Microphthalmia with single central incisor and hypopituitarism

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Abstract

A patient is described with a new association of microphthalmia, single central incisor, and hypopituitarism believed to represent a holoprosencephaly malformation. In view of the genetic ramifications of this malformation and its variable manifestations, we would like to alert the clinician to consider holoprosencephaly whenever midline malformations are detected.

In 1977 Rappaport *et al*¹ described the syndrome of 'monosupero-centroincivodontic dwarfism', characterised by a single central incisor associated with growth retardation. Since then a variety of midline facial defects have been described, including single central maxillary incisor associated with slow growth secondary to growth hormone deficiency.¹⁻³ Holoprosencephaly, an anatomical defect of failure of division of the embryonic forebrain, is associated with midline facial defects and suggests that this condition might have a wide variety of clinical manifestations. The case described reports a newly delineated association of a single central incisor in a patient with microphthalmia and growth retardation as possible manifestations of holoprosencephaly.

Case report

The proband, a 5 year 1 month old female, was referred to the Department of Pediatrics, University of Nevada School of Medicine for evaluation of 'slow growth'. She was born at term, birth weight 2948 g, to a 19 year old G2P1 female whose pregnancy was unremarkable; there was no exposure to alcohol or drugs. The proband's only pertinent past medical history included 'slow growth', periodic severe headaches requiring treatment with paracetamol (Tylenol),

intermittent nasal congestion, and near complete blindness secondary to microphthalmia. Neuromotor development and intelligence were otherwise normal.

Family history was entirely negative including anosmia. Physical examination showed a small, well proportioned female with microphthalmia (figure). Her height was 82.5 cm and weight 8.8 kg, both well below 3 SD and at the 50th centile for an 18 month and 9 month old respectively. Additional findings included opaque corneas and a single central maxillary incisor. Laboratory assessment for thyroid function, electrolyte abnormalities, and serum glucose were normal. Urine osmolality showed normal concentrating ability and blood chromosome studies using banding techniques was normal. Radiological evaluation indicated a bone age of 2 years 5 months and CT scan showed a small sella turcica with a hypoplastic appearing pituitary gland. The optic chiasm and nerves appeared normal, as did the orbital sockets. A small bony ridge was noted in the roof of the hard palate. Magnetic resonance imaging of the brain was normal except for a diminished hypo-

The proband aged 6 1/2 years. Note single central maxillary incisor and opaque corneas.

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physal stalk. Provocative stimulation tests for growth hormone, using clonidine 0.15 mg/m², followed by L-dopa 125 mg, yielded a peak growth hormone level of 1.3 ng/ml (normal >7 ng/ml). Insulin hypoglycaemia (0.1 U/kg iv) elicited no growth hormone response; however, there was a normal cortisol response with a peak level of 43.6 µg/dl. GHRH-44 (1.0 µg/kg) showed a growth hormone peak of 5 ng/ml at 15 minutes, well below that of normal controls (>10 ng/ml).⁴ GNRH (100 µg) elicited a normal prepubertal FSH and LH response (peak FSH 12.2 mIU/ml at 120 minutes, peak LH 13.7 mIU/ml at 30 minutes). TRH stimulation (7 µg/kg) yielded a normal peak TSH at 9.1 IU/ml. Based on these data, the patient has been defined as having isolated growth hormone deficiency.

Discussion

Holoprosencephaly is an embryonic malformation involving the forebrain and midface. There is wide range of variability in the manifestation of this abnormality. Brain malformations may range from an abnormally small forebrain with no hemispherical development to normal brain differentiation. In addition, there are varying degrees of dysplasia of olfactory bulbs and nerves, optic nerves, and the corpus callosum. Facial anomalies have been noted to have a wide range of severity, from anophthalmia and cyclopia to mild hypotelorism or a single central incisor.⁵ Recently, an ocular abnormality, coloboma, has been reported associated with single central incisor and growth failure. The mother of this patient had hyposmia and the authors pointed out that this case probably represents an autosomally dominant inherited form of holoprosencephaly.⁶ We believe that our patient with the ocular abnormality of microphthalmia, a single central incisor, and hypopituitarism, all individually known to be associated with holoprosencephaly, probably represents a mild manifestation of this abnormality.^{5,7} In fact, the sole

clinical manifestation of holoprosencephaly may be a single central incisor.

The importance of recognising these milder manifestations of holoprosencephaly relates to the need for genetic counselling, as holoprosencephaly may be inherited as an autosomal dominant trait.^{6,8,9} A number of case reports describe a parent with minor manifestations of holoprosencephaly, that is, a single central incisor, hypotelorism, or hyposomia, and offspring with severe manifestations.^{6,8,9} Lastly, it is hoped that this report emphasises a new ocular abnormality associated with a single central incisor, and brings to the clinician's attention the wide spectrum of clinical abnormalities associated with holoprosencephaly.

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