Holoprosencephaly Flashcards:  
A Summary for the Clinician  

BENJAMIN D. SOLOMON, DANIEL E. PINEDA-ALVAREZ, SANDRA MERCIER,  
MANU S. RAAM, SYLVIE ODENT, AND MAXIMILIAN MUENKE*  

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.  

KEY WORDS: holoprosencephaly; flashcards  

How to cite this article: Solomon BD, Pineda-Alvarez DE, Mercier S, Raam MS, Odent S, Muenke M.  

Prevalence of holoprosencephaly  

Unaffected conceptions: 219/250  
Affected conceptions: (1/250)  
Fetal demise: 39/40 affected conceptions  
Affected liveborns: 1/10,000 overall conceptions  
(most of these do not survive past 1 year)  

Other epidemiological information  
No clear ethnic predilection  
May be slightly more common in females in some subgroups  

Benjamin D. Solomon, M.D. is a fellow in the Combined Pediatrics and Medical Genetics Residency Program, based at the National Human Genome Research Institute. He is a member of the Muenke lab and is involved in investigating the genetics behind holoprosencephaly.  
Daniel E. Pineda-Alvarez, M.D. is a medical graduate trained in Colombia and is currently a Clinical Molecular Genetics fellow in the Medical Genetics Branch of the National Human Genome Research Institute. He is a member of the Muenke lab and is involved in investigating the genetics behind holoprosencephaly and attention deficit hyperactivity disorder.  
Sandra Mercier, M.D. is a researcher in the holoprosencephaly group in the “Génétique des Pathologies Liées au Développement” branch of UMR 6061 CNRS, IGDR, at the University of Rennes 1, France. She is also a senior registrar in the Clinical Genetics Service at CHU Hôpital Sud in Rennes.  
Manu S. Raam, B.S.E. is a trainee in the HHMI-NIH Research Scholars Program, which is a medical student training program jointly administered by the Howard Hughes Medical Institute and the National Institutes of Health. He is a member of the Muenke lab and is involved in investigating the genetics behind holoprosencephaly.  
Sylvie Odent, M.D., Ph.D. is a professor of genetics and a member of the holoprosencephaly group in the “Génétique des Pathologies Liées au Développement” branch of UMR 6061 CNRS, IGDR, at the University of Rennes 1, France. She is the chief of the Clinical Genetics Service at CHU Hôpital Sud in Rennes and is a coordinator of a Center of Reference for Rare Diseases, focusing on developmental abnormalities and dysmorphology. Her clinical and research interests mainly concern holoprosencephaly and mental retardation.  
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.  
*Correspondence to: Maximilian Muenke, Building 35, 18203, 35 Convent Drive, MSC 3717, Bethesda, MD 20892-3717, USA.  
E-mail: muenke@nih.gov  
DOI 10.1002/ajmg.c.30245  
Published online 26 January 2010 in Wiley InterScience (www.interscience.wiley.com)  

Published 2010 Wiley-Liss, Inc.  
†This article is a US Government work and, as such, is in the public domain in the United States of America.
Causes of holoprosencephaly

- Unknown genes, environmental factors
- Cholesterol metabolism defects
- Intragenic mutations in SHH, ZIC2, SIX3, TGIF
- Intragenic mutations in other known genes
- Submicroscopic chromosomal alterations

Syndromic examples include Smith-Lemli-Opitz syndrome, Pallister-Killian syndrome, etc.
Unknown genes and environmental factors known risk factors include maternal use of retinoic acid or radiation in gestation, and genetic syndromes
Cholesterol metabolism defects baseline susceptibility to cholesterol downstream, possibly in conjunction with environmental factors include SLO syndrome
Intragenic mutations in other known genes the majority of these genes are currently only described in research.
Submicroscopic chromosomal alterations: detectable by FISH, MLPA, microarray, etc.
Cytogenetic anomalies: detectable by high-resolution karyotype

Types of holoprosencephaly

**Alobar**
- 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

**Semilobar**
- 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

**Lobar**
- 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 agenous anterior cerebral artery

**MIVH**
- Failure of separation of posterior frontal and parietal lobes
- Frequent incomplete separation of thalamus and caudate nuclei
- Absent body of the corpus callosum
- Gray matter heterotopias or cortical dysplasia in majority of patients
- Agyous anterior cerebral artery

**Microform**
- 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.)

*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

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.

[Roesler et al., 1990; Laesehen et al., 2000]

Axial MRI scans of holoprosencephaly patients

ALOBAR SEMILOBAR LOBAR MIHV

[Hahn and Flawner, 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
- Proptosis 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
REFERENCES

All previously published images reprinted with permission. Reproduced from: [Hahn and Plawner, 2004 Evaluation and management of children with holoprosencephaly, 31:80, Copyright (2004), with permission from Elsevier; [Roessler et al., 1996 Mutations in the human Sonic Hedgehog gene cause holoprosencephaly, 14:357, Copyright (1996), with permission from Nature Publishing Group; [Lacbawan et al., 2009 Clinical spectrum of SIX3-associated mutations in holoprosencephaly: correlation between genotype, phenotype and function, 46:390, copyright notice 2009, with permission from BMJ Publishing Group, Ltd.

REFERENCES (for images)