clear. The disorders are highly heterogeneous in the age of onset, severity, and distribution of the predominant muscle weakness. The distal, bulbar, scapuloperoneal, and facioscapulohumeral forms seem to be distinct entities, but usually the weakness is generalised or mainly proximal. Acute Werdnig-Hoffmann disease, which is of early infantile onset and has a rapidly progressive course, seems to be a specific autosomal recessive disorder within this group.¹ In most of the more chronic cases inheritance appears to be recessive.² Yet the great variation in severity and age at onset within sibships, the characteristically intermittent progression of the disease, and the low segregation ratio² suggest that the genetic element might consist of a predisposition to the disease, which requires a trigger to become manifest. Thus a possible association with the HLA system is reasonable.

Subjects, methods, and results

We identified those patients with spinal muscular atrophy living in the Northern Region whose records were at the Regional Neurological Centre, Newcastle, and who satisfied the diagnostic criteria of having a predominantly proximal distribution of muscle weakness, a clinical diagnosis supported by results of electromyography and muscle biopsy, and having survived beyond the age of 2 years.

Patients aged over 17, or the parents of younger patients, were asked whether they and their families would participate in the investigation. Altogether, 55 patients from 50 families took part; 26 had spinal muscular atrophy type II and 23 type III,³ while in six patients the onset had occurred after the age of 30. In three families two sibs were affected, and in a fourth family three sibs were affected. Controls comprised 110 healthy unrelated medical students and subjects attending the Regional Genetic Advisory Service. Specimens were HLA typed by the microcytotoxicity method standard in this laboratory.⁴ We examined 15 specificities at the HLA-A locus, 16 at the HLA-B locus, and four at the HLA-C locus, using a minimum of 73 different antisera, at least two for each specificity.

A significantly higher incidence of B18, a highly significant increase in B7, and a barely significant increase in A10 and decrease in A2 were apparent in the patients compared with controls (table). Since 31 antigens were studied, some apparently significant association is likely to occur by chance. When correction was made for this only the association with B7 remained highly significant. Since bias may be introduced by including several patients from a particular family, one patient was randomly selected from each family. B7 was then the only antigen that was significantly more common in patients than controls before and after correction. The incidences of the antigens were similar in patients with type II and type III disease.

No (%) of patients and controls positive for each antigen

HLA antigen	No (%) of patients (n=55)	No (%) of controls (n=110)	χ^2	P
A1	26 (47.3)	37 (33.6)	2.34	
A2	16 (29.1)	51 (46.4)	3.84	
A3	14 (25.5)	30 (27.3)	0.004	
A9 (incl 23, 24)	16 (29.1)	24 (21.8)	0.34	
A10 (incl 25, 26)	7 (12.7)	4 (3.6)		0.044
A11	8 (14.5)	13 (11.8)	0.01	
A28	4 (7.3)	3 (2.7)		0.142
A29	1 (1.8)	8 (7.3)		0.097
AW30	2 (3.6)	6 (5.5)		0.263
AW31	0	2 (1.8)		0.422
AW32	0	1 (0.9)		0.651
B5	1 (1.8)	11 (10.0)		0.079
B7	36 (65.5)	26 (23.6)	21.53	
B8	16 (29.1)	34 (30.9)	0.004	
B12	16 (29.1)	42 (38.2)	0.96	
B13	1 (1.8)	3 (2.7)		0.388
B14	0	4 (3.6)		0.176
B15	2 (3.6)	9 (8.2)		0.138
BW16	1 (1.8)	5 (4.5)		0.244
B17	4 (7.3)	8 (7.3)		0.245
B18	10 (18.2)	7 (6.4)	5.33	
BW21	1 (1.8)	3 (2.7)		0.399
BW22	0	4 (3.6)		0.194
B27	4 (7.3)	8 (7.3)		0.245
BW35	1 (1.8)	7 (6.4)		0.135
B37	0	0		
B40	3 (5.5)	12 (10.9)	0.97	
CW1	0	5 (4.5)		0.113
CW2	0	5 (4.5)		0.113
CW3	3 (5.5)	7 (6.4)		0.259
CW4	1 (1.8)	8 (7.3)		0.097

Comment

These results indicate that the HLA system is implicated in this group of disorders. This is the third disorder of the central nervous system to be associated with the B7 antigen (the others being multiple sclerosis and paralytic poliomyelitis, though the strengths and existence of the associations are not consistent in all the series). The

B7 antigen may perhaps be as specific for neurological disorders as the B8 antigen appears to be for the autoimmune disorders, and the B27 antigen for the arthropathies.

These findings, which are important for understanding the aetiology of the disease, relate to nearly all cases of spinal muscular atrophy in this region but should obviously be confirmed by other studies.

