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 'monosuperoentrocincivodontic 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-
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physiologic 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). GNRH (100 µg) elicited a normal pre-
pubertal 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 hemispheric
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. 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 autosomal dominant
inherited form of holoprosencephaly. We believe
that our patient with the ocular abnormality of
microphthalmia, a single central incisor, and hypo-
pituitarism, all individually known to be associated
with holoprosencephaly, probably represents a mild
manifestation of this abnormality. In fact, the sole
clinical manifestation of holoprosencephaly may be a
single central incisor.

The importance of recognising these milder mani-
festations of holoprosencephaly relates to the need for
genetic counselling, as holoprosencephaly may be
inherited as an autosomal dominant trait. A
number of case reports describe a parent with minor
manifestations of holoprosencephaly, that is, a single
central incisor, hypotelorism, or hyposomma, and
offspring with severe manifestations. 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.

We appreciate the cooperation of Dr S Kaplan of the
University of California, San Francisco, in providing the
GHRH-44 studies.

1. Rappaport EB, Ulstrom RA, Gorlin RJ, Lucky AW, Colle E,
Miser J. Solitary maxillary central incisor and short stature.
2. Züppinger KA, Sutter M, Zurbrugg RP, Joss EE, Oetiker O.
Cleft lip and choioideal coloboma associated with multiple
hypothalamic-pituitary dysfunctions. J Clin Endocrinol Metab
3. Sadeghi-Nejad A, Senior B. Autosomal dominant transmission of
isolated growth hormone deficiency in iris-dental dysplasia
release in response to human pancreatic tumor growth hormone-
releasing hormone-40 in children with short stature. J Clin
5. Munke M, Emanuel BS, Zackai EH. Holoprosencephaly:
association with interstitial deletion of 2p and review of the
6. Liberfarb RM, Abdo OP, Pruett RC. Ocular coloboma associated
with a solitary maxillary central incisor and growth failure:
manifestations of holoprosencephaly. Am Ophthalmol 1987;19:
226-7.
K. Single central maxillary incisor and holoprosencephaly. Am
9. Berry SA, Pierpont ME, Gorlin RJ. Single central incisor in
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doi: 10.1136/jmg.27.3.192

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