Facial dysmorphism: a marker of autosomal dominant cranial diabetes insipidus

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Abstract

We report a family with autosomal dominant cranial diabetes insipidus in which a characteristic facial appearance of hypertelorism, broad and prominent nasal bridge, short nose, and long philtrum is seen in affected members.

Familial cranial diabetes insipidus in man is inherited as either an autosomal dominant¹ or an X linked recessive trait.² In the rat, an autosomal recessive form of cranial diabetes insipidus is associated with a mutation in the gene encoding vasopressin. We report a family with autosomal dominant cranial diabetes insipidus in which a characteristic midline facial dysmorphism was found in affected subjects. This finding, which has not been recorded previously, is consistent with an embryonic or developmental origin of the endocrine dysfunction.

Case reports

CASE 1

Case 1 (IV·5) presented at the age of 13 with a lifelong history of thirst, polydipsia, and polyuria. There was a family history of diabetes insipidus (fig 1). On examination he was 175·9 cm tall (above the 97th centile); visual field testing and olfactory assessment proved normal and sexual development was at pubertal stage V. Ocular hypertelorism, epicanthic folds, and a broad, prominent nasal bridge with relatively short nose and long philtrum were noted (fig 2, table 1) and his mother commented that other affected family members had a similar facial appearance. CT head scan showed no abnormality

Figure 1 Family pedigree.

and a water deprivation test with DDAVP (1-deamino-8-D-arginine vasopressin) challenge was consistent with cranial diabetes insipidus (table 2A).

CASE 2

Case 2 (III·3), a 38 year old woman, presented after her son had been diagnosed as having diabetes insipidus. She gave a history of polydipsia, polyuria, and nocturia which began in her teens. She had breast fed both her children. Physical examination, including visual field and olfactory assessment, was normal and, apart from the absence of epicanthic folds, a similar dysmorphism was evident (fig 3, table 1). The biochemical results during water deprivation with DDAVP challenge (table 2B) were consistent with cranial diabetes insipidus.

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Figure 2 Anterior and lateral facial views of case 1 (IV·5). Note epicanthus, ocular hypertelorism, broad nasal bridge, short nose, and long philtrum.

Table 1 Measurements of inner canthal distance (ICD) and occipitofrontal circumference (OFC) in two dysmorphic and two normal family members.

Family member	ICD (cm)	OFC (cm)
IV·5 (case 1)	3·5 (+2 SD)	56 (90th centile)
IV·4	3·0 (−0·5 SD)	56·5 (97th centile)
III·3 (case 2)	3·4 (+1 SD)	54·5 (50th centile)
III·2	3·2 (mean)	58·0 (>97th centile)

Family history

IV·4 was investigated at the same time as her mother and found to have a normal response to water deprivation. She did not share the facial dysmorphism of her mother and brother (fig 4, table 1). II·2, III·1, and IV·2 were investigated elsewhere and confirmed to have cranial diabetes insipidus by water deprivation test. We are told that, unlike other family members,

Figure 3 Facial appearance of case 2 (III·3) showing hypertelorism, broad nasal bridge, short nose, and long philtrum.

Figure 4 Facial appearance of IV·4 (normal).

Table 2 Results of water deprivation test in cases 1 and 2.

Time (h)	Weight (kg)	Urine osmolality (mmol/kg)	Urine volume (ml)	Serum osmolality (mmol/kg)
A CASE 1				
0	56.5	189	—	286
1	—	181	300	290
4	55.0	126	800	292
6	55.0	—	560	—
7	54.5	218	760	294
Given 2 µg DDAVP at 8 hours				
8½	54.5	666	200	287
B CASE 2				
0	57.0	145	—	290
1	—	99	400	293
4	56.5	104	550	300
6	56.0	—	450	—
7	56.0	117	690	296
Given 2 µg DDAVP at 8 hours				
8½	56.0	187	300	306

the latter three patients share the dysmorphic features of cases 1 and 2 and this has been verified by review of family photographs.

Discussion

It is known that there is considerable interfamilial variation in the severity of autosomal dominant cranial diabetes insipidus, but there is also a tendency within families to regard the disease, even when severe, to be no more than an unpleasant family habit.³ This appears to have been the case for II·2 and III·3 who, despite having been symptomatic for many years, did not present to medical attention until their seventh and fourth decades respectively.

In the family reported here, there exists a definite correlation between the facial dysmorphism described and the presence of cranial diabetes insipidus. Furthermore, the history of breastfeeding in case 2 indicates that oxytocin deficiency is not a feature.

In the Brattleboro rat³ cranial diabetes insipidus is inherited as an autosomal recessive trait in which an abnormal, inactive vasopressin is produced owing to a frameshift mutation in the gene encoding the vasopressin hormone precursor.⁴ In man, the usual familial form of the disease is dominantly inherited and it is difficult to envisage how an abnormal peptide could produce a dominantly inherited effect. A developmental anomaly, rather than an abnormal vasopressin molecule, would seem a more likely aetiology in the human disease and this hypothesis is supported by the finding of a midline facial anomaly in the family reported.

Global or near global pituitary deficiency is well known in the major cranial midline developmental malformation syndromes such as holoprosencephaly.⁵ In addition, midline anomalies such as olfactory lobe hypo/aplasia and hyper- or hypotelorism may be associated with isolated anterior pituitary hormone deficiencies, such as GH deficiency⁵ and LHRH deficiency (Kallman's syndrome).⁶ Midline developmental anomalies of the brain associated with cranial diabetes insipidus have been reported in isolated cases.⁷ This is the first report describing evidence of an inherited midline developmental anomaly (dysmorphic facial features) associated with cranial diabetes insipidus.

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