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Holoprosencephaly Overview

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Summary

Disease characteristics. Holoprosencephaly (HPE) is a structural anomaly of the brain in which the developing forebrain fails to divide into two separate hemispheres and ventricles. HPE encompasses a continuum of brain malformations including alobar HPE (a single ventricle and no separation of the cerebral hemispheres); semilobar HPE (the left and right frontal and parietal lobes are fused and the interhemispheric fissure is only present posteriorly); and lobar HPE (most of the right and left cerebral hemispheres and lateral ventricles are separated but the most rostral aspect of the telencephalon, the frontal lobes, are fused, especially ventrally). Other CNS abnormalities not specific to HPE may also occur. HPE is accompanied by a spectrum of characteristic craniofacial anomalies in approximately 80% of individuals with HPE. Developmental delay is present in virtually all individuals with the HPE spectrum of CNS anomalies. Seizures are common. Almost without exception, severely affected children do not survive beyond early infancy; a significant proportion of more mildly affected children survive past 12 months.

Diagnosis/testing. Imaging of the brain by CT scan or (preferably) MRI confirms the diagnosis of HPE, defines the anatomic subtype, and identifies associated CNS anomalies. Approximately 25%-50% of individuals with HPE have a numerical or structural chromosomal abnormality. Approximately 18%-25% of individuals with monogenic HPE have a recognizable syndrome and the remainder have nonsyndromic HPE. Nonsyndromic HPE-causing mutations and/or deletions/duplications in the genes *SHH*, *ZIC2*, *SIX3*, *TGIF*, *PTCH1*, and *TMEM1* and deletion of the HPE6 locus (2q37.1-q37.3) can be identified using clinically available testing.

Management. *Treatment of manifestations:* treatment by a multidisciplinary team when possible; hormone replacement therapy for pituitary dysfunction; antiepileptic drugs for seizures; gastrostomy tube/Nissen fundoplication for feeding difficulties/gastroesophageal reflux; special feeding devices and surgical repair of cleft lip and/or palate; ventriculo-peritoneal shunt placement for hydrocephalus; parental support and counseling. *Prevention of secondary complications:* prompt evaluation of children with hormonal disturbances during

times of stress (e.g., illness, surgery); attention to fluid and electrolyte management during surgery. *Surveillance:* during health maintenance evaluations, measurement of height, weight, and head circumference and evaluation for endocrine deficiencies.

Genetic counseling. HPE can result from environmental causes, from an inherited or *de novo* chromosome abnormality, an inherited monogenic disorder, a *de novo* mutation for an autosomal dominant disorder, or from unknown causes. Genetic counseling and risk assessment depend on determination of the specific cause of HPE in an individual.

Definition

Clinical Manifestations

Holoprosencephaly (HPE) is a structural anomaly of the brain in which the developing forebrain fails to divide into two separate hemispheres and ventricles. The forebrain (prosencephalon) incompletely cleaves into right and left hemispheres, and into the olfactory and optic bulbs and tracts (for review, see Golden 1998, Muenke & Cohen 2000, Lacbawan & Muenke 2002, Ming & Muenke 2002, Edison & Muenke 2003, Gropman & Muenke 2005).

Phenotypes of HPE identified in a continuum of brain malformations include the following:

- **Alobar HPE,** the most severe, in which there is a single ventricle and no separation of the cerebral hemispheres
- **Semilobar HPE,** in which the left and right frontal and parietal lobes are fused and the interhemispheric fissure is only present posteriorly
- **Lobar HPE,** the mildest, in which most of the right and left cerebral hemispheres and lateral ventricles are separated but the most rostral aspect of the telencephalon, the frontal lobes, are fused, especially ventrally
- **Middle interhemispheric fusion variant (MIHF or syntelencephaly),** in which there is failure of separation of the posterior frontal and parietal lobes, with varying lack of cleavage of the basal ganglia and thalami, and absence of the body of the corpus callosum but presence of the genu and splenium of the corpus callosum. It is debated whether MIHF is part of the HPE spectrum or a separate entity [Barkovich & Quint 1993].

Other structural CNS findings that may occur but are not specific to HPE include anomalies of midline structures: undivided thalami, absent corpus callosum [OMIM 217990], callosal dysgenesis [Barkovich 1990, Rubinstein et al 1996], absent septum pellucidum and absent or hypoplastic olfactory bulbs and tracts (arrhinencephaly) and optic bulbs and tracts; macrocephaly secondary to hydrocephalus; Dandy-Walker malformation; neuronal migration anomalies; abnormal circle of Willis [Arnold et al 1996]; and caudal dysgenesis [Martinez-Frias et al 1994].

A spectrum of craniofacial anomalies accompanies HPE in approximately 80% of affected individuals. In the majority of individuals with HPE, a correlation exists between the facial anomalies and the subtype of HPE (see **Figure 1** and **Subtypes of HPE and Range of Craniofacial Findings**); however, many examples exist in which this correlation cannot be made, particularly in individuals with milder forms of HPE and those with mutations in *ZIC2* [Brown et al 1998,Brown et al 2001]. Of note, individuals with all subtypes of HPE can have a relatively normal facial appearance. Conversely, some individuals with typical facial findings for HPE who have mutations in *GLI2* have hypopituitarism but no CNS findings consistent with HPE [Roessler et al 2003].

The spectrum of facial anomalies begins with cyclopia and extends in an unbroken continuum to the normal face as seen in individuals who have, but are not expressing, a mutation for HPE inherited in an autosomal dominant manner. The extremely variable phenotypic expression occurs both in simplex HPE (i.e., a single occurrence in a family) and among members of the same family with an inherited form of HPE.

Malformations of the nose include complete absence, agenesis of the nasal cartridge, and proboscis (flat nose with a single central nostril without nasal bones) [Hennekam et al 1991].

Palatal anomalies include various midline and lateral clefts, midline palatal ridge [Kjaer et al 1997], bifid uvula, and absence of the superior labial frenulum [Martin & Jones 1998].

A single central incisor may be present [Nanni et al 2001]. Although a single central incisor is a nonspecific finding, it is a distinctive microform in autosomal dominant HPE [Berry et al 1984].

Subtypes of HPE and the Range of Possible Craniofacial Findings—Alobar HPE (Figure 2). Range of findings:

- Cyclopia: single eye or partially divided eye in single orbit with a proboscis above the eye
- Cyclopia without proboscis
- Ethmocephaly: extreme ocular hypotelorism but separate orbits with proboscis between the eyes
- Cebocephaly: ocular hypotelorism with single-nostril nose
- Premaxillary agenesis with median cleft lip, ocular hypotelorism, flat nose
- Bilateral cleft lip
- Ocular hypotelorism only
- Anophthalmia or microophthalmia
- Relatively normal facial appearance

Semilobar HPE (Figure 3). Range of findings:

- Bilateral cleft lip with median process representing the philtrum-premaxilla anlage
- Flat nasal bridge
- Absent nasal septum
- Flat nasal tip
- Midline cleft (lip and/or palate)
- Ocular hypotelorism
- Flat nose
- Anophthalmia/microophthalmia
- Relatively normal facial appearance

Lobar HPE (Figure 4). Range of findings:

- Bilateral cleft lip with median process
- Ocular hypotelorism

- Flat nose
- Relatively normal facial appearance

Middle interhemispheric fusion (MIHF) variant (Figure 5). Range of findings:

- Relatively normal facial appearance

Microforms of HPE that can be observed in relatives of probands with HPE (see Figure 6) include the following:

- Microcephaly [Heussler et al 2002]
- Single central maxillary incisor [Nanni et al 1999, Nanni et al 2000]
- Ocular hypotelorism
- Anosmia/hyposmia (resulting from absence of olfactory tracts and bulbs)
- Iris coloboma
- Absent superior labial frenulum [Martin & Jones 1998]
- Midface hypoplasia
- Congenital nasal pyriform aperture stenosis [Arlis & Ward 1992, Lo et al 1998]
- Developmental delay [Heussler et al 2002]

