1-4	—	1-4	+	+	—	+
5	5-50	1-46	1-9	1-6	—	+	—	+	+
6	4-52	1-4	1-3	1-7	—	+	—	+	+
7	7-510	1-57	—	2-10	—	+	+	+	+
8	9-70	1-41	1-14	1-14	—	+	—	+	—
9	7-68	—	—	—	1-7	—	—	—	+

Numbers indicate the first and last days of the symptom or sign counted from the onset of the first symptom.

— or + indicates the absence or presence of the symptom or sign.

\* Described in detail in Table I.

† Described in detail in Table III.

were experienced before the onset of the joint symptoms. The abdominal pain was felt in the epigastrium in three cases, but in one patient (Case 8) in the right lower quadrant of the abdomen, simulating the pain of acute appendicitis. Four patients had muscular pains simultaneously with the arthritis. Two patients had pharyngitis at the time of the arthritis (Cases 7 and 8) and one patient (Case 5) had pharyngitis which had already begun 2 weeks before the onset of the joint symptoms. It is impossible to say whether this was due to *Y. enterocolitica* infection. None of the patients had erythema nodosum.

#### HEART

On the basis of auscultory findings, ECG, and *x* ray examinations, six patients had signs of cardiac involvement (Table III). In five of these patients physical examination revealed some abnormalities. Four patients, who had no previous history of cardiac disease or pathological auscultatory findings, had

systolic murmurs of changing character and intensity on auscultation. Six patients showed electrocardiographic changes. Two patients had definite and one of the others possible variation in heart size during the disease. Three out of the four patients with systolic murmurs still had mild systolic murmurs at the follow-up examination. In addition, Case 9, a patient who had suffered from rheumatic fever at the age of 16 and who had since had a systolic murmur, possibly had some variation in the auscultatory finding during the *Y. enterocolitica* infection. The cardiac involvement, although indisputably present in several cases, was benign in all cases, and none of the patients developed a progressive cardiac disease or cardiac decompensation.

#### LABORATORY FINDINGS

Some of the laboratory findings are recorded in Table IV. In the acute phase of the arthritis, the agglutination titres against *Y. enterocolitica* varied from 160 to

**Table III** *Signs of cardiac involvement: symptoms, findings on auscultation, electrocardiogram, and chest x ray changes in nine patients with Yersinia enterocolitica infection*

Case no.	Symptoms and findings on auscultation	Electrocardiogram	Chest x-ray examination
1	—	—	—
2	—	—	—
3	Extrasystoles Apical systolic murmur (gr. II)	Frequent supraventricular extrasystoles	Transient cardiac enlargement
4	Precordial pain Apical holosystolic murmur (gr. II)	Deep symmetric negative T waves in leads V <sub>1</sub> -V <sub>4</sub> S-T segment depression in leads V <sub>2</sub> -V <sub>4</sub>	—
5	—	Transient inverted T wave in III, aVF S-T segment depression in leads V <sub>2</sub> -V <sub>6</sub> Notching of QRS complex in lead V <sub>3</sub>	Slight variation in heart size
6	Intermittent precordial pain Holosystolic basal parasternal murmur (gr. I-II)	—	—
7	Tachycardia (unrelated to fever) Systolic pulmonary murmur Accentuated second heart sound	Transient inverted T wave in III, aVF, V <sub>2</sub> -V <sub>3</sub> Isoelectric T in V <sub>4</sub>	—
8	—	—	—
9	Tachycardia (unrelated to fever) Intermittent extrasystoles Pre-existing systolic murmur	Transient inverted T wave in leads III, aVF	Transient cardiac enlargement

Table IV Laboratory findings in nine patients with Yersinia enterocolitica infection

