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Diabetes insipidus, diabetes mellitus, optic atrophy, and deafness

3 cases of 'DIDMOAD' syndrome

Juvenile diabetes mellitus may be associated with diabetes insipidus, optic atrophy, perceptive deafness, Friedreich's ataxia, Refsum's syndrome, and Laurence-Biedl syndrome (Rose *et al.*, 1966). Of these variants, the association of diabetes mellitus, diabetes insipidus, optic atrophy, and neurosensory hearing loss is becoming frequently recognized, and is thought to represent a single genetic trait, inherited as a Mendelian recessive (Sunder *et al.*, 1972; Page *et al.*, 1976). Because polyuria and polydipsia are features of both diabetes mellitus and diabetes insipidus, the continuing presence of the latter tends to be overlooked after adequate treatment of the former. In addition, since the onset of the optic atrophy, the diabetes insipidus, and the high tone deafness is usually during childhood and adolescence, evidence of the 'DIDMOAD syndrome' (DI diabetes insipidus; DM diabetes mellitus; OA optic atrophy; D deafness) should probably be sought more frequently. The following 3 case reports are illustrative, 2 patients being brothers.

Case reports

Case 1. A boy was born on 27 June 1961 in the UK of healthy, unrelated Italian parents, and weighed 3·2 kg. He progressed well but from the history obtained when he was 9·6 years he had had polyuria and polydipsia 'all his life', this having worsened during the previous year. Glycosuria in association with a fasting blood glucose of 12·5 mmol/l was noted and he was subsequently stabilized on Lente insulin 8 units daily with a diet containing 170 g carbohydrate. After 6 months insulin was withdrawn because glycosuria ceased, though polyuria and polydipsia persisted.

At 11·2 years because of growth failure he was reinvestigated and found to be frankly diabetic but without ketosis. Good control was achieved with Lente insulin 24 units daily. At 13·5 years when he complained of blurring of vision, height was 140 cm (3rd centile) and weight 38 kg (25th centile). There was no evidence of puberty and the bone age was 13·1 years. Blood pressure 110/65 mmHg. Vision in both eyes was 6/36. There was no vascular evidence of diabetic retinopathy but there was an enlarged blind spot bilaterally. Colour vision was markedly abnormal showing a red/green polarity indicating primary optic atrophy. Clinically the other systems were normal. An audiogram indicated bilateral high tone sensorineural hearing loss. Electroencephalogram (EEG) showed only a minor excess of slow-wave activity. Plasma and urinary antidiuretic (ADH) levels (Table) in the fluid-replete and fluid-deprived states were low, with little change across water deprivation. There was no specific aminoaciduria and the blood picture was normal.

Case 2. A boy was born on 27 September 1959 in Persia of healthy unrelated parents. Although the birthweight is not known he was normal at birth, was breast fed, and progressed satisfactorily, the milestones being reached at average times. At age 3·1 years he developed weight loss, polyuria, and polydipsia. A diagnosis of diabetes mellitus was made and insulin therapy begun without dietary control.

From age 6 years his growth was noted to be slower than average and from age 12 years he experienced progressive loss of vision and colour blindness. At age 16·5 years height was 147·8 cm (far below 3rd centile) and weight 37·6 kg (below 3rd centile). There was no evidence of puberty and the bone age was 13·4 years. BP 120/80 mmHg. Both optic discs showed central pallor, but the retinae were normal. No stigmata of disease were found in the other systems but there were several healing lesions of cutaneous leishmaniasis. Vision in both eyes was 1/60 and there was secondary type colour blindness with red/green polarity indicating optic atrophy. It was noted during his inpatient period that he had polyuria and polydipsia and fluid restriction caused considerable thirst and irritability.

An oral glucose tolerance test confirmed the presence of diabetes mellitus (fasting blood glucose 16·1; 30 min 29·0; 60 min 33·4; 90 min 31·0; 120 min 28·6 mmol/l (1 mmol/l glucose $\approx$ 18 mg/100 ml)).

Table *Urinary and plasma antidiuretic hormone levels before and after water deprivation*

Case no.	*0–1 hours Osmolality (mOsm/kg)*		*11–12 hours Osmolality (mOsm/kg)*		*Antidiuretic hormone**			
					Plasma (pg/ml)		*Urine (ng/h)*	
	Plasma	*Urine*	*Plasma*	*Urine*	*0–1 h*	*11–12 h*	*0–1 h*	*11–12 h*
1	293	113 (7·58 l)	291	312 (1·9 l)	*3·3	4·0	0·88	0·88‡
2	296	195 (2·5 l)	298	200 (1·8 l)	†0·6	0·7	0·23	0·61
3	300	345 (2 l)	305	327 (1·2 l)	†0·8	0·8	0·66	0·77

Normal values at 12 h

Plasma osmolality	< 294 mOsm/kg
Urine osmolality	> 828 mOsm/kg
Urine ADH	2·5–17 ng/h (Morton *et al.*, 1975‡)
Plasma ADH	4·0–9·0 pg/ml* } Normal range dependent on activity of the antibody used 2·0–4·0 pg/ml† }

Note: Volume of urine voided is given in parentheses.

Plasma and urinary ADH levels (Table) in the fluid-replete and fluid-deprived states were low and the increases after water deprivation were abnormally small. An audiogram indicated bilateral high tone sensorineural hearing loss of moderate severity. EEG and electroretinogram were normal but visual evoked response (VER) was reduced to peak-to-peak amplitude with increased latencies.