Clinical manifestations commonly observed in children with HPE include the following:

- **Developmental delay** is present in virtually all individuals with the HPE spectrum of CNS anomalies. The degree of delay is variable, correlating with the severity of the brain malformation.
- **Short stature and failure to thrive** are common, especially in more severely affected children. Growth hormone deficiency and/or chromosomal anomalies may in part be responsible for poor growth in selected cases. Many children are born with normal length, weight, and head circumference, but it is common for growth to fall off postnatally. Appropriate growth may occur with lower than expected caloric intake. When growth delay is present at birth, the phenomenon of "catch-up" growth does not occur despite adequate caloric intake.
- **Seizures** are common.
- **Hydrocephalus** can occur.
- **Hypothalamic and brain stem dysfunction** may lead to swallowing difficulties and instability of temperature, heart rate, and respiration.
- **Pituitary dysgenesis** is manifested by partial or complete panhypopituitarism with abnormal function of any or all of the anterior and/or posterior pituitary hormones.
- **Feeding difficulties** may be a major problem in children with HPE. At least part of the difficulty may derive from axial hypotonia, poor suck because of neurologic complications, lethargy, seizures and their effects, side effects of medications, and lack of interest. Often gastroesophageal reflux, choking, and gagging occur with feeds. More common problems include slowness in eating, frequent pauses, and frank vomiting with risk of aspiration. Oral-sensory dysfunction may affect feeding especially when associated with textural aversion and labial and lingual weakness. Children with cleft lip and/or palate often have additional difficulties with oral feeding.

- **Excessive intestinal gas/colic,** irritability, and constipation frequently occur [Barr & Cohen 1999].
- **Aspiration pneumonia** can be a complication of poor coordination of swallowing.
- **Erratic sleep patterns** can occur.

A common misperception is that children with HPE do not survive beyond early infancy. While this is the case for the most severely affected children, a significant proportion of more mildly affected children survive past age 12 months. Among affected individuals with a normal karyotype, an inverse relationship exists between the severity of the facial phenotype and length of survival.

- Infants with cyclopia or ethmocephaly generally do not survive beyond age one week [Croen et al 1996].
- Approximately 50% of children with alobar HPE die before age four to five months and 20% live past the first year of life [Barr & Cohen 1999].
- More than 50% of children with isolated semilobar or lobar HPE without significant malformations of other organs are alive at age 12 months [Olsen et al 1997, Barr & Cohen 1999].

Almost all survivors have apparently normal vision and hearing; they smile and demonstrate memory [Barr & Cohen 1999].

Establishing the Diagnosis

Imaging of the brain by CT scan or MRI confirms the diagnosis of HPE, defines the subtype, and identifies associated CNS anomalies such as hydrocephalus [Barkovich & Maroldo 1993, Barkovich et al 2002]. The study of choice is cranial MRI examination, preferably obtained with adequate sedation at a pediatric center experienced in evaluating children for structural brain anomalies. Review of the study by a radiologist or other clinician familiar with the subtypes of HPE is essential.

HPE is most frequently diagnosed during the newborn period when abnormal facial findings (see **Subtypes of HPE and Range of Craniofacial Findings**) prompt further evaluation. Infants with normal facies or only mildly abnormal facies and either mild or intermediate brain anomalies may not be diagnosed as having HPE until later during the first year of life when neuroimaging studies are obtained during evaluation for developmental delay and/or failure to thrive.

Prevalence

HPE is the most common forebrain defect in humans, with a prevalence of 1:250 in embryos (for review see Edison & Muenke 2003) and 1:10,000 to 1:20,000 at birth [Orioli et al 2001].

Causes

Environmental Causes

The most common teratogen in humans known to cause holoprosencephaly (HPE) is maternal diabetes mellitus. Infants of diabetic mothers have a 1% risk (a 200-fold increase) for HPE [Barr et al 1983]. Other teratogens, including alcohol and retinoic acid, have been associated with HPE in animal models, although their significance in humans is not established.

More recently, cholesterol-lowering agents have been associated with HPE, although a causal relationship between prenatal statin use and HPE in the infant has not yet been proven [Edison & Muenke 2004a, 2004b].

An animal model of maternal hypocholesterolemia has been shown to cause HPE. Preliminary studies in humans show that maternal hypocholesterolemia can be associated with HPE in her offspring [Edison & Muenke 2003; Kelley & Muenke, unpublished].

Heritable Causes

Chromosomal—Approximately 25%-50% of individuals with HPE have a chromosomal abnormality. Chromosomal abnormalities are nonspecific and either numeric or structural. Those with HPE and a normal karyotype cannot be distinguished from those with an abnormal karyotype on the basis of craniofacial abnormality or subtype of HPE; however, individuals with HPE as a result of a cytogenetic abnormality are more likely to have other organ system involvement [Olsen et al 1997].

Numeric chromosomal abnormalities include trisomy 13, trisomy 18, and triploidy. Arrhinencephaly is seen in approximately 70% of individuals with trisomy 13, which has a birth prevalence of 1:5000. Defects of the corpus callosum have been reported with trisomy 18.

Structural chromosomal abnormalities have been reported in virtually all chromosomes, but the most frequent in descending order are deletions or duplications involving various regions of 13q, del(18p), del(7)(q36), dup(3)(p24-pter), del(2)(p21), and del(21)(q22.3) [M Muenke, personal observations]. Significant phenotypic variation exists among individuals with a similar cytogenetic deletion [Schell et al 1996].

Single Gene —Syndromic HPE. Approximately 18%-25% of individuals with HPE have a mutation in a single gene causing syndromic HPE. At least 25 different conditions have been described in which HPE is an occasional finding; the majority of these disorders are rare. Some of the more common include the following, categorized by mode of inheritance:

- **Autosomal Dominant**
  - Pallister-Hall syndrome
  - Rubinstein-Taybi syndrome
  - Kallmann syndrome
  - Martin syndrome (with clubfoot, spinal anomalies)
  - Steinfeld syndrome (with congenital heart disease, absent gallbladder, renal dysplasia, radial defects) [OMIM 184705]
  - Ectrodactyly and hypertelorism
- **Autosomal recessive**
  - "Pseudotrisomy 13 syndrome," in which affected individuals have a normal karyotype and polydactyly. Other commonly seen features of trisomy 13, including scalp defects, overlapping fingers, and nail hypoplasia, are not generally observed [Cordero et al 2007].
  - Smith-Lemli-Opitz syndrome [Kelley et al 1996]
  - Meckel syndrome
  - Genoa syndrome (with craniosynostosis) [OMIM 601370]
  - Lambotte syndrome (with microcephaly, prenatal growth retardation, hypertelorism) [OMIM 245552]

- Hydrolethalus syndrome (with hydrocephalus, polydactyly, and other anomalies) [OMIM 236680]
- Facial clefts and brachial amelia [OMIM 601357]

- **Autosomal dominant vs multifactorial**
  - Microtia-anotia [OMIM 600674] and other anomalies
- **Unknown mode of inheritance**
  - Caudal dysgenesis [Martinez-Frias et al 1994]

Nonsyndromic HPE. The nonsyndromic forms of HPE that are best understood at a molecular genetic level are inherited in an autosomal dominant manner (see Table 1).

The phenotype of individuals with *SHH*, *SIX3*, or *TGIF* mutations is extremely variable even within the same family, ranging from alobar HPE with cyclopia to clinically normal [Gillessen-Kaesbach 1996, Nanni et al 1999, Wallis & Muenke 1999, Gripp et al 2000].