Case no.	Y. enterocolitica agglutinins*				Yersinia culture of stool specimen	Highest ESR (mm./hr.)	CRP (mm.)	ASO	Waalser-Rose test	Latex test	Gonococcal CF titre	Lowest Hb (g./l.)	Highest WBC mm. <sup>3</sup>	Throat culture
	Sero-type	Titre I	Titre II	Titre III										
1	3	10,240	1,280	80	—	75	4+	50	—	—	16	11.3	9,700	Normal flora
2	3	10,240	1,280	80	—	128	1+	50	—	—	—	11.9	10,600	Normal flora
3	3	320	80	20	+	50	0	800	—	—	—	9.5	7,400	Haemolytic streptococci†
4	9	2,560	80	40	+	91	6+	50	—	—	16	11.2	15,300	Normal flora
5	3	5,120	320	80	—	42	2+	50	—	—	8	14.8	8,200	Normal flora
6	3	1,280	320	320	—	48	0	50	—	—	—	10.8	8,400	Normal flora
7	3	10,240	1,280	40	—	148	6+	100	—	—	8	9.1	13,500	Normal flora
8	3	160	160	160	+	37	0	100	—	—	—	12.2	5,300	Normal flora
9	9	640	320	80	—	60	0	100	—	—	—	13.5	11,800	Normal flora

\* Titre I represents the highest titre measured, Titre II was the last measured before discharge from hospital and Titre III 5-17 months after the onset of the first symptoms.

† Not group A.

10,240. The titres fell significantly during the observation period in all except Case 8, in which the initial titre of 1:160 had been the lowest in the whole series. *Yersinia* culture of a stool specimen was positive in this patient. The decrease in the agglutination titre did not run parallel with the clinical improvement of the disease in all cases. This was most clearly seen in Case 7, in which there was similar decline in the agglutination titres against *Y. enterocolitica* to that in the other patients, in spite of persistent signs of acute arthritis.

Because of cross-agglutination between *Y. enterocolitica* Type 9 and *Brucella* (Ahvonen, Jansson, and Aho, 1969b), cross-absorption was performed in Cases 4 and 9. Absorption of the sera with *Y. enterocolitica* Type 9 removed all agglutinins against both *Y. enterocolitica* and *Brucella*. Absorption with *Brucella abortus* reduced the *Yersinia* titre by two to three 2-fold dilution steps and removed all *Brucella* agglutinins.

The gonococcal complement-fixation test was slightly positive in four cases. The test showed progressively lower and finally negative values as the acute signs of inflammation subsided. Since none of the patients had signs of gonorrhoea or a history of genito-urinary infection, a cross-reaction between *Y. enterocolitica* and gonococci was suspected, but no constant pattern of cross-reaction could be detected. As seen in Table IV, a positive gonococcal complement-fixation titre was noted only in cases with very high *Y. enterocolitica* agglutinin titres (and a strongly positive C-reactive protein test). On the other hand, in a series of patients with high gonococcal complement-fixation titres, no significant *Yersinia* agglutinin titres were detected. Consequently, the significance of the positive gonococcal complement-fixation tests remained unsolved.

Antistreptolysin-O titres were within normal limits except in Case 3, in which the ASO titre of 800 did not drop significantly within 8 months. The Waaler-Rose and latex tests were negative. Serum uric acid was also within normal limits in all cases. Throat culture yielded a normal flora in all except Case 2, in which the culture was positive for beta-haemolytic strepto-

cocci, which did not belong to group A according to the bacitracin sensitivity test. The Widal reaction, as well as the stool cultures for *Salmonella* and *Shigella*, were negative.

During hospitalization, the erythrocyte sedimentation rates were high in all cases. The C-reactive protein test was positive in the acute phase of the arthritis in five patients and the high values became lower and finally negative with decreasing activity of the disease. A moderate degree of anaemia was found in the majority of the patients. The anaemia was normocytic and normochromic in every case. The lowest values of haemoglobin were measured 1 to 3 months after the onset of the first symptoms. Serum iron values were low, from 3.6 to 4.5  $\mu\text{M/l.}$ , in those patients (Cases 1, 3, 6, and 9) which showed the lowest haemoglobin values, whereas total iron-binding capacity was normal or low-normal (47.9 to 72.1  $\mu\text{M/l.}$ ) at the same time. Moderate leucocytosis, up to 15,300, with an increase in the percentage of polymorphonuclear forms, was also associated with the acute phase of the disease.

#### X-RAY EXAMINATIONS

The affected joints were x-rayed at the time when the arthritic signs were acute and again in connexion with the follow-up study. The findings were normal except in Case 9, in which there were slight signs indicative of left-sided sacroiliitis.

