

## Coxsackie B infection and arthritis

The clinical manifestations of acute infection with Coxsackie B virus are varied and include epidemic pleurodynia, myopericarditis, meningoencephalitis, and pancreatitis. In most cases the infection is self limiting and does not result in chronic tissue damage, but it has also been associated with the development of polymyositis,<sup>1</sup> cardiomyopathy,<sup>2</sup> and diabetes mellitus.<sup>3</sup> Arthritis is not widely recognised as either an acute or a chronic manifestation of infection with Coxsackie virus, and only one series, of six patients, has been reported previously.<sup>4</sup> We report on three further patients, who developed febrile seronegative arthritis in association with clinical and serological evidence of Coxsackie infection; one subsequently developed a progressive erosive polyarthritis.

### Case histories

**Case 1**—A 31 year old man with a history of low backache developed pleurisy, myopericarditis, and polyarthritis affecting the hips, shoulders, wrists, distal interphalangeal joints, knees, ankles, and left sternoclavicular joint. He also developed severe low backache and spinal stiffness. Erythrocyte sedimentation rate was 97 mm in the first hour, haemoglobin concentration 11.7 g/dl, and white cell count  $11.9 \times 10^9/l$ . Viral antibody titres were consistent with recent infection with Coxsackie B2, with a late rise in antibody against the cross reacting serotype Coxsackie B4 (table). All other viral and bacteriological studies yielded negative results. Although the myopericarditis resolved rapidly, the arthritis persisted and required treatment with prednisolone. At reassessment six months later the only abnormal clinical finding was digital flexor tenosynovitis. X-ray films of his sacroiliac joints showed early sacroiliitis, and tissue typing showed that he carried the HLA-B27 antigen.

**Case 2**—A 36 year old woman developed acute arthritis in the right first metatarsophalangeal joint, severe headache, stiff neck, pleurisy, and malaise. The arthritis spread to the shoulders and several proximal and distal interphalangeal joints of the right hand, as well as the metatarsophalangeal joints of both feet, before resolving after a two week course of prednisolone. Serological studies performed six weeks later showed high stable antibody titres to Coxsackie B4, but all other viral studies yielded normal results (table). HLA tissue typing showed an A1, B8, B22, BW6 haplotype.

**Case 3**—An 18 year old man developed fever, sore throat, myalgia, arthralgia, neck stiffness, pleuropericarditis, and a papular rash. Erythrocyte sedimentation rate was 102 mm in the first hour and white cell count  $16 \times 10^9/l$  (83% neutrophils); antibody titres to Coxsackie B4 showed a diagnostic rise (table). All other viral and bacteriological investigations yielded negative

patients with febrile arthritis developing in association with Coxsackie infection has been reported previously<sup>4</sup>; two of those patients were clinically similar to two of ours (cases 2 and 3). The patient in case 1, however, who was positive for HLA-B27 and had a history suggestive of pre-existing mild sacroiliitis, did not resemble the previously reported cases. Although he may represent an example of reactive arthritis in response to Coxsackie infection in a patient with HLA-B27, we cannot exclude the possibility that direct infection of joints by virus occurred.

Coxsackie infection should be considered in the differential diagnosis in patients presenting with febrile systemic illness in association with seronegative arthritis of either symmetrical or asymmetrical patterns, with or without spondylarthritis.

We thank the Edinburgh and South-east Scotland Blood Transfusion Service for performing tissue typing in cases 2 and 3.

<sup>1</sup> Travers RL, Hughes GRV, Cambridge G, Sewell JR. Coxsackie B neutralisation titres in polymyositis and dermatomyositis. *Lancet* 1977; i:1268.

<sup>2</sup> Lerner AM. Coxsackie virus cardiomyopathy. *J Infect Dis* 1969;120:496-9.

<sup>3</sup> Yoon JW, Austin M, Onodera T, Notkins AL. Isolation of a virus from the pancreas of a child with diabetic ketoacidosis. *N Engl J Med* 1979; 300:1173-9.