Varying findings in children with *SIX3* mutations are: alobar HPE with cleft lip and palate [Nanni et al 2000]; semilobar HPE with microphthalmia and iris coloboma consistent with the role described for *SIX3* in eye development; typical HPE face with microcephaly, bilateral cleft lip and palate, and mental retardation, but without any detectable structural CNS anomalies on brain scan.

Preliminary data suggest that individuals with *ZIC2* mutations have normal or only mildly abnormal facial findings despite severe CNS anomalies. The observed abnormal facial features include ocular hypotelorism, flat nasal bridge, mild flattening of the midface, and microcephaly.

Table 1. Autosomal Dominant Nonsyndromic HPE

Locus Name	Gene Symbol	Chromosomal Locus	% of Individuals with HPE and Mutations in this Gene		Summary Tables of Sequence Variants	OMIM	Test Availability
			Autosomal Dominant	Simplex Cases			
HPE3	*SHH*	7q36	30%-40%	<5%	Table 2 (pdf)	600725 142945	Clinical Testing
HPE5	*ZIC2*	13q32	5%	2%	Table 3 (pdf)	603073 609637	Clinical Testing
HPE2	*SIX3*	2p21	1.3%	Rare	Table 4 (pdf)	603714 157170	Clinical Testing
HPE4	*TGIF*	18p11.3	1.3%	Rare	Table 5 (pdf)	602630 142946	Clinical Testing
HPE7	*PTCH1*	9q22.3	Rare	Rare		601309 610828	Clinical Testing [1]
HPE6	?	2q37.1-q37.3	?	?		605934	Clinical Testing [1]
HPE1	*TMEM1*	21q22.3	?	?		602103	Clinical Testing [1]

1. Testing by array comparative genomic hybridization (array CGH) only. All abnormalities found by array CGH should be verified by another molecular genetic test method (e.g., fluorescence in situ hybridization [FISH] or sequencing).

***SHH*.** The human sonic hedgehog gene *(SHH)*, one of three *Drosophilia* homologous genes, was the first HPE-causing gene to be identified. Heterozygous deletions and nonsense, frameshift, and missense mutations in *SHH* predict a loss-of-function mechanism [Roessler et al 1996, Roessler et al 1997, Vargas et al 1998, Nanni et al 1999, Odent et al 1999]. *SHH* encodes a secreted protein, sonic hedgehog protein, involved in establishing cell fates at several points during development. It is expressed in the Hensen node, the floor plate of the neural tube, the early gut endoderm, and the posterior of the limb buds, and throughout the notochord. It has been implicated as the key inductive signal in patterning of the ventral neural tube, the anterior-posterior limb axis, and the ventral somites [Muenke & Beachy 2001].

***ZIC2*.** Heterozygous insertions and deletions leading to frameshifts, nonsense mutations, and expansion of an alanine repeat of the *ZIC2* gene have been observed [Brown et al 1998, Brown et al 2001]. The protein encoded by the *ZIC2* gene, zinc finger protein ZIC2, is a member of a family of proteins that includes the *Drosophila* odd-paired gene (opa) [Aruga et al 1996] and the zebrafish odd-paired like gene (opl) [Grinblat et al 1998], which contain zinc finger DNA binding motifs of specificity very closely related to that of the Gli proteins. *ZIC2* may have a role in mediating the response to sonic hedgehog protein signaling.

***SIX3*.** Heterozygous deletions and missense and nonsense mutations in the *SIX* domain and the homeodomain of *SIX3* have been observed [Wallis et al 1999, Ribiero et al 2006]. Homeobox protein SIX3 participates in midline forebrain and eye formation in several organisms [Oliver et al 1996, Kobayashi et al 1998, Loosli et al 1999] and is present in the rostral, anterior region of the neural plate, optic recess, developing retina, and midline ventral forebrain [Kawakami et al 1996]. The *SIX*/so (sine oculis) family of transcription factors form a distantly related subclass of homeobox-containing genes that are further characterized by the presence of a contiguous homology domain, the *SIX* domain, which is also thought to participate in transcriptional activation [Kawakami et al 1996].

***TGIF*.** Heterozygous deletions and missense mutations of the gene encoding the 5'- TG- 3' interacting factor *(TGIF)* have been observed [Gripp et al 2000, El-Jaick et al 2007]. Mutations in *TGIF* predict amino acid substitutions in the amino terminal transcription repression domain. *TGIF* modulates the TGF beta pathway, components of which have been shown to be involved in HPE in animal models.

***PTCH1*.** PATCHED-1 *(PTCH1)*, the receptor for *SHH*, normally represses SHH signaling. The repression is relieved when *SHH* binds to *PTCH1*. Four different mutations in *PTCH1* have been detected in five unrelated individuals with HPE [Ming & Muenke 2002]. Upon binding of *SHH,* the repressive activity of *PTCH1* is relieved, and the SHH signaling pathway is activated. Haploinsufficiency for *PTCH1* has been shown to cause nevoid basal cell carcinoma syndrome (Gorlin syndrome). The *PTCH1* mutations have been found in clinically normal individuals in HPE pedigrees, consistent with the phenotype described in pedigree analysis of autosomal dominant HPE, including kindreds with *SHH* mutations. It is estimated that approximately one-third of individuals with a mutation in a gene causing autosomal dominant forms of HPE are asymptomatic with normal cognitive function. As with those individuals who have mutations in *SHH*, craniofacial anomalies are present in those with *PTCH1* mutations. No clinical features distinguish individuals with *PTCH1* mutations from those in the HPE population as a whole or those with identified *SHH* mutations.

Other. Candidate genes and their chromosomal loci are summarized in Table 6 (pdf).

Multifactorial—HPE is etiologically heterogeneous, and both environmental and genetic causes have been identified. Environmental causes include maternal diabetes mellitus during gestation, retinoic acid, and hypocholesterol. Severe phenotypes of HPE may involve both

genetic and environmental causes. Recently, abnormal sterol metabolism has been demonstrated in cultured lymphoblasts of individuals with alterations in HPE-causing genes. The accumulation of sterol intermediates may be caused by either defective regulation of cholesterol biosynthesis or defects in its intracellular transport. These mechanisms may aggravate SHH signaling, leading to the brain malformation syndrome [Haas et al 2007].

Evaluation Strategy

Identification of the cause of holoprosencephaly (HPE) aids in establishing prognosis and mode of inheritance for genetic counseling.

To help establish the cause of HPE, the work-up for an individual with HPE includes the following:

- **Prenatal history** to identify possible environmental causes
- **Physical examination** to identify findings that could establish the diagnosis of monogenic syndromic HPE
- **A detailed family history** with emphasis on pregnancy loss, neonatal deaths, and relatives with abnormal craniofacial findings and/or developmental delay to determine if monogenic nonsyndromic HPE is a consideration
- **Focused examination of the parents** to identify microforms of HPE
- **Genetic testing**
  - For affected children in whom environmental or monogenic causes seem unlikely, chromosome analysis of blood that examines at least 20 metaphases at the 550-band level or greater should be performed.

    Note: Chromosome analysis of the parents is recommended only if the proband has an abnormal karyotype (other than a trisomy or triploidy) or if the child with HPE is deceased, and therefore chromosome analysis on the proband is not possible.
  - Submicroscopic deletions for HPE-causing genes (i.e., *SHH*, *TGIF*, others) have been identified by quantitative PCR, FISH, and multiple ligation-dependent probe amplification (MLPA) in up to 5% of individuals with HPE [Bendavid, Dubourg, et al 2006; Bendavid, Haddad, et al 2006; Bendavid et al 2007]; therefore, these methods should be performed to detect submicroscopic deletions in the currently known HPE-causing genes.
  - In selected cases, array CGH may be pursued.
  - If monogenic nonsyndromic HPE is confirmed or likely, molecular genetic testing of the genes known to cause HPE *(SHH*, *ZIC2*, *SIX3*, and *TGIF)* should be considered (Table 1).

