Triophthalmia and facial clefting: a case report

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Abstract

We describe a Libyan boy with an unusual phenotype of multiple congenital anomalies, including triophthalmia, dolichocephaly, porencephaly, cleft lip/palate, facial asymmetry, microgastria, and VSD. The reported phenotype is likely to represent a new entity of non-chromosomal syndromic triophthalmia. Other possibilities are discussed. (J Med Genet 1998;35:875–877)

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The formation of additional eyes in animals has recently been achieved through experimental genetic manipulations.1,2 The human eye develops from the optic primordium at about 4 weeks' gestation. The neural ectoderm induces the formation of the optic vesicle/cup from the forebrain which gives rise to the retina. The somatic ectoderm is in turn induced by the optic vesicle giving rise to the lens, which then induces the formation of the corneal epithelium from somatic ectoderm.3 Several genes involved in the regulation of eye development have now been identified, including the mouse Pax6 gene, which is believed to play a master role in triggering the development of eye components.4 The development of the eye is also under the influence of several growth factors, for example, the nerve growth factor and transforming growth factor β.5 Retinoic acid and its receptors also represent key molecules in the development of the eye6 that, in high concentrations, have recently been shown to induce duplication of eye components in animals.7 The proband in the present report had unusual craniofacial dysmorphism with a unique phenotype of syndromic non-chromosomal triophthalmia. The phenotype, which is likely to represent a new syndrome, is critically discussed with emphasis on the possible causal mechanism.

Case report

The proband was a male, delivered at term by caesarian section because of macrocephaly. The pregnancy was uneventful and there was no history of drug intake or exposure to irradiation, infection, or teratogens during the pregnancy. The Libyan parents and the 3 year old older sister were phenotypically normal. At 6 months of age the proband's weight was 4800 g (<3rd centile), length 54 cm (<3rd centile), and head circumference (OFC) 44 cm (50th centile). The baby had dolichocephaly and a prominent, asymmetrical forehead with a widow's peak. The left eye was larger than the right eye with a downward slanting left palpebral fissure, hypoplasia/ectropion of the left lower eyelid, and corneal opacity. The right microphthalmic eye had intact extraocular muscular movements and normal vision. An additional third eye was noted on the left temporal side with a complete globe, upper/lower lids, and

Figure 1 Photographs of the proband showing facial dysmorphism and triophthalmia.
lashes, extraocular muscles, and lacrimal apparatus (fig 1). The right eyebrow was normally placed while the left eyebrow extended above both the left eye and the supernumerary third eye. There was a left sided complete cleft lip/palate with hypoplasia of the left nasal ala and deformed left nostril. The ears were low set and posteriorly angulated. The baby had micrognathia and his face was asymmetrical with a more prominent left cheek and more posteriorly rotated left ear (fig 1). He was fed by nasogastric tube, had no vomiting, and his growth and speech development were appropriate for age. He could hear and respond to sounds by turning his head towards the appropriate side. All four limbs, back, spine, and genitalia were normal and there was no abnormality detected on chest and abdominal examination. A left parasternal murmur was clinically detected over the 3rd and 4th intercostal spaces, which was confirmed by echocardiography to be related to the presence of VSD. Examination of the nervous system showed intact sensation, normal muscle power, tone, and reflexes with a positive grasp reflex, age appropriate Babinski response, normal tendon jerks, and absence of clonus. Head CT scan showed porencephaly, dilated ventricles, and brain atrophy. A defective left maxilla was shown on skull x-ray. Chromosomal study with banding techniques indicated that the child had a normal male karyotype (46,XY) while a urine spot test and TLC for amino acids and mucopolysaccharides showed normal/negative results. The child died at the age of 6 months after reconstructive surgery for his cleft lip/palate. No necropsy was attempted.

Discussion

The unique craniofacial malformation described here is characterised by the presence of syndromic triphalialia associated with dolichocephaly, porencephaly, brain atrophy, cleft lip/palate, micrognathia, and VSD. In humans, an additional ectopically placed eye has been described in only one previous report. The profile in the present report, in addition to the previous report, could well represent a new syndromic entity caused by a mutation in a pleiotropic gene of the patterning hierarchy involved in early embryogenesis. Of particular interest are those genes implicated in the regulation of eye development, of which several members have now been identified in different species with a remarkable degree of structural/functional conservation. Recent experimental work has shown that ectopic expression of some of these genes results in the formation of additional eyes. 1 2

Before we designate the described phenotype a new syndrome, other possible causal mechanisms also need to be considered. Some features of the reported profile show similarity to the human homologue of the mouse disorganisation (Ds, MIM 222300). In the mouse, the phenotypic expression of the mouse mutant Disorganisation gene is so diverse that no two affected mice have identical malformations. The developmental anomalies associated with Ds involve structures derived from all three germ layers. The mutation is semidominant with variable penetrance, depending on the genetic background of the mice, and is usually lethal in homozygotes. 3 4

The anomalies described in Ds mice include body surface projections, such as hamartomas, nodules, and papillae. Also seen are supernumerary limbs and anomalies of the extremities, such as duplications and reductions. Body wall defects include gastroschisis and thoracosphisis and various anomalies of the internal organs. 5

Craniofacial anomalies and eye defects also exist, 6 although triphalialia has never been described before. The abnormal findings of the human homologue of the mouse mutant Disorganisation (Ds) have been reviewed in numerous reports. 7 9 13 20

Features of the reported baby which are compatible with the diagnosis of Ds include the presence of facial asymmetry, cleft lip/palate, micrognathia, low set ears, and CNS anomalies with brain atrophy, porencephaly, and dilated ventricles. The absence of limb anomalies, abdominal wall defects, and body projections in a described phenotype makes the diagnosis of Ds less likely, albeit not totally excluded, since limb anomalies were detected in only a third of the Ds mice described by Hummel et al and were absent in the patient reported by Van Langen and Hennekam. 21 However, the possibility of holoprosencephaly 22 should not be considered because of the absence of its characteristic facial features and the lack of brain cleavage disorder on head CT scan.

It is clear that the gene(s) related to the expression of the unusual phenotype of the proband represents an integral part of the patterning hierarchy involved in early development of the eye, face, and heart.

References

11 Robin NH, Adeawale OO, McDonald-McGinn D, Nadeau JH. Human malformations similar to those in the mouse mutant disorganisation (Ds). Hum Genet 1993;92:461-4.