<sup>4</sup> Rahal JJ, Millian SJ, Moriega ER. Coxsackie virus and adenovirus infection: association with acute febrile and juvenile rheumatoid arthritis. *JAMA* 1976;235:2496-501.

(Accepted 23 November 1982)

**Rheumatic Diseases Unit, Northern General Hospital, and Department of Medicine, Western General Hospital, University of Edinburgh**

N P HURST, MB, MRCP, senior registrar

A G MARTYNOGA, MB, MRCP, senior registrar

G NUKI, MB, FRCP, professor

**Rheumatology Unit, Department of Medicine, Royal Postgraduate Medical School, University of London**

J R SEWELL, MB, MRCP, lecturer (present appointment: consultant in rheumatology, William Harvey Hospital, Ashford, Kent)

A MITCHELL, MB, MRCP, registrar

G R V HUGHES, MB, FRCP, reader

Titres of Coxsackie virus in patients during their illnesses

Case No	Week of illness	Coxsackie titres		
		B2	B4	B1,3,5,6
1	3	512	<16	<16
	5	≥1024	128	<16
	10	256	32	<16
	14	≥1024	128	<16
	34	512	256	<16
	42	≥1024	256	<16
	50	≥1024	512	<16
2	62	≥1024	16	<16
	7	<16	256	<16
	11	<16	256	<16
3	2	<16	<16	<16
	3	<16	256	<16
	4	<16	512	<16

results, and HLA tissue typing showed an A26, B13/B16, BW6, CW3 haplotype. He failed to respond to high dose aspirin, and prednisolone was required to control his disease. When steroids were withdrawn symptoms recurred and a symmetrical polyarthritis developed affecting proximal interphalangeal joints, metacarpophalangeal joints, shoulders, knees, and metatarsophalangeal joints. Three years later he had continuing arthritis and radiological evidence of erosions in the carpal joints; he failed to respond to hydroxychloroquine, and gold treatment was started. Attempts to isolate virus from throat, rectum, and synovial fluid were unsuccessful, and immunofluorescence failed to detect viral antigens within synovial cells.

### Comment

Of the three cases we report, one showed a diagnostic rise in monospecific neutralising antibody to a Coxsackie group B virus while the others had high monospecific titres consistent with recent infection. The clinical signs and symptoms in all three patients were typical of Coxsackie infection with the addition of arthritis. One series of

## Long term consequences of arsenical treatment for multiple sclerosis

Arsenic was widely used in the past to treat neurological disease, especially epilepsy and neurosyphilis, and psoriasis. Its use was limited by frequent toxic side effects, and most patients developed hyperkeratotic dermatitis, which occasionally progressed to squamous carcinoma. Other tumours occur after prolonged exposure, and tumours of the nasopharynx and bronchus and haemangiosarcoma of the liver are well recognised. More recently arsenic has been implicated in the development of non-cirrhotic portal hypertension.<sup>1 2</sup> In the 1940s and 1950s a trial of arsenical drugs in multiple sclerosis was conducted in Birmingham.<sup>3</sup> We report on a patient with possible long term sequelae of this treatment.

### Case report

In 1957 a 32 year old car delivery man presented with recurrent transient neurological disturbances including paraplegia, blindness, cerebellar ataxia, and monoparesis. Multiple sclerosis was diagnosed. He was entered into the arsenic trial and received alternate-day injections of neoarsphenamine (sodium 3-amino-4,4-dihydroxy-3-sulphinomethylaminoarsenobenzene) for three months and Fowler's Solution (arsenic trioxide 1%) by mouth, which he continued to take daily for four years until his skin became "grey and scaly." In 1967 haematuria led to the diagnosis and treatment of a transitional cell tumour of the bladder. Later that year he presented with the first of 32 major gastrointestinal haemorrhages.

In 1969, during a severe haemorrhage not responding to conservative measures, emergency laparotomy was performed. No ulcer was seen, gastric erosions were noted, and the left gastric artery was ligated. Six months later laparotomy for severe haematemesis produced similar findings, and a Polya gastrectomy was performed. Subsequently liver biopsy specimens repeatedly