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,¹ cardiomyopathy,² and diabetes mellitus.³ 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.⁴ 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

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

patients with febrile arthritis developing in association with Coxsackie infection has been reported previously⁴; 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.

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

³ 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.

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

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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.^{1 2} In the 1940s and 1950s a trial of arsenical drugs in multiple sclerosis was conducted in Birmingham.³ 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

showed a normal histological appearance. Splenoportal venography in 1974 showed a dilated tortuous portal vein and gastric and oesophageal varices but no extrahepatic obstruction to portal blood flow. Results of liver function tests remained normal. Over the next two years he underwent repeated endoscopic sclerotherapy of the varices and had no further haemorrhages. He had few neurological symptoms attributable to multiple sclerosis, and examination showed optic atrophy. The spleen was just palpable, and cystoscopy showed no residual tumour.

Comment

Non-cirrhotic portal hypertension is rare in the United Kingdom and the aetiology usually unknown. Arsenic and vinyl chloride monomer are well recognised aetiological agents. In India environmental exposure to arsenic is more common, and so is non-cirrhotic portal hypertension.²

Neoarsphenamine, with an amino-substituted benzene ring, has a similar structure to -2-naphthylamine and other organic dyes that cause transitional cell tumours of the bladder.

We suggest that non-cirrhotic portal hypertension in this patient was the direct result of administration of inorganic arsenic and that the bladder tumour was caused by neoarsphenamine. The coincidence of these complications in our patient suggests that other patients similarly treated in this trial may develop one or other lesion.

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³ McAlpine D, Compston ND, Lumsden CE. *Multiple sclerosis*. Edinburgh and London: E and S Livingstone, 1955:195-9.

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Sodium cromoglycate and verapamil alone and in combination in exercise induced asthma

The mechanism of exercise induced asthma remains unclear. The effectiveness of sodium cromoglycate in exercise induced asthma together with its ability to prevent mast cell degranulation *in vitro* has led to the view that mediator release probably plays a part in the pathogenesis of exercise asthma. The release of mast cell mediators depends on influx of calcium ions across the cell membrane. The calcium antagonists verapamil and nifedipine, which prevent transmembrane influx of calcium, are effective in modifying exercise induced asthma.¹⁻³ I report the effects of inhaled saline, sodium cromoglycate, verapamil, and a combination of verapamil and sodium cromoglycate in eight patients with reproducible exercise induced asthma.

Patients, methods, and results

Eight patients aged 19-35 with extrinsic and reproducible exercise induced asthma were studied. Patients taking oral or aerosol corticosteroids, anti-histamines, and anticholinergic drugs were excluded. Sodium cromoglycate and bronchodilator drugs were stopped for 24 hours before each test. Forced expiratory volume in one second was recorded on a water sealed spirometer (Godart Pulmotest). The exercise test consisted of steady static running on a treadmill at submaximal work loads for up to eight minutes under controlled conditions of temperature and humidity. The study was carried out in a random single blind fashion using saline (9 g/l), sodium cromoglycate nebuliser solution (10 g/l), verapamil (2.5 g/l), and sodium cromoglycate plus verapamil. The drugs were delivered through a Wright nebuliser driven by compressed air at 8 l/min. Saline, sodium cromoglycate, and verapamil were inhaled for five minutes at tidal breathing; the combination of sodium cromoglycate and verapamil was inhaled for 10 minutes. The estimated nebulised dose of sodium cromoglycate and verapamil was 12 mg and 3 mg respectively. The nebulised dose of the combination contained 12 mg sodium cromoglycate and 3 mg verapamil. Spirometry was repeated at 30 minutes after inhalation and then at two, five, 10, 15, and 30 minutes after exercise. The results of the tests were expressed as the maximal percentage fall in forced expiratory volume in one second from the baseline value after the drug had been taken; they were analysed with Student's paired *t* test.

The table shows the results. There was no significant difference between the mean baseline values of forced expiratory volume in one second before and after inhalations of saline, sodium cromoglycate, and verapamil on four days of exercise testing. After exercise the mean maximal percentage falls in forced expiratory volume in one second after saline, sodium cromoglycate, verapamil, and sodium cromoglycate plus verapamil were $25.9 \pm \text{SEM } 3.7$, 12.6 ± 2.4 , 8.8 ± 2.0 , and 5.3 ± 1.1 respectively. The inhibitory effects of sodium cromoglycate and verapamil were significant, and no significant difference was found between the two treatments. The inhibitory effect of the combination of sodium cromoglycate and verapamil was greater than that of sodium cromoglycate alone ($p < 0.02$) but not significantly different from that of verapamil alone. Considerable intrasubject variability in response to verapamil and sodium cromoglycate was observed.

Comment

Sodium cromoglycate alone, verapamil alone, and the combination of these drugs significantly inhibited exercise induced asthma in the patients studied. Although the combination was superior to sodium cromoglycate alone, the results do not support potentiation or a summation effect. Foreman and Garland⁴ postulated that sodium cromoglycate may act on the calcium entry pathway. The variability of responses to verapamil and sodium cromoglycate in individual patients may suggest that the site of action of these drugs in exercise induced asthma is different; it is difficult to postulate whether their action is on mast cell degranulation or bronchial smooth muscle.

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³ Patel KR. The effect of calcium antagonist nifedipine in exercise-induced asthma. *Clin Allergy* 1981;**11**:429-32.

⁴ Foreman JC, Garland LG. Cromoglycate and other antiallergic drugs: a possible mechanism of action. *Br Med J* 1976;**3**:820-1.

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Effect of saline, sodium cromoglycate, verapamil, and sodium cromoglycate plus verapamil on exercise induced fall in forced expiratory volume in one second in eight patients (baseline data before and after inhalation expressed as absolute values (l); change after exercise expressed as percentage)

Case No	Age (years)	Sex	Saline			Sodium cromoglycate			Verapamil			Verapamil + sodium cromoglycate		
			Baseline		% Change	Baseline		% Change	Baseline		% Change	Baseline		% Change
			Before	After		Before	After		Before	After		Before	After	
1	35	F	2.11	2.11	23.2	2.09	2.28	4.4	1.79	1.94	11.9	2.31	2.24	5.8
2	19	M	4.92	4.92	16.0	4.08	4.25	1.6	4.89	4.32	6.5	5.22	5.36	1.3
3	35	M	2.24	2.24	42.0	2.21	2.34	19.2	2.43	2.29	18.3	2.61	2.58	11.6
4	24	M	4.62	4.25	16.4	3.96	4.28	14.7	4.37	4.69	5.1	4.29	4.69	5.8
5	32	M	2.44	2.54	20.8	2.64	2.91	9.2	2.21	2.41	4.2	3.31	3.31	2.4
6	28	F	3.28	3.21	18.7	3.26	3.38	15.3	3.13	3.08	3.6	4.15	4.35	6.2
7	21	M	4.22	4.22	28.7	4.15	4.35	16.1	4.22	4.42	3.6	4.15	4.35	6.2
8	32	F	2.56	2.58	41.1	2.68	2.63	20.0	2.78	2.70	15.0	2.66	2.71	4.0
Mean	28.3		3.29	3.26	25.9	3.13	3.30	12.6	3.23	3.23	8.8	3.49	3.56	5.3
SEM	2.2		0.40	0.38	3.7	0.30	0.31	2.4	0.40	0.38	2.0	0.35	0.39	1.1
p*								<0.01			<0.01			<0.001

*Compared with saline.