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

If a proband is found to have an inherited or *de novo* chromosome abnormality, a specific syndrome associated with holoprosencephaly (HPE), or a disease-causing mutation in a single gene, counseling for that condition is indicated. For probands without a clear etiology, recurrence risk for family members is likely to be low, but may be as high as 50% because of the possibility of germline mosaicism for a mutation in one of the genes causing nonsyndromic HPE.

Mode of Inheritance

Nonsyndromic HPE may be inherited in an autosomal dominant manner or may be the result of an inherited or *de novo* chromosome abnormality.

Risk to Family Members — Autosomal Dominant

Parents of a proband

- Some individuals diagnosed with autosomal dominant nonsyndromic HPE have an affected parent.
- However, a proband with autosomal dominant nonsyndromic HPE may have the disorder as the result of a *de novo* gene mutation. The proportion of cases caused by new gene mutations is unknown.
- Recommendations for the evaluation of parents of a child with nonsyndromic HPE and no known family history of HPE include evaluation for microforms of HPE. In some cases, a single microform is the only clue that a given individual has autosomal dominant nonsyndromic HPE and thus is at increased risk of having affected offspring. Note, however, that none of the microforms is pathognomonic for HPE and each can occur as an isolated finding apart from the HPE spectrum.

Sibs of a proband

- The risk to the sibs of the proband depends on the status of the parents.
- If a parent is affected or has a disease-causing mutation (with or without clinical manifestations), the risk to sibs of inheriting the gene mutation is 50%. Studies have identified empiric risks to the sibs of 20% for HPE, 15% for an HPE microform, and 15% for a normal phenotype.
- If the parents are clinically unaffected and the family history is negative, the risk to the sibs of a proband appears to be low. Germline mosaicism has been suggested based on the finding of several families in which apparently unaffected parents with a negative family history have more than one affected child. These children have features of HPE and gene mutations confirmed in a research laboratory [Nanni et al 1999, Brown et al 2001].

Offspring of a proband. Every child of an individual with a gene mutation for autosomal dominant nonsyndromic HPE has a 50% chance of inheriting the mutation. Although severely affected individuals do not reproduce, individuals with mild forms and microforms of autosomal dominant HPE may do so. The clinical symptoms and severity are variable; the phenotype may range from mild to severe.

Other family members of a proband. The risk to other family members depends on the status of the proband's parents. If a parent is found to be affected or to have a disease-causing mutation, his or her family members are at risk.

Risk to Family Members — Chromosomal

Parents of a proband

- Parents of a child with a numeric chromosome abnormality (e.g., trisomy or triploidy) are expected to be chromosomally and phenotypically normal.
- Parents of a child with a structural unbalanced chromosome rearrangement (e.g., deletion, duplication) are at risk of having a balanced chromosome rearrangement and should be offered chromosome analysis.

Sibs of a proband

- Sibs of a child with a numeric chromosome abnormality have a slightly increased risk of having a similar chromosome abnormality (depending on the specific abnormality and the age of the mother) with a similar or different phenotype.
- The risk to the sibs of a child with a structural unbalanced chromosome rearrangement depends on the chromosome status of the parents. If neither parent has a structural rearrangement, the risk to sibs is negligible; if a parent has a balanced structural rearrangement, the risk is increased and depends on the specific rearrangement and possibly other variables.

Offspring of a proband. Individuals with HPE and a chromosome rearrangement are unlikely to reproduce.

Other family members of a proband. The risk to other family members depends on the status of the proband's parents. If a parent is found to have a chromosome rearrangement, his or her family members are at risk and can be offered chromosome analysis.

Carrier Detection

If a parent is found to have a chromosome rearrangement, at-risk family members can be tested by chromosome analysis.

Related Genetic Counseling Issues

Family planning. The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal testing is before pregnancy. It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

Experiences of families with prenatal diagnosis. Redlinger-Grosse et al (2002) reviewed the experiences of individuals who received a prenatal diagnosis of HPE.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA. DNA banking is particularly relevant when the sensitivity of currently available testing is less than 100%. See Testing for a list of laboratories offering DNA banking.

Prenatal Testing

High-risk pregnancies

- **Molecular genetic testing.** For families in which a disease-causing *SIX3*, *SHH*, *TGIF*, or *ZIC2* mutation or deletion/duplication of *PTCH1* has been identified in an affected family member, molecular genetic prenatal diagnosis is available on a clinical basis. Testing is performed using DNA extracted from fetal cells obtained by amniocentesis usually performed at approximately 15-18 weeks' gestation or chorionic villus sampling (CVS) at approximately ten to 12 weeks' gestation.

- **Fetal ultrasound examination.** For families with autosomal dominant nonsyndromic HPE and no identifiable disease-causing mutation, alobar HPE can be diagnosed by prenatal ultrasound examination by 16 weeks' gestation [Blaas et al 2000, Leonard et al 2000]. Milder degrees of HPE including semilobar or lobar HPE cannot reliably be detected by prenatal ultrasound examination.

  Lobar HPE can be recognized in utero with sonography. However, a specific diagnosis is often difficult and relies on qualitative evaluation of ventricle morphology. MRI may demonstrate an abnormal appearance of the fornices, which are rudimentary and fused in to a single fascicle running within the third ventricle. This finding was demonstrated by sonography in a 30-week-old fetus affected by lobar HPE; the finding was confirmed after birth by both ultrasound and MRI. Therefore, antenatal demonstration of an echogenic linear structure running within the third ventricle is a specific sign of lobar HPE, and can assist this difficult diagnosis.

  Fetal MRI has been utilized in several centers to evaluate CNS structure when ultrasound studies have suggested the presence of an anomaly [Guo et al 2001, Blaicher et al 2003, Sharma et al 2003, Blaicher et al 2004, Wald et al 2004]. MRI is particularly useful for the evaluation of the posterior fossa and the median telencephalon as well as for etiologic clarification of hydrocephalus. Ultrafast MRI minimizes artifacts of fetal motion. Because MRI involves no exposure to radiation, it appears to be safe.

- **Chromosomal analysis.** For families in which a parent has a balanced chromosomal rearrangement, fetal karyotype can be analyzed from fetal cells obtained by CVS at approximately ten to 12 weeks' gestation or amniocentesis usually performed at approximately 15-18 weeks' gestation.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Low-risk pregnancies. When HPE is found on routine prenatal ultrasound examination in a fetus not known to be at increased risk for HPE, a high-resolution ultrasound examination to determine the presence of additional structural anomalies is indicated [Sonigo et al 1998]. Additional testing on amniotic fluid may be done to establish the cause of the HPE for recurrence risk counseling of the parents. Such testing can include the following:

- Fetal karyotype
- Sequence analysis of the following genes (in order from most to least common): *SHH, ZIC2, SIX3,* and *TGIF*
- If the karyotype is normal, array CGH to detect microdeletions of the four main genes in HPE, a possible common cause of HPE detected prenatally [Bendavid, Haddad, et al 2006; Bendavid et al 2007]

If the fetus has HPE identified by ultrasound examination, decision making about the pregnancy may occur independent of the specific diagnosis established.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutation has been identified. For laboratories offering PGD, see Testing.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in a child diagnosed with holoprosencephaly (HPE), the following evaluations are recommended:

- **Cleft lip and/or palate**
- **Hydrocephalus and/or features of HPE or other cortical anomalies.** All children with midline facial anomalies should undergo brain MRI; attention should also be paid to the pituitary region, which often requires high-resolution thin sections.
- **Growth deficiency.** Height, weight, and head circumference should be measured. It is important to compare weight to height in addition to plotting absolute measurements. Evaluation should include thyroid function tests, bone age, complete blood count, blood chemistries, sedimentation rate, insulin-like growth factor-1, and insulin-like growth factor binding protein-3. If growth hormone deficiency is found, panhypopituitarism should be assessed by specific hormone testing and brain MRI.
- **Pituitary dysfunction.** Sagittal MRI can be used to determine pituitary absence or ectopia and anatomic information. CNS anomalies and absent corpus callosum and/or septum pellucidum may accompany endocrine dysfunction.
- **Oral feeding and swallowing.** Evaluation should include assessment of caloric intake, swallowing abilities, oral motor skills, and presence of gastroesophageal reflux. Occupational and speech evaluations are warranted to evaluate and address feeding concerns. Studies for diagnosis of reflux including esophageal pH probe, milk scan, barium swallow, and/or endoscopy may be considered.