There was no specific aminoaciduria; the urinary glucose was not greater than 7·5% of the daily carbohydrate intake while on Lente insulin 42 units daily; the blood picture was normal and a full blood screen showed no indication of LE cells. Plasma proteins were normal in quantity and in fractionation; the cholesterol was 4·9 mmol/l (189·2 mg/100 ml) and serum triglycerides 0·95 mmol/l (84·1 mg/100 ml).

Case 3. A boy was born on 22 June 1965, the younger brother of Case 2 (a third boy, born in 1962, is healthy). The birthweight is not known but he was normal at birth and progressed well, milestones being reached at average times. At age 3 years he developed weight loss, polyuria, and polydipsia. Diabetes mellitus was diagnosed and he was treated with insulin but without dietary control. He has continued to grow 'normally' and there is no history of visual disturbance.

At age 10·7 years height was 132·3 cm (above 10th centile) and weight 29·4 kg (above 25th centile). There was no evidence of puberty and the testes were 8 ml volume each. BP 110/80 mmHg. The optic fundi showed no abnormality. Visual acuity was 6/6 but early evidence of blue colour blindness was present (i.e. loss of blue appreciation at periphery of visual fields); red and green were normally appreciated. No abnormalities were found in the other systems. It was noted during inpatient investigation that he had increased thirst and polyuria but he was able to sustain fluid deprivation better than his brother. A glucose tolerance test confirmed the presence of diabetes mellitus (fasting 8·2; 30 min 19·8; 60 min 26·8; 90 min 27·2 and 120 min 26·8 mmol/l). Plasma and urinary ADH levels (Table) in the fluid-replete and fluid-deprived states were low and did not increase significantly after water deprivation. An audiogram indicated slight bilateral high tone sensorineural hearing loss.

EEG, electroretinogram, and VER were all normal. There was no aminoaciduria and the daily urinary glucose was 8·5% of the daily carbohydrate intake when he was on Lente insulin 24 units daily. The blood picture was normal without evidence of LE cells. Plasma proteins were normal; plasma cholesterol was 6·2 mmol/l (239·4 mg/100 ml) and the serum triglycerides 1·6 mmol/l (141·6 mg/100 ml).

Discussion

The 3 patients conform to the clinical description of others in published reports. The onset of the various features of the syndrome is not regular. Most cases first present with diabetes mellitus. Optic atrophy however may be the presenting feature (Rorsman and Söderström, 1967) but it is not associated with retinitis pigmentosa as it is in other hereditary syndromes, e.g. Laurence-Moon-Biedl syndrome. The optic atrophy is of the primary type and is progressive, early cases showing only loss of blue appreciation while more advanced cases have complete colour blindness with severe loss of visual acuity. The diabetes insipidus, also of varied time of onset, is reported to be vasopressin sensitive, but we believe that the present data on ADH studies are the first to confirm that there is a lack of circulating

vasopressin. Nonetheless, vasopressin being elaborated by the cells of the supraoptic hypothalamic nuclei, the diabetes insipidus must represent a progressive degeneration of these hypothalamic cells or of the supra-optico-hypophyseal tract.

Many of the reported cases have had urinary tract abnormalities ranging from atonic bladder to hydronephrosis and hydroureter (Moore, 1971). While congenital absence or progressive degeneration of the neural plexus of ureter and bladder is a possible cause, it could be that the diabetes insipidus is contributory to the urinary tract dilatation. Reinvestigation after adequate treatment with vasopressin is clearly desirable.

The deafness in the syndrome has uniformly been reported to be of high-tone type; the afferent fibres of the cochlear nerve from the basal coils of the cochlea thus being involved. Published reports give no clear indication that there is progression of the deafness to suggest involvement of the afferent fibres from the middle and upper cochlear coils. However, the three neurological features of the syndrome (DI, OA, D) are almost certainly expressions of a progressive degenerative condition. Only the diabetes mellitus appears to be of extracranial aetiology, but a unifying pathology may ultimately be offered to account for all the clinical features.

Summary

Three children with diabetes insipidus, diabetes mellitus, optic atrophy, and high-tone deafness were shown to lack vasopressin, indicative of degeneration of the cells of the hypothalamic supraoptic nuclei. The syndrome being due to a single gene defect, inherited as an autosomal recessive, is therefore likely to be the result of an inborn error of metabolism with variable periods of latency in those affected.

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Pseudohypoparathyroidism

Variable manifestations within a family

The term pseudohypoparathyroidism (PHP) was first used by Albright *et al.* (1942) to describe a syndrome characterized by a typical facial appearance and short stature, with clinical and biochemical features suggestive of hypoparathyroidism. One of their 3 patients had short 3rd, 4th, and 5th fingers. All had an absent phosphaturic response to administered parathyroid extract. Surgical exploration of one patient showed normal parathyroid tissue. Similar developmental anomalies, but associated with normal serum calcium and phosphorus levels, were reported by Albright *et al.* in 1952, and this variant was termed pseudopseudohypoparathyroidism (PPHP). Several other conditions have now been described with dysfunction at various levels of the parathyroid-target tissue axis, with or without abnormal somatic features.

Case reports

We here report a family with 5 affected members (Fig.) showing different manifestations of this group of conditions. Their clinical, radiological, and biochemical features are summarized in the Table.

Discussion

It has been recognized for some time that PHP and PPHP can occur within the same family (Mann *et al.*, 1962). The expression of the physical and biochemical abnormalities in this group of conditions is extremely variable and ranges from short stature, mental retardation, subcutaneous calcification, hypocalcaemia, and many other manifestations to a single small metacarpal. The urinary cyclic adenosine 3′5′ monophosphate (cyclic AMP) response to exogenous