document any similar environmental exposures or events in either of the mothers' pregnancies. The possibility of a neural crest disorder with low penetrance in the father offers the most likely explanation for the occurrence of half sibs with these disorders.

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Holoprosencephaly: variation of expression in face and brain in three sibs

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SUMMARY A family is described containing three sibs with holoprosencephaly. They showed a striking diversity of both cerebral and facial abnormalities. Autosomal recessive inheritance seems most likely. Because of the great variety in expression of this disorder, it is of importance for genetic counselling to examine both sibs and parents.

Holoprosencephaly is a malformation disorder comprising a basic defect in the development of the embryonic forebrain, which is often associated with facial anomalies.¹ The aetiology is heterogeneous. We report a family containing three sibs with holoprosencephaly showing a striking variation in expression of both cerebral and facial abnormalities. No similar published report could be found.

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Case reports

CASE 1

The first child, a girl, was normocephalic (OFC 33 cm, 50th centile=34 cm) and had shortening of the frontal skull, flattening of the nose, and severe microphthalmia of the right eye with a normal left eye. She was treated for seizures on the first day and she died two days later.

Necropsy showed shortening of the anterior fossa and hypoplasia of the lamina cribrosa. The brain (weight 255 g) showed a monoventricle, a marginal frontal indentation, hypoplasia of the frontal cortex and aplasia of the corpus callosum and the olfactory bulbs. No other congenital defects were found.

CASE 2

The second child, a boy, died on the first day of life. He was microcephalic (OFC 27 cm, 2nd centile=32 cm) and had a proboscis of 3.5 cm protruding from the glabellar region between two extremely

dysplastic and hypoplastic eyeballs. He had no nose and the mouth was very small.

Necropsy showed shortening of the anterior fossa and agenesis of the lamina cribrosa. The brain (weight 80 g) had a monoventricular, bag shaped telencephalon with agenesis of the septum pellucidum, the corpus callosum, and the olfactory bulbs. No other congenital defects were found. Chromosomes were normal.

CASE 3

The proband, the youngest child, a four year old boy, was admitted because of epileptic fits. He was born at 37 weeks after an uncomplicated pregnancy. His birth weight was 3860 g with an OFC of 34 cm (50th centile). At the age of three months a left sided cleft lip and palate was closed. Because of brachycephaly, a CT scan was performed at five months and showed bifrontal cortical atrophy, absence of the corpus callosum, and an interhemispheric fissure that could be traced from the occipital to the frontal pole. At the age of eight months diabetes insipidus was diagnosed.

Examination on admission showed a severely retarded, microcephalic boy (OFC 47 cm, 2nd centile=48 cm) with a scar on his upper lip, asymmetrical nostrils, a small penis, undescended testes, a divergent strabismus, and spastic tetraparesis (fig 1). He smiled at cuddling sounds and there was eye contact, but there were no intentional movements. Ophthalmological examination showed right optic atrophy and coloboma-like features of the left papilla. Another CT scan showed almost complete absence of both frontal lobes (fig 2). Extended laboratory investigations including chromosomal examination and endocrine screening showed no further abnormalities.

The parents were healthy and non-consanguineous. The mother was healthy during all pregnancies and did not take any medication. Physical examination of both parents showed no abnormalities, particularly no signs of hypotelorism, anosmia, or palatal or dental abnormalities. A six year old brother had developed normally. He showed no obvious dysmorphic features. Further examination was not permitted.

FIG 2 CT scan at four years of age showing loss of frontal brain parenchyma, resulting in a wide frontal pericerebral cerebrospinal fluid space.

FIG 1 The proband.

Discussion

Holoprosencephaly implies a whole or undivided forebrain. It includes a broad spectrum of abnormalities ranging from complete failure of differentiation of the telencephalic vesicles to a partial fusion of otherwise well developed hemispheres. According to DeMyer,¹ three cerebral types can be recognised: alobar, semilobar, and lobar. As a result of diencephalic dysgenesis, endocrine disorders are sometimes present.²

There is often an association with a range of facial midline deformities,³ probably resulting from a failure of embryonic interaction between the notochordal plate, the neuroectoderm of the brain-plate, and the oral plate.⁴

The correlation shown by DeMyer *et al*³ and summarised as 'the face predicts the brain' is illustrated by the reported cases. The least affected sib (case 3) had a cleft lip, flat nose, hypotelorism, and lobar holoprosencephaly on CT scan. The next (case 1) had hypotelorism with microphthalmia of the left eye and semilobar holoprosencephaly. The most severely affected (case 2) had cyclopia with alobar holoprosencephaly. We were unable to find any published report describing a comparable variation in one family.

The aetiology of holoprosencephaly is heterogeneous. Most cases are sporadic. Environmental factors, maternal disease, and several distinct chromosomal syndromes are associated with it.¹⁻⁵ Autosomal dominant inheritance with incomplete penetrance and wide variability, sometimes with minimal involvement, as well as autosomal recessive inheritance have been described.⁵

Although in most disorders with autosomal recessive inheritance the extent of the malformation is usually similar, the absence of minor signs in the parents, the negative medical history in all the pregnancies, and the fact that three out of four

children in one sibship were affected makes autosomal recessive inheritance in this family most likely.

In a study of 30 families in which a child with a severe form of holoprosencephaly was born, Roach *et al*⁶ found that two out of 35 subsequent children of 18 of the mothers had holoprosencephaly. The empirical recurrence risk was estimated as 6% (± 4). Because of the wide variation in expression of this disorder, extensive examination of sibs and parents for minor manifestations, such as anosmia, single central incisor, hypo- and hypertelorism, and hypothalamic-pituitary dysfunction, is essential for genetic counselling. If Mendelian patterns of inheritance are established for particular families, the recurrence risk increases accordingly.¹⁻⁶

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Thanatophoric dysplasia in identical twins

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SUMMARY Female twins concordant for thanatophoric dysplasia are presented. Monozygosity was confirmed using minisatellite DNA genetic fingerprinting. The evidence

supporting new dominant mutations as the likely cause of thanatophoric dysplasia is reviewed.

Conflicting conclusions have been reached regarding the mode of inheritance of thanatophoric dysplasia.

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