Treatment of Manifestations

Treatment for HPE varies according to the brain malformations and associated anomalies. Most children benefit from a multidisciplinary team approach.

- Hormone replacement therapy has been successful in some children with pituitary dysfunction.
- Antiepilectic drugs can help decrease the frequency and intensity of seizures.
- Feeding difficulties and failure to thrive may be managed with gastrostomy tube placement and Nissen fundoplication if gastroesophageal reflux and vomiting are issues. Thickening of feeds and upright positioning after feeding may be helpful to alleviate gastroesophageal reflux. To achieve the best growth in the child with HPE, the quality of the feeds is more important than the quantity.
- Accommodations for oral feeding with cleft lip and/or palate may require specific nipples, cups, and parental training. Early surgical repair may improve feeding.
- Placement of a ventriculo-peritoneal shunt may be necessary in children with HPE and hydrocephalus.
- In older children, surgical repair of cleft lip and /or palate may be indicated.
- For children with cleft lip and/or palate, referral to a specialized cleft or craniofacial clinic is recommended.
- Onset of new neurologic findings or deterioration warrant evaluation for seizures and/or hydrocephalus and/or shunt malfunction. Such evaluation would include vital sign monitoring, neurologic examination, EEG, and MRI.

- A major aspect of treatment is support and counseling of the parents.

Prevention of Secondary Complications

Children with hormonal disturbances should receive prompt evaluation during times of stress (e.g., illness, surgery).

Consultation with subspecialists regarding fluid and electrolyte management should be sought if elective surgery is planned.

Children with diabetes insipidus need careful monitoring of fluid and electrolyte intake.

Surveillance

Height, weight, and head circumference should be measured during health maintenance evaluations.

Evaluation for endocrine deficiencies should be undertaken at appropriate intervals and during health maintenance visits.

Therapies Under Investigation

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Other

Assessment of the risks and benefits of surgery and of the individual's brain abnormality is essential in determining the extent and benefit of surgical intervention.

Consistent with the ethical principle of beneficence, intervention at the earliest time possible is advised.

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select*  *for the most up-to-date Resources information.*—ED.

The Carter Centers for Brain Research in Holoprosencephaly and Related Malformations
hpe.stanford.edu

National Institute of Neurological Disorders and Stroke
Holoprosencephaly Information Page

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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Chapter Notes

Revision History

- 5 March 2008 (me) Comprehensive update posted to live Web site
- 11 March 2005 (me) Comprehensive update posted to live Web site
- 27 January 2003 (me) Comprehensive update posted to live Web site
- 27 December 2000 (pb) Overview posted to live Web site
- August 2000 (mm) Original submission

