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Holoprosencephaly Flashcards:
A Summary for the Clinician

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This material contains general information regarding the approach to patients with holoprosencephaly. For more detailed discussion, please refer to specific articles in this issue. Published 2010 Wiley-Liss, Inc.†

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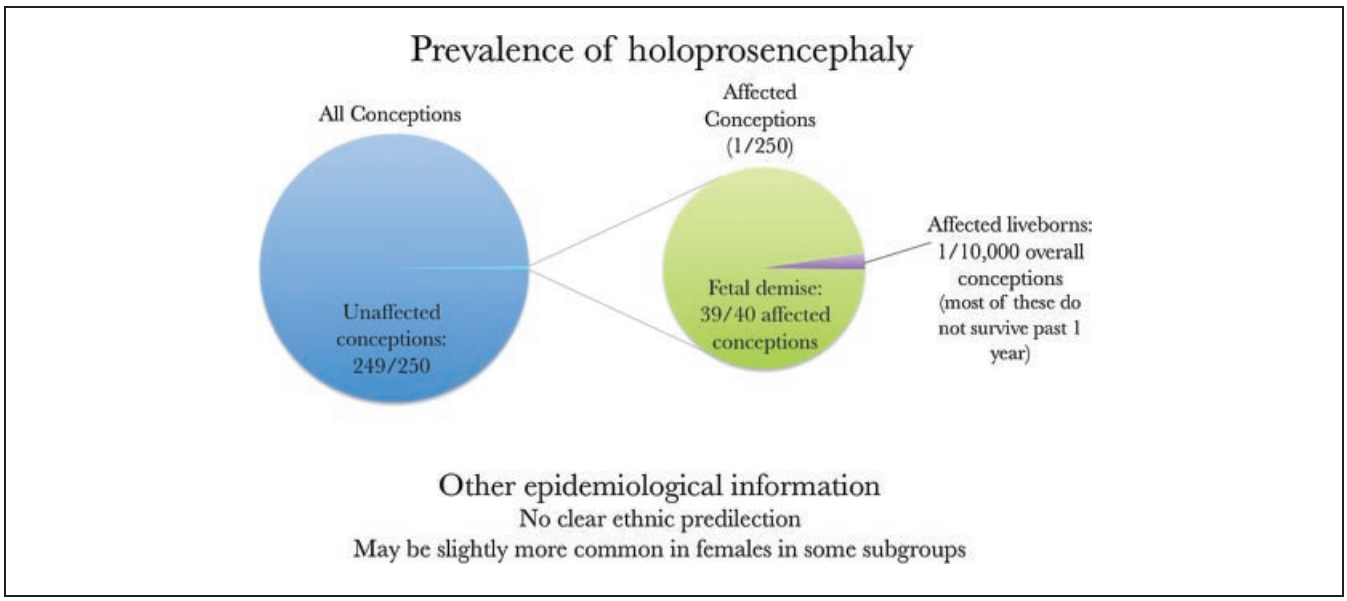

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Maximilian Muenke, M.D. is the chief of the Medical Genetics Branch at the Division of Intramural Research in the National Human Genome Research Institute. He has a longstanding interest in elucidating the genetics behind holoprosencephaly, craniofacial malformation syndromes, and attention deficit hyperactivity disorder, as well as an interest in improving knowledge about the formation of the central nervous system.

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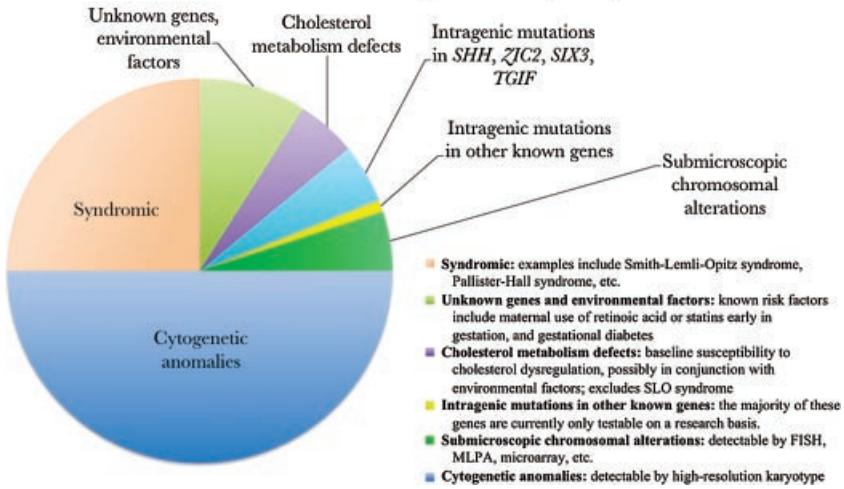
Causes of holoprosencephaly