We are grateful to Mrs J Le Gassicke and Mrs D Gibson for their help with the patients and their families; to Mrs A Stephenson for her assistance with the computations; and to the National Institute of Allergy and Infectious Diseases, Bethesda, Maryland, and the National Tissue Typing Reference Laboratory, Bristol, for tissue-typing antisera.

¹ Pearn, J H, Carter, C O, and Wilson, J, *Brain*, 1973, **96**, 463.

² Pearn, J H, et al, *Journal of the Neurological Sciences*, 1978, **37**, 227.

³ Fried, K, and Emery, A E H, *Clinical Genetics*, 1971, **2**, 203.

⁴ Kissmeyer-Nielsen, F, and Thorsby, E, *Transplantation Reviews*, 1970, **4**, 121.

(Accepted 29 January 1979)

Departments of Human Genetics and Neurology, University of Newcastle upon Tyne, Newcastle upon Tyne NE2 4AA

G UPSTILL-GODDARD, BMEDSCI, medical student

D GARDNER-MEDWIN, MD, FRCP, consultant paediatric neurologist

D F ROBERTS, SCD, professor

J WENTZEL, MSC, scientific officer

Peripheral skin necrosis complicating beta-blockage

Cold extremities and Raynaud's phenomenon are reported as complications of most beta-blocking drugs used in hypertension.^{1,2} Peripheral gangrene complicating the use of propranolol and metoprolol has been reported in two hypertensive patients with peripheral vascular insufficiency.^{3,4} We describe three hypertensive patients who developed painful ischaemic lesions of the feet during treatment with beta-blockers, prompt and complete recovery occurring when treatment was stopped.

Case reports

Case 1—A 71-year-old man treated for moderate hypertension with propranolol 80 mg four times daily, clonidine, and hydrochlorothiazide-K complained in February 1976 of cold extremities; oxprenolol 80 mg thrice daily was substituted for propranolol. In December 1977 he complained of severe pain in both feet and was found two months later to have multiple areas of skin necrosis on the toes and soles of both feet (see figure). Foot pulses remained palpable throughout. Oxprenolol was stopped and he was treated with aspirin 300 mg twice daily and dipyridamole 25 mg four times a day. The ischaemic lesions resolved completely within one month. Erythrocyte sedimentation rate, cryoglobulin determination, and tests for rheumatoid factor and DNA-binding antibodies were all normal.

Case 1. Area of skin necrosis on fifth toe of right foot.

Case 2—A 73-year-old man was treated from May 1977 with atenolol 100 mg daily and chlorthalidone for mild hypertension. In December he complained of symptoms of Raynaud's phenomenon in the hands. The dose of atenolol was reduced to 50 mg daily but four months later he complained of extremely painful feet and was found to have necrotic patches 0.5-2 cm diameter on the toes and sole of the right foot. Foot pulses were normal in both feet, and results of investigations were normal, as in case 1. The ischaemic lesions resolved completely within one month of discontinuing atenolol.

Case 3—A 48-year-old housewife was treated with bethanidine and cyclopentiazide-K for hypertension after her fifth pregnancy in 1972. In December 1976 propranolol 80 mg thrice daily was added because of poor control. Two weeks after starting propranolol she noticed pain in both feet and developed extensive areas of skin necrosis on the toes. Foot pulses were normal but loud epigastric and femoral bruits were heard. In view of her uncontrolled hypertension the dose of propranolol was increased to 160 mg thrice daily. Two months later the feet were more painful, with weeping of the areas of infarction. Femoral and renal angiography showed classical fibromuscular hyperplasia causing narrowing of both renal arteries and the left iliac arteries but no atheroma. Results of other investigations were normal. Propranolol was stopped and the necrotic patches cleared completely.

Comment

These patients present a distinctive picture of severe pain in the feet with multiple small areas of skin necrosis. All were non-smokers receiving recommended doses of beta-blockers, and none had a history of peripheral vascular disease. Symptoms worsened with increase in the dose of propranolol in one patient (case 3), and complete, rapid resolution occurred in each case after beta-blocker withdrawal. This picture differs from other reports of gangrene complicating beta-blockade^{3,4} in that foot pulses remained palpable in all cases. The onset of symptoms during the winter in each case supports a vascular aetiology affecting the small vessels. The mechanism of this complication is unknown; alpha-adrenergic agonist potentiation by beta-blocking agents may be responsible.⁵ Beta-blockers should be used with extreme caution in the presence of known peripheral vascular insufficiency.² The complaint of cold extremities during the winter in patients taking beta-blockers may precede serious tissue damage and is an indication for close observation or a change in treatment.

¹ Zacharias, F J, *et al*, *American Heart Journal*, 1972, **83**, 755.

² Marshall, A J, Roberts, C J C, and Barritt, D W, *British Medical Journal*, 1976, **1**, 1498.

³ Vale, J A, Van de Pette, S J, and Price, T M L, *Lancet*, 1977, **2**, 412.

⁴ Vale, J A, and Jefferys, D B, *Lancet*, 1978, **1**, 1216.

⁵ White, C de B, and Udwardia, B P, *British Journal of Clinical Pharmacology*, 1975, **2**, 99.

(Accepted 22 January 1979)

Nuffield Department of Medicine, Radcliffe Infirmary, Oxford OX2 6HE

R GOKAL, MRCP, research fellow (now lecturer in medicine, University of Newcastle upon Tyne)

T L DORNAN, MRCP, senior house officer

J G G LEDINGHAM, DM, FRCP, May reader in medicine

Poisoning with tricyclic antidepressants: an avoidable cause of childhood deaths

Imipramine and amitriptyline are frequently prescribed for bed wetting in young children. These drugs are potentially lethal and are now the commonest cause of fatal poisoning in children under the age of 5 years.

Case report

A 4-year-old boy weighing 14 kg drank 90 ml of Tofranil Syrup (= 450 mg imipramine), which had been prescribed for his bed wetting. His mother, who was unaware of the poisonous nature of the drug, gave him a salt and water mixture, after which he vomited and then went to sleep. Four hours later he had a generalised fit, which lasted until he was given intravenous

diazepam in hospital. After this he remained unconscious but responded to painful stimuli. The electrocardiograph showed sinus rhythm with a rate of 180/min; his blood pressure was 110/70. Shortly after admission he developed ventricular tachycardia. Intravenous physostigmine and lignocaine failed to control this but after disopyramide, 25 mg given intravenously, sinus rhythm was restored. Cardiac monitoring was continued and he remained in sinus rhythm with a heart rate of 160-180 per minute until 18 hours after ingestion of the drug when he developed ventricular fibrillation. Sinus rhythm and an adequate circulation were restored by DC countershock but he had a further episode of ventricular fibrillation two hours later and could not be resuscitated.

Deaths due to accidental poisoning in children under 5 years of age

Years	No of patients		
	Salicylates	Iron preparations	Tricyclic antidepressants
1962-71	66	29	32
1972-6	6	6	17

Comment

Although accidental ingestion of drugs by young children is a common cause of hospital admissions, fatal poisoning is rare. In 1972 there were 16 000 such admissions and 25 deaths in the United Kingdom.¹ The numbers of deaths due to poisoning by preparations containing salicylates and iron have fallen dramatically in recent years and tricyclic antidepressants are now the commonest cause of fatal poisoning in children under the age of 5 years.²

Tricyclic antidepressants are the only drugs which are of any benefit in nocturnal enuresis and are widely prescribed for this purpose.³ Their exact mode of action is unknown but they affect both sleep patterns and the contractility of smooth muscle. They are seldom effective before the age of 7 or 8 years but are often prescribed, as in this case, for much younger children. Overdosage can cause convulsions, coma, cardiac arrhythmias, hypotension, and respiratory depression; there is no specific antidote, and treatment of massive overdosage is difficult. These effects have been well reported⁴ but there still seems to be widespread ignorance of the lethal nature of the drugs.

The age at which children acquire bladder control is very variable. Most are dry by day at the age of 5 years but roughly 10% of 5-year-olds wet the bed, as do 5% of 10-year-olds. While this is a great nuisance to the mother it seldom worries the child until he is 7 or 8 years old and its treatment with dangerous drugs cannot be justified. An explanation of the nature of enuresis to the child and his parents together with the use of a "star chart" will often produce dramatic improvement; if this fails a buzzer alarm, properly used, will cure at least 80% of enuretics in three months.⁵ We recommend, therefore, that no child with nocturnal enuresis should be treated with tricyclic antidepressants until he is at least 8 years old and has failed to respond to the above measures. The drugs should be dispensed only in tablet form in childproof containers which should carry a clearly visible warning about the lethal properties of their contents.

We are grateful to Mrs D J Folwell of the Office of Population Censuses and Surveys who supplied the statistics on the numbers of deaths from poisoning.

¹ Medicines Commission, *Report on the Presentation of Medicine in Relation to Child Safety*. London, Department of Health and Social Security, 1974.

² Office of Population Censuses and Surveys, *Deaths by Accidental Poisonings 1962-1976*. London, HMSO, 1978.

³ Blackwell, B, and Currah, J, in *Bladder Control and Enuresis*, ed I Kolvin, R C MacKeith, and S R Meadow, p 231. London, Heinemann Medical, 1973.

⁴ Steel, C M, O'Duffy, J, and Brown, S S, *British Medical Journal*, 1967, **3**, 663.

⁵ Dische, S, *Practitioner*, 1978, **221**, 323.

(Accepted 29 December 1978)

All Saints' Hospital, Chatham, Kent

A J CRONIN, MB, BCHIR, registrar in paediatrics

R KHALIL, MB, MRCP, registrar in paediatrics

T M LITTLE, MB, MRCP, consultant paediatrician