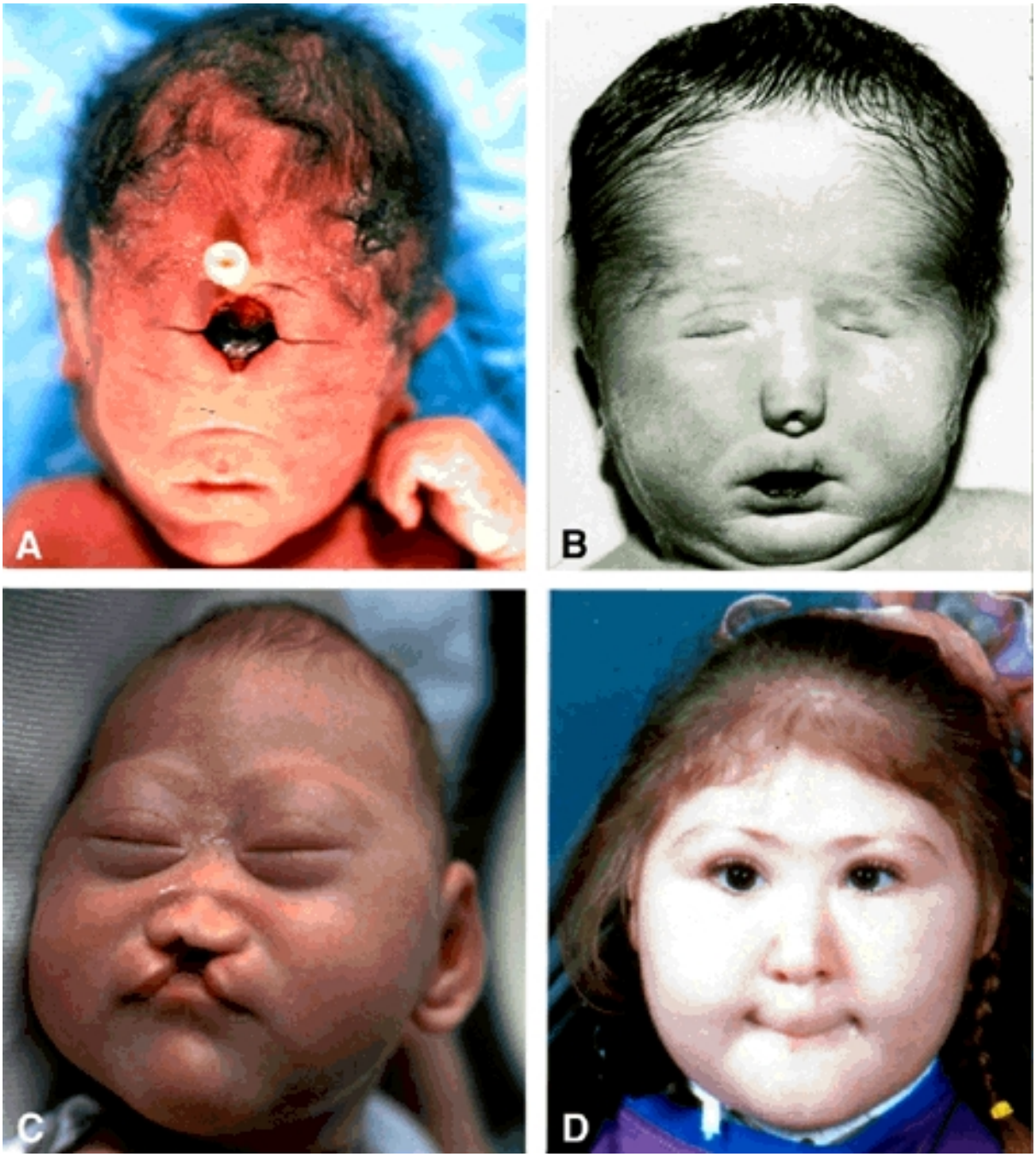

Figure 1. Facial findings in holoprosencephaly (HPE)
A. Alobar HPE with cylopia and proboscis above the singe eye
B. Alobar HPE with cebocephaly and hypotelorism
C. Semilobar HPE with microcephaly, premaxillary agenesis, and midline cleft lip and palate
D. Semilobar HPE with hypotelorism, midface hypoplasia, and mild dysmorphism
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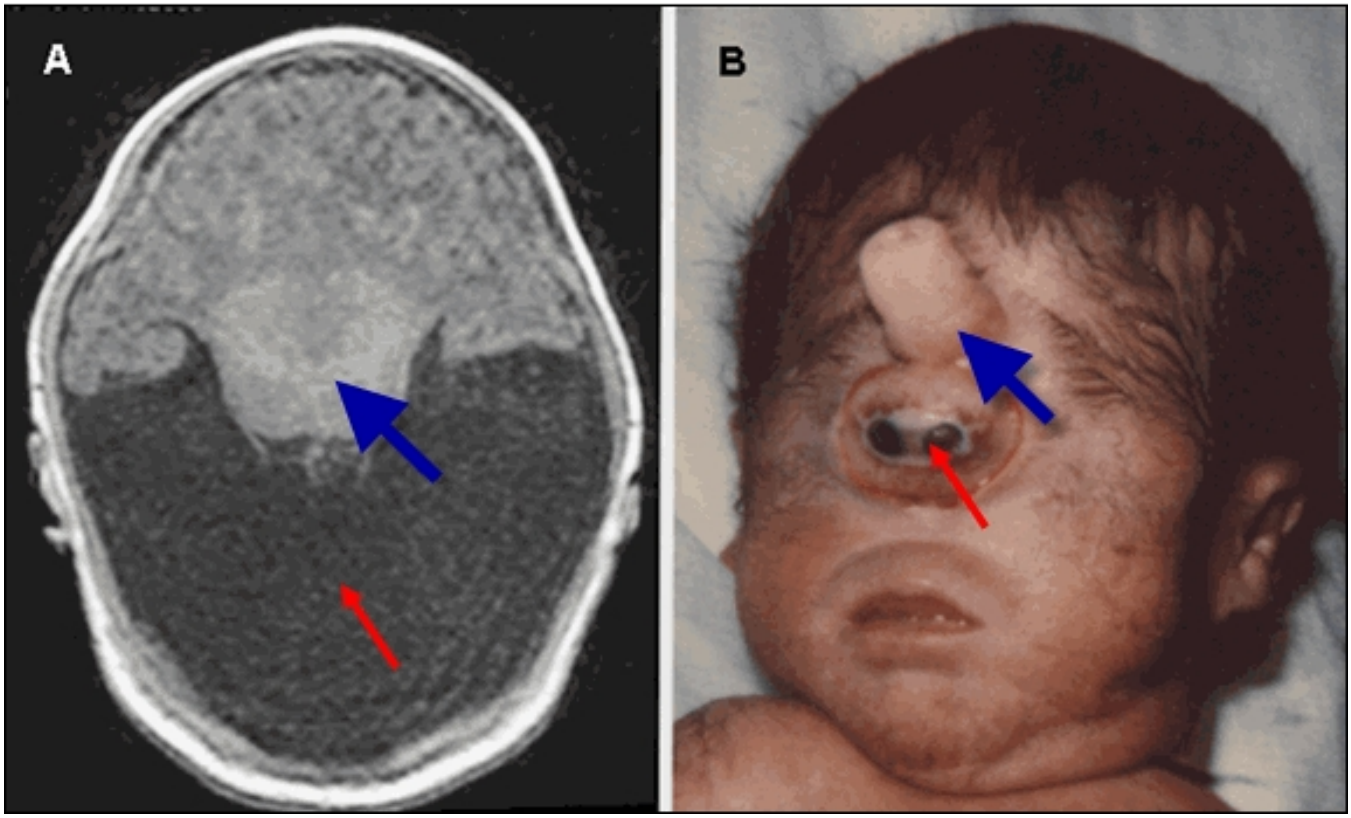

Figure 2. Alobar HPE

A. MRI of alobar holoprosencephaly (HPE), the most severe form of HPE, characterized by an enlarged midline monoventricle (holoventricle, red/thin arrow) with fusion of the frontal lobes and the midline gray matter structures (thalami and basal ganglia, blue/thick arrow). Typically, the corpus callosum and the third ventricle are absent.

B. Facial features seen in the alobar HPE spectrum, characterized by a single eye-like structure (cyclopia, red/thin arrow) and an overriding nose-like structure (proboscis, blue/thick arrow).

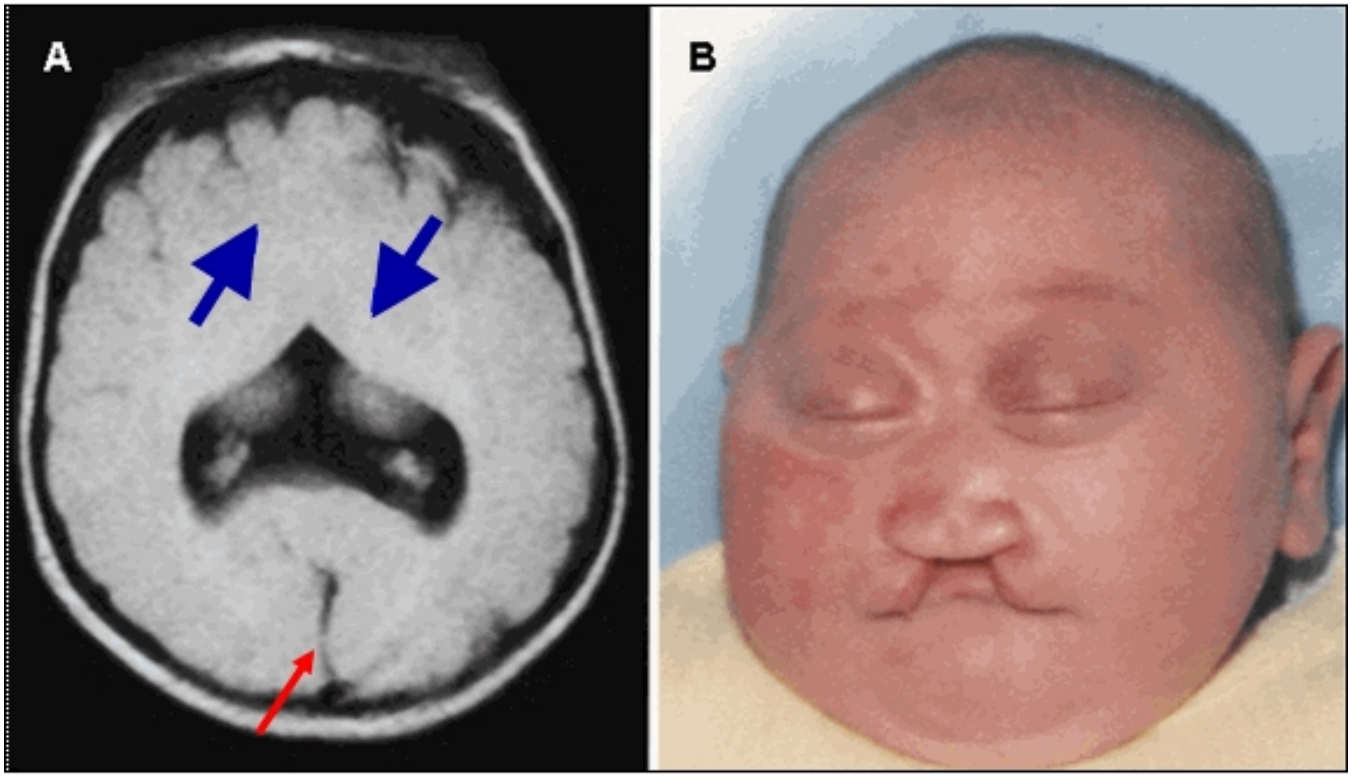

Figure 3. Semilobar HPE

A. MRI showing semilobar HPE. Note fusion of the frontal lobes, but presence of some septation posteriorly with presence of a falx and interhemispheric fissure (red/thin arrow). The splenium of the corpus callosum is present but more anterior portions are usually absent. A small, partially formed third ventricle is seen. More significant fusion of anterior brain structures (cortex, basal ganglia, thalamus) persists in this variant (blue/thick arrows). A dorsal cyst may be seen. In mild cases, lack of frontal horn development distinguishes this from the lobar type.