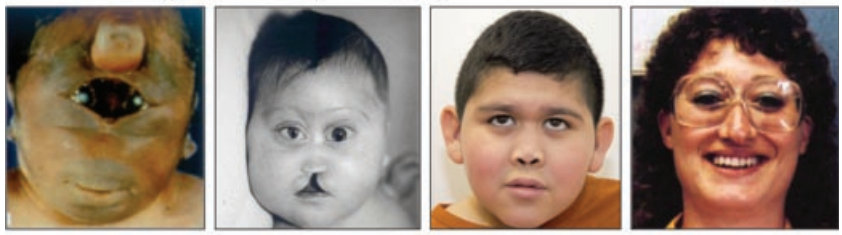
Types of holoprosencephaly

Alobar	Semilobar	Lobar	MIHV	Microform
• Complete or near-complete lack of interhemispheric separation • Single midline forebrain ventricle • Absent interhemispheric fissure, falx cerebri, olfactory bulbs, and corpus callosum • Nonseparation of deep gray nuclei	• No anterior interhemispheric separation; some posterior separation • Absent frontal horns of lateral ventricle, septum pellucidum, and anterior corpus callosum • Absent or hypoplastic olfactory bulbs • Incomplete separation of deep gray nuclei • May have dorsal cysts	• Nonseparation of only the most rostral/ventral frontal neocortex • Absent corpus callosum in affected region • Hypoplastic falx cerebri, olfactory bulbs, and interhemispheric fissure, usually containing azygous anterior cerebral artery	• Failure of separation of posterior frontal and parietal lobes • Frequent incomplete separation of thalami and caudate nuclei • Absent body of the corpus callosum • Gray matter heterotopias or cortical dysplasia in majority of patients • Azygous anterior cerebral artery	• Absence of interhemispheric fusion; may have other subtle midline brain defects (e.g. agenesis of corpus callosum) • Presence of milder craniofacial anomalies (e.g. microcephaly, single central incisor, hypotelorism, etc.)

SEVERE ← Continuum of severity → MILD

Note: The above description is a general overview of findings in HPE types, but exceptions are not uncommon. HPE-type brain findings may be accompanied by other structural CNS anomalies (e.g. neural tube defects, schizencephaly). See figure: "Axial MRI scans of holoprosencephaly patients."

Craniofacial findings in patients with holoprosencephaly-spectrum disorders



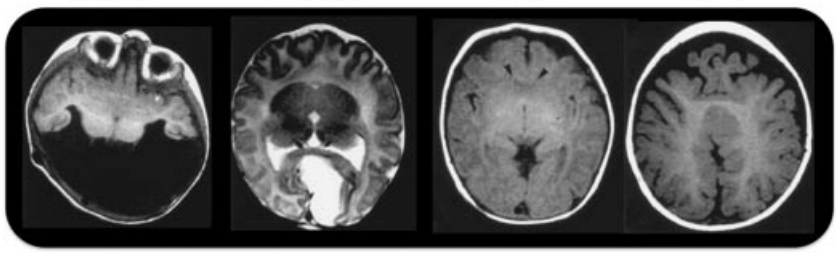
SEVERE — Continuum of severity — MILD

From left to right: (A) synophthalmia (two fused eyes in one orbit) and a proboscis in a patient with alobar HPE; (B) severe hypotelorism, flat nasal bridge, bilateral colobomas, and midline cleft lip and palate in a patient with alobar HPE; (C) hypotelorism, flat nasal bridge, and closely spaced nostrils in a patient with lobar HPE; (D) hypotelorism, sharp nasal bridge, and single maxillary central incisor in an individual with a microform of HPE.

[Roessler *et al.*, 1996; Lacbawan *et al.*, 2009]

Axial MRI scans of holoprosencephaly patients

ALOBAR SEMILOBAR LOBAR MIHV



[Hahn and Plawner, 2004]

Spectrum of physical examination features (patients with full HPE)

Facial features

- Microcephaly (can be extreme)
- Macrocephaly (in cases with hydrocephalus)
- Continuous spectrum of eye anomalies from cyclopia to hypotelorism
- Proboscis or nose with single nostril
- Flat nasal bridge
- Cleft lip/palate
- Single maxillary central incisor
- A subset of patients may also have relatively normal facial appearances or may have anomalies not typically associated with HPE
- See figure: "Craniofacial findings in patients with holoprosencephaly-spectrum disorders"

Extracranial features

- Signs of major organ malformations (e.g. cardiac, GI, GU defects)
- Limb anomalies
- Skeletal anomalies

Possible physical examination features (patients with microform HPE)

Facial features

- Microcephaly (typically less severe than in full HPE)
- Midface hypoplasia
- Hypotelorism
- Iris coloboma
- Flat or sharp nasal bridge
- Cleft lip/palate
- Single maxillary central incisor
- Relatively normal facial appearance in a subset of patients
- See figure: "Craniofacial findings in patients with holoprosencephaly-spectrum disorders"

Clinical approach to holoprosencephaly

Prenatal diagnosis

- Detailed radiologic examination, including fetal ultrasound and/or MRI
- Consultation with clinicians and geneticists familiar with HPE
- Discussion of testing options (e.g. amniocentesis, chorionic villus sampling, and including parental testing)

Postnatal diagnosis

- Detailed evaluation, including family history, by clinicians familiar with HPE
- Neuroimaging (MRI preferred)
- Discussion of testing options to identify underlying etiologies (see figure: "Causes of holoprosencephaly")

Management

- Thorough genetic counseling, including detailed family history
- Consultations that may include: neurology, endocrinology, rehabilitative medicine (speech therapy, physical therapy, occupational therapy, physiatry), ophthalmology, development, genetics, complex care, surgery (e.g. general surgery, oromaxillofacial), orthopedics, adjunctive therapy
- Referral to family support groups (e.g. Families for HoPE)

Frequent complications of holoprosencephaly

Neurocognitive impairment	Seizure disorders	Diabetes insipidus (and associated electrolyte imbalances)
Autonomic instability	Cleft lip/palate	Other endocrine abnormalities
Recurrent infections (e.g. aspiration pneumonia)	Other major organ malformations (e.g. cardiac defects)	Feeding intolerance

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