#### THERAPY

All the patients received antibiotics during hospitalization (tetracycline in all cases and penicillin in several before the establishment of the diagnosis), but there was no conclusive evidence that this therapy had a beneficial effect on the course of the disease. On the other hand, prednisone in doses of 20 to 40 mg./day had a dramatic ameliorating influence on the arthritic pain and even in Cases 4 and 7, with severe symptoms, the pain was markedly relieved by adding prednisone to the medication and no analgesic drugs were needed after that. In Case 7, with relapsing hydrops in both knees, the right knee was treated with an intra-articular injection of osmium tetroxide. Since then the effusion has not reappeared.

## Discussion

The results of this study indicate that arthritis due to *Y. enterocolitica* infection is a relatively common cause of acute polyarthritis in Finland. During the period of 1 year and 8 months when the nine patients of this series and three others suspected to be cases of *Yersinia* arthritis (see Patients and Methods) were admitted to the department of rheumatic diseases, a total of 717 patients with rheumatic disease was treated in the department. Although, on the basis of this study, it is impossible to give figures for the general incidence of arthritis due to *Y. enterocolitica* infection, the above figures may be of some interest, since they have been obtained from a rheumatic centre, to which cases with rheumatic diseases and related conditions in Helsinki are referred. Comparison with the number of patients with rheumatic fever—twenty suspected cases, eight of which fulfilled the revised Jones criteria (Stollerman, Markowitz, Taranta, Wannamaker, and Whittmore, 1965)—may also be worth mentioning. On this basis it seems that the number of hospitalized cases of arthritis due to rheumatic fever and to *Y. enterocolitica* infection were roughly equal during the observation period.

In several cases, the clinical picture of *Yersinia* arthritis resembled the arthritis of rheumatic fever. Because of the mild but definite carditis, which has not been reported in the earlier studies on *Y. enterocolitica* infection, and because of the acute onset of polyarthritis, most of the patients of this series were at first considered to be suspected cases of rheumatic fever. Similar clinical features are found in several other nonpurulent types of arthritis associated with bacterial infections, e.g. in salmonella, shigella, brucella, and gonococcal infections (cf. Ahvonen and others, 1969a). Therefore, it is impossible to diagnose arthritis due to *Y. enterocolitica* infection only on the basis of symptoms and clinical findings, and laboratory investigations are also necessary. Serological and other laboratory tests may be used to rule out the other possible causes of arthropathy. It must be kept in mind, however, that the *Brucella* agglutinin test

and possibly also the gonococcal complement-fixation test may give false positive results in *Y. enterocolitica* infection. Accordingly, the agglutination test against *Y. enterocolitica* and/or *Yersinia* culture of stool specimen is decisive in the diagnosis of arthropathy due to *Y. enterocolitica* infection.

## Summary

During the years 1969–1970, nine patients with severe arthritis due to *Y. enterocolitica* infection were treated in the department for rheumatic diseases at one of the municipal hospitals in Helsinki. In a typical case, polyarthritis involved several joints within a few days. The joints most usually affected were the ankles, knees, toes, fingers, and wrists. All the patients had periarticular swelling and arthritic pain in several joints, and five had effusion in at least one joint. In eight patients the duration of the acute arthritic symptoms varied from 5 weeks to 4 months. The ninth patient, in whom the arthritis was very severe, has had acute joint symptoms with arthritic pain, periarticular swelling, and relapsing effusion in several joints for 17 months. In the follow-up study 5 to 18 months after hospitalization, only three of the patients were symptom-free. The most usual sequelae of the disease were arthralgic pain, and stiffness or crepitation in the joints that were affected during the acute phase of the arthritis. In two of the patients ingestion of alcohol induced arthritic or muscular pains.

Fever, a sense of weakness, gastrointestinal symptoms, headache, and muscular pains were the most common associated symptoms. On the basis of physical signs, electrocardiograms, and x ray examinations, six patients had signs of carditis. Three patients had a sore throat. Since the clinical picture of arthritis induced by *Y. enterocolitica* infection often resembles the arthritis of rheumatic fever or of other polyarthritis of diverse aetiology, bacteriological or serological evidence of *Y. enterocolitica* infection is necessary for a correct diagnosis.

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