B. Note microcephaly, hypotelorism, flat nose with cleft lip.

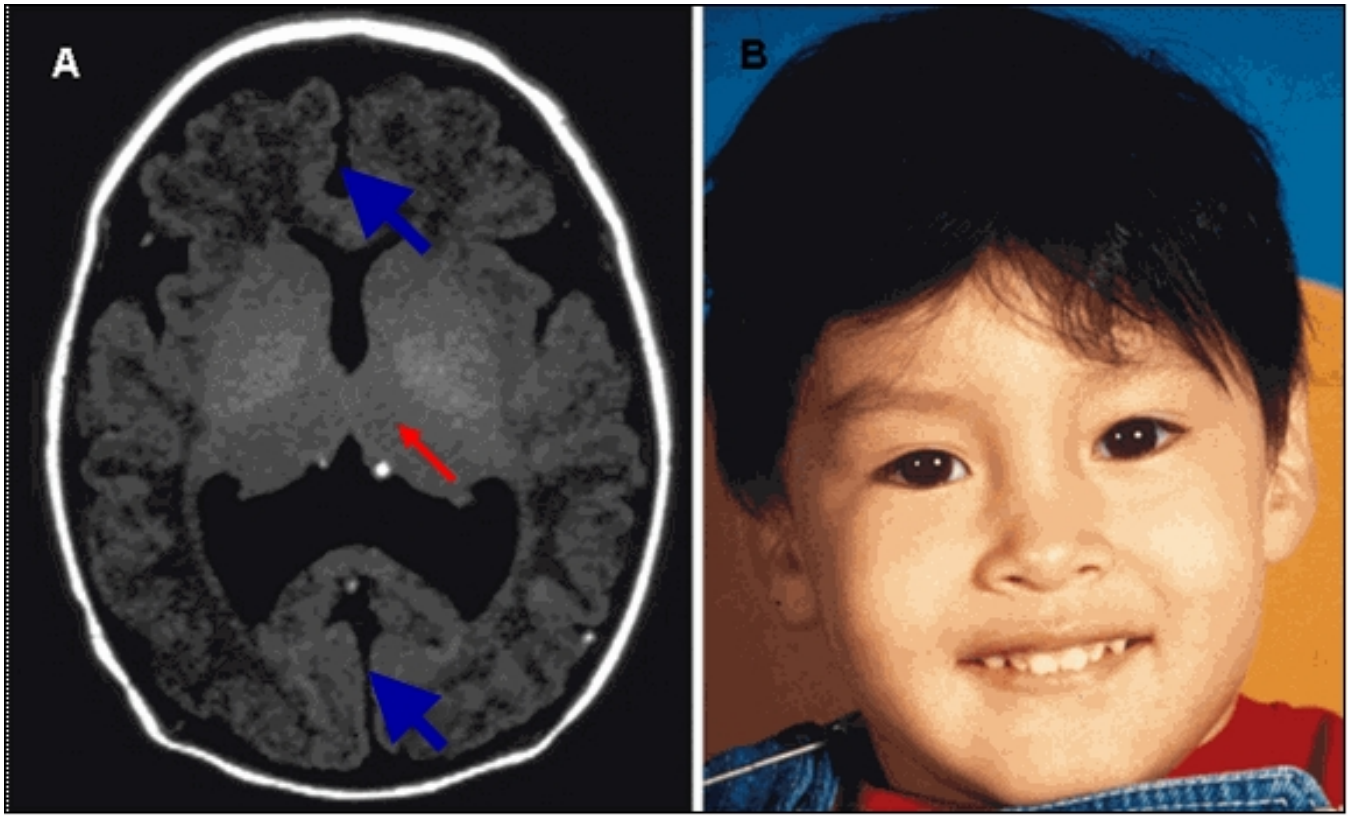

Figure 4. Lobar HPE

A. MRI in axial plane depicting lobar HPE, the least severe of the major types of HPE. The cerebral hemispheres are separated (blue/thick arrows); the ventricles are misshapen as a result of absence of the septum pellucidum. The posterior portion of the corpus callosum may be normally formed. There is varying degree of fusion of the midline gray structures (thalami, basal ganglia, red/thin arrow).

B. Relatively normal facial appearance of a child with lobar HPE

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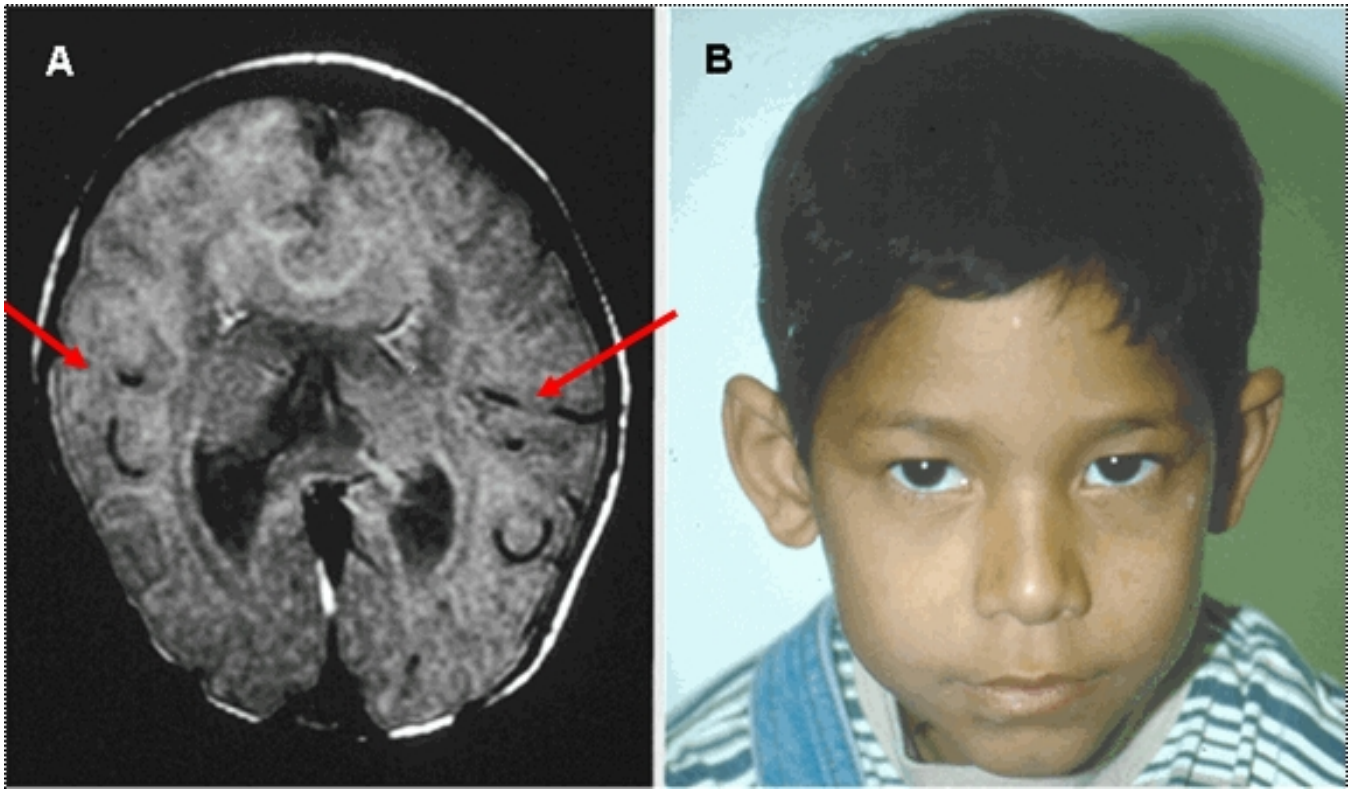

Figure 5. MIHF

A. MRI in axial plane depicting middle interhemispheric variant of HPE in which the anterior portions of the frontal lobes and the occipital lobes are well separated. The sylvian fissures are oriented nearly vertically and are abnormally connected across the midline over the vertex of the brain (red/thin arrows). The genu and splenium of the corpus callosum appear normally formed, but the callosal body is typically absent. The hypothalamus and lentiform nuclei are normally separated; however, the caudate nuclei and the thalami remain incompletely separated.

