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Synonyms of Holoprosencephaly

- alobar holoprosencephaly
- holoprosencephaly sequence
- HPE
- lobar holoprosencephaly
- middle interhemispheric fusion
- semilobar holoprosencephaly

Subdivisions of Holoprosencephaly

- No subdivisions found

General Discussion

Holoprosencephaly (HPE) is the failure of the prosencephalon, or forebrain, to develop normally. The forebrain is a region of the brain in the fetus that develops into parts of the adult brain, including the cerebral cortex. Instead of the normal complete separation of the left and right halves of the forebrain, there is an abnormal continuity between the two sides. There are several different types of holoprosencephaly. In the alobar form, there is no separation between the right and left halves at all. In semilobar HPE, at least some separation of the two halves is present. In the lobar form, most of the brain has separated into right and left sides, though there is incomplete division into the two halves.

Signs & Symptoms

Holoprosencephaly is a malformation sequence with a very variable degree of severity for both the brain and facial abnormalities. Intellectual disability is associated with HPE and seizures are often present.

Children diagnosed with this disorder may have a small head (microcephaly), excessive fluid in the brain (hydrocephalus), facial abnormalities, tooth abnormalities (single central incisor), cleft lip and/or palate, epilepsy, and/or endocrine abnormalities. The most severely affected individuals may have cyclopia, a single central eye that is the most severe eye finding seen in holoprosencephaly, though this is very rare. Abnormalities in the formation of the nose may also occur.

Holoprosencephaly may also affect other systems in the body. Defects in the pituitary gland can cause an abnormally low level of sugar in the blood (hypoglycemia), low levels of sodium in the blood, or genital abnormalities.

Causes

Holoprosencephaly is a birth defect that arises during the first few weeks of the pregnancy. Diabetes in the mother during the pregnancy can increase the risk of holoprosencephaly in the fetus. However, for most children, there is no

known intrauterine exposure that can be related to holoprosencephaly.

Some children will have an identifiable genetic cause of holoprosencephaly. Approximately one-third of children born with holoprosencephaly have an abnormality of the chromosