Delayed diagnosis in angiokeratoma corporis diffusum (Anderson-Fabry's disease)

Angiokeratoma corporis diffusum is a rare X-linked disorder caused by a deficiency of the enzyme α -galactosidase within the cellular lysosomes.¹ The circulating and urinary levels of the glycolipid ceramidetrihexoside are increased, causing gradual deposition of the abnormal lipid in the small vessels throughout the body.²

Clinical features

Pains in the fingers and toes beginning in late childhood are a major feature of the disorder. These are frequently transient but often excruciating. The cardinal sign is a cutaneous eruption consisting of tiny, painless, angiomatous punctae, confined mainly to the lower half of the body, although occasionally found within the mouth. Clusters occur over both trochanters and around the umbilicus, to which they impart a characteristic rosette appearance. Rare in women, the eruption in men may be concealed by the underpants. Corneal opacities, retinal vein abnormalities, and disturbances of temperature regulation are common, and renal failure or intracranial haemorrhages are the usual terminal events.³ Diagnosis based on biochemical assay alone is rare.⁴ We describe here three cases.

Case 1

At the age of 9 this patient was seen by a paediatrician for pains in the terminal finger joints and intermittent episodes of mild fever. All routine investigations were normal and a second opinion excluded any deficiency state as a cause of his diminutive stature. At 19 years investigations by a physician with an interest in arthritic conditions disclosed no abnormality. Domestic disharmony was noted and the development of similar symptoms in a younger brother (case 2) seemed to support the suggestion of a psychological disturbance. Diazepam was prescribed. At 24 years his distress was pronounced and dermatological advice was sought about the significance of a facial eruption and angiomatous flecks on the trunk.

Examination disclosed slowness of stature, elfin features, facial rosacea, and tiny angiomatous lesions concentrated over both hips and around the umbilical rim. The blood pressure was 160/100 mm Hg and the optic fundal veins were slightly tortuous. The electrocardiogram and chest radiograph were normal but the leucocyte α -galactosidase levels were low (see table).

Leucocyte enzyme levels

Enzyme	Values (nmol methylumbelliferone/min/mg protein)
α -Galactosidase	0.018
Controls (n = 14)	0.18-0.7
N-acetyl hexosaminidase	18.95
Controls (n = 3)	7.5-21.5
α -Mannosidase	2.73
Controls (n = 3)	0.6-5.3

Conversion: SI to traditional units—Methylumbelliferone: 1 nmol $\approx$ 176 ng/l.

Case 2

This patient, brother of the first, was 15 years old at the time of examination. His pain was less severe. He had attended many times for chronic bronchitis, strabismus, and chronic otitis media, which had left him deaf to conversational tones. The deafness, slight mental backwardness, a low pain threshold, and a jocular disposition all militated against an early diagnosis. Moreover, he was normotensive and had no cutaneous eruption. He had bilateral corneal opacities and grossly distorted retinal vessels, however. The electrocardiograph was normal, and as in case 1 the renal function was unimpaired.

Case 3

This patient, a cousin of the other two, was attending yet another doctor for hypertension. Maternal consent for full examination or investigation was withheld. The skin displayed the characteristic stigmata of the disorder, however.

Comment

Clinical diagnosis of this disorder eluded the endeavours of four skilful and experienced practitioners of general medicine. Furthermore, the third patient was investigated for jaundice in the medical

department of a teaching hospital, where his characteristic eruption passed without comment.

Recent advances in replacement treatment have increased the need for early recognition of this disorder,^{1,5} and, as little has been written about symptomatic support of these patients, wider discussion in the general medical press should facilitate detection and stimulate research. This is particularly the case with regard to the management of pain, about which relatively little has been written. We found that our patients benefited from carbamazepine in low doses.

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Hyponatraemia during carbamazepine treatment

Since the discovery in 1966 that the anticonvulsant carbamazepine has antidiuretic activity,¹ there has been only one report of water intoxication attributed to this drug.² The finding of hyponatraemia in an epileptic patient receiving carbamazepine led us to conduct a prospective study of the frequency of electrolyte imbalance in a group of carbamazepine recipients attending a neurology clinic. We present here the preliminary results.

Patients, methods, and results

Sixteen patients attending the neurology clinic of Glasgow Royal Infirmary were reviewed. Their average age was $37.1 \pm \text{SE}$ of mean 4.2 years, the average daily dose of carbamazepine 690 ± 81 mg, and the duration of treatment 22.4 ± 5.5 months. All were taking carbamazepine for epilepsy (14 patients) or trigeminal neuralgia (2 patients). Six patients were receiving the drug alone and the others were taking it with other anticonvulsants.

Details of patients on carbamazepine

Case No	Age (years)	Sex	Carbamazepine treatment		Cpss ($\mu\text{mol/l}$)	Plasma sodium (mmol/l)	Plasma osmolality (mmol/kg)	Other drugs
			Duration (months)	Daily dose (mg)				
1	60	M	60	1400	70	130	256	
2	60	F	60	1200	29	136	271	
3	29	F	60	1000	42	124	250	P
4	65	F	1	800	40	126	251	S
5	30	F	5	800	36	130	256	P
6	17	F	36	800	39	133	270	P
7	28	F	4	800	44	135	277	
8	68	F	21	750	29	142	300	V
9	27	M	11	600	31	135	278	V
10	14	F	36	600	22	135	280	Pr
11	34	M	4	600	24	138	281	
12	32	F	24	400	25	136	294	P
13	27	M	22	400	23	137	287	Pb
14	34	F	2	300	16	137	283	
15	39	M	11	300	21	138	280	V
16	30	M	2	300	18	141	295	

Cpss = Carbamazepine steady-state concentration. P = Phenytoin. S = Salbutamol. V = Valproic acid. Pr = Primidone. Pb = Phenobarbitone.

Conversion: SI to traditional units—Cpss: $1 \mu\text{mol/l} \approx 0.24 \mu\text{g/ml}$. Plasma sodium: $= 1 \text{ mmol/l} = 1 \text{ mEq/l}$. Plasma osmolality: $1 \text{ mmol/kg} = 1 \text{ mOsm/kg}$.

A 10-ml plasma sample was taken from each patient and analysed for urea, electrolyte, and carbamazepine concentrations, the latter being measured by gas chromatography, methaqualone being used as an internal standard. Plasma osmolality was measured by means of the depression of freezing point technique. The results were analysed with Wilcoxon's sum of ranks test.

Details of the 16 patients are given in the table. Five patients were hyponatraemic. All were receiving carbamazepine in a daily dose exceeding 700 mg, and all had steady-state carbamazepine blood concentrations exceeding 35 $\mu\text{mol/l}$ (8.3 $\mu\text{g/ml}$). There was a strong statistical association between hyponatraemia and daily doses of carbamazepine over 700 mg ($P=0.025$) and between hyponatraemia and steady-state carbamazepine blood concentrations exceeding 35 $\mu\text{mol/l}$ ($P=0.005$). The mean plasma sodium concentration in patients receiving more than 700 mg carbamazepine daily was $132 \pm \text{SE}$ of mean 2.0 mmol (mEq)/l, compared with 137 ± 0.7 mmol/l in patients receiving smaller doses. Comparable figures for plasma osmolality were 266 ± 6.0 mmol (mOsm)/kg and 285 ± 2.3 mmol/kg respectively. Mean plasma sodium concentrations in those with steady-state carbamazepine concentrations above and below 35 $\mu\text{mol/l}$ were 129.7 ± 1.7 mmol/l and 137.5 ± 0.7 mmol/l respectively, and the mean plasma osmolalities were 260 ± 4.5 mmol/kg 285 ± 2.80 mmol/kg respectively. There was no obvious relationship between hyponatraemia and age, sex, or duration of carbamazepine treatment. Two of the five hyponatraemic patients had been taking the drug for less than six months.

Comment

Carbamazepine has an action similar to antidiuretic hormone and is useful in the management of diabetes insipidus.³⁻⁵ Except for a patient who also suffered from psychogenic polydipsia,² there have been no reports of water intoxication in patients receiving carbamazepine for epilepsy or trigeminal neuralgia. Our study, which shows significant electrolyte disturbances in five out of 16 randomly chosen carbamazepine recipients, suggests that the antidiuretic activity of this drug is not confined to patients with diabetes insipidus. Although none of our patients complained of symptoms of water intoxication such as weakness, lethargy, or confusion, patients with plasma sodium concentrations below 135 mmol (mEq)/l, or osmolalities below 255 mmol (mOsm)/kg, may be at risk.

Our study shows that the risk of hyponatraemia is related to dose and blood concentration of carbamazepine. The data were insufficient to show whether there is a predisposition related to age or sex, but showed that duration of treatment was not important.

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Steroid responsiveness in phaeochromocytoma

Patients with a phaeochromocytoma suffer from disturbances of blood pressure and cardiac rhythm that are related to catecholamine release.¹ The pressor response in individual patients depends on several factors, which include levels of corticosteroids.² We report a case of phaeochromocytoma in which the typical hypertensive crises were related to steroids.

Case report

In 1973 a 69-year-old woman presented with giant-cell arteritis, which was confirmed histologically. Prednisone at an initial dosage of 60 mg daily produced rapid improvement and the erythrocyte sedimentation rate returned to normal. In December 1974, when taking 5 mg prednisone daily, she had forceful palpitations and generalised tremor three times in one week. These occurred without warning and lasted about 15 minutes. Between attacks her pulse rate remained about 80/min and her blood pressure about

160/90 mm Hg. No cause of the attacks was found, and there were no more for three months. Since the giant-cell arteritis was apparently in remission prednisone was withdrawn in April 1975. Within two weeks, however, severe headache had returned and her erythrocyte sedimentation rate was 80 mm in the first hour. Prednisone, 45 mg daily, rapidly abolished this syndrome, but the palpitations and tremor returned within three days. While on the high dose attacks occurred once or twice daily, and during them the blood pressure was about 240/140 mm Hg. When the prednisone was reduced to 5 mg daily the attacks almost ceased and the blood pressure remained normal. The presence of a phaeochromocytoma was confirmed by finding high levels of urinary vanillylmandelic acid and plasma catecholamines (see table). After location of the tumour by intravenous pyelography, arteriography was carried out, the premedication for which included 100 mg hydrocortisone. Before induction of anaesthesia one hour later, the blood pressure was 280/130 mm Hg despite preparatory blockade of adrenoreceptors with phenoxybenzamine and propranolol by mouth. Premedication for removing a large right adrenal tumour again included parenteral hydrocortisone, and again the patient's blood pressure was high on arrival in theatre. Blood pressure was controlled preoperatively with an infusion of sodium nitroprusside, and the phaeochromocytoma was removed uneventfully. After surgery the blood pressure was about 170/100 mm Hg despite large doses of steroids in the immediate postoperative period (100 mg hydrocortisone daily for the first three days, reducing to 10 mg prednisone daily within two weeks). There were no further hypertensive episodes, and maintenance steroid treatment was uncomplicated.

Levels of urinary vanillylmandelic acid and plasma catecholamines in present case compared with normal

	Normal value	Present case
Urinary vanillylmandelic acid ($\mu\text{mol}/24 \text{ h}$)	<40	58.5 66.0 64.5
Plasma catecholamines ($\mu\text{g/l}$): Total	0.6-1.0	6.9 6.6 5.4
Adrenaline	Nil-0.2	5.1 1.5
Noradrenaline	0.5-0.9	1.5 1.5

Conversion: SI to traditional units—Urinary vanillylmandelic acid: 1 $\mu\text{mol}/24 \text{ h} \approx 0.2 \text{ mg}/24 \text{ h}$.

Comment

Catecholamine crises in this patient were related to taking steroids, both by mouth and parenterally. After removal of the tumour, steroids exerted no hypertensive effect, and thus there appears to be a clear connection. Corticosteroids are important in the synthesis and action of catecholamines.² The enzyme that converts noradrenaline to adrenaline (phosphoethanolamine-N-methyltransferase, PNMT) is corticosteroid-dependent, so that only adrenal medullary tissue close to cortical tissue produces adrenaline in appreciable amounts.³ Systemic corticosteroid levels are unlikely to affect adrenaline synthesis, and a peripheral action is more likely to explain the phenomenon seen in our patient. Steroids control sodium metabolism within smooth-muscle cells of arterial walls, and depletion of sodium (consequent on low steroid levels) impairs the pressor response to catecholamines. This may be restored by infusing saline⁴ or replacing steroids. Our patient possibly had low circulating corticosteroid levels owing to suppression of the pituitary-adrenal axis caused by prednisone. Raising the steroid level allowed the pressor effect of catecholamines to become apparent. We agree with Critchley *et al*⁵ that steroids should be given only with care to patients with a phaeochromocytoma.

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