B. The facial appearance is usually normal.

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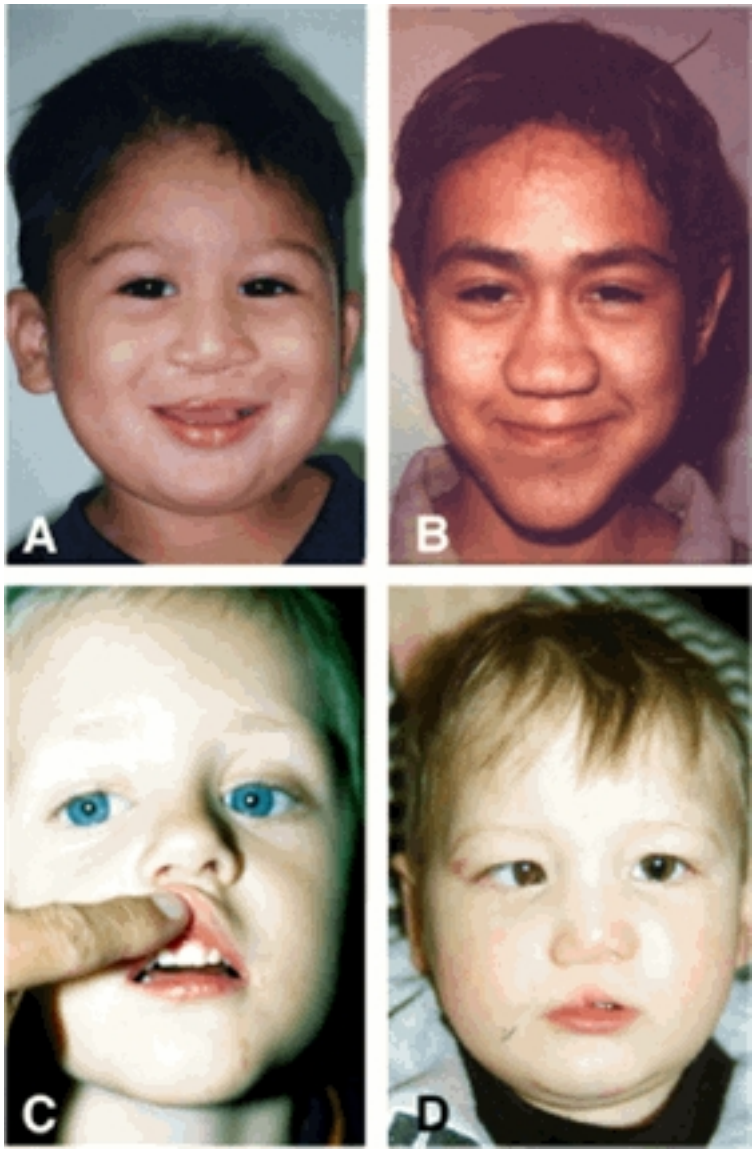

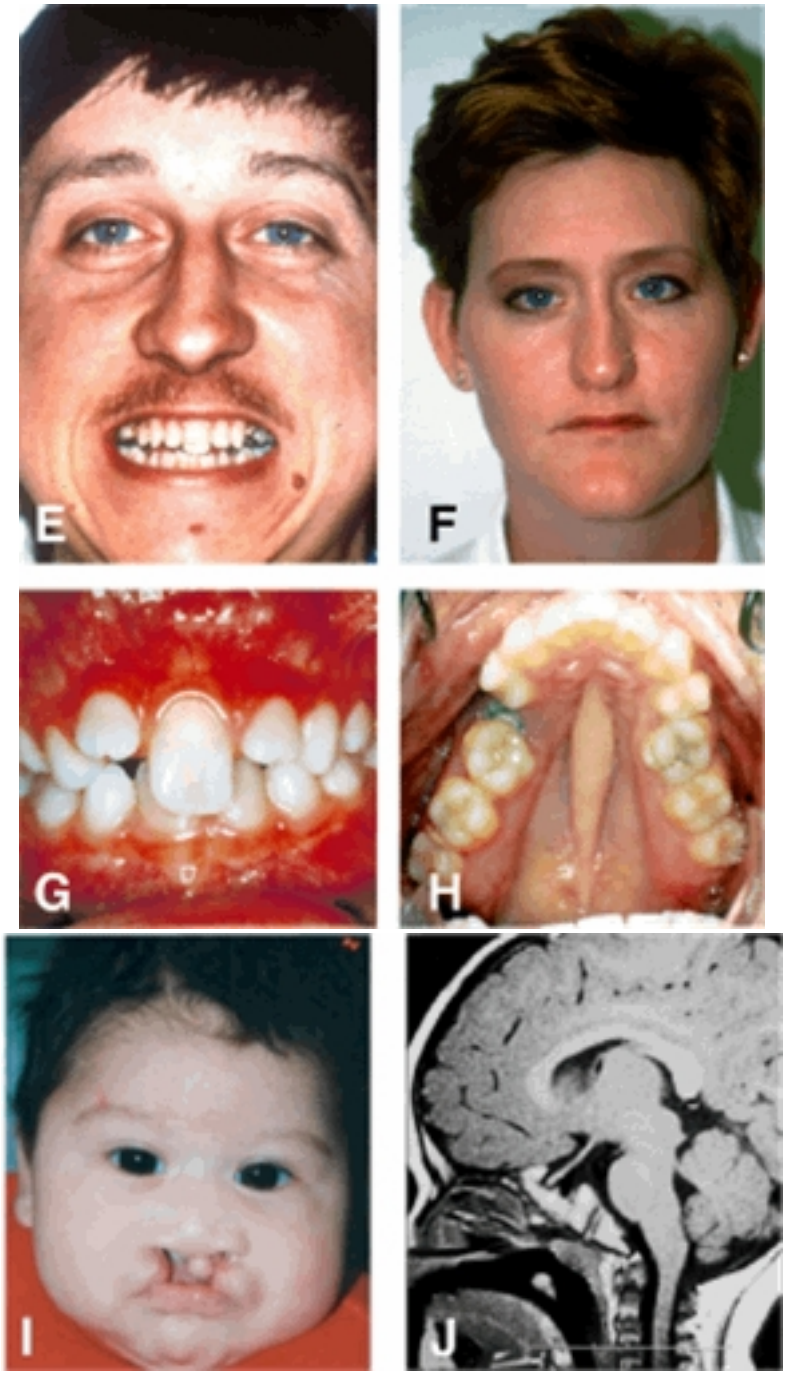

Figure 6. Microforms of holoprosencephaly (HPE) spectrum with milder craniofacial anomalies in the absence of neurologic findings

A. Premaxillary agenesis with repaired bilateral clefts of the lip

B. Absence of nasal bones and cartilage with a narrow nasal bridge

C. Single central maxillary incisor

D. Premaxillary agenesis, repaired unilateral cleft of the lip and bilateral iris coloboma

E. Close-up showing single central maxillary incisor

F. This mother has a child with HPE. She has hypotelorism and narrow nasal bridge as her only manifestations.

G. Single central incisor
H. Prominent midline palatal ridge
I. Premaxillary agenesis with bilateral cleft lip and palate in a child with pituitary hypoplasia and growth hormone deficiency
J. Sagittal T1 weighted MRI showing pituitary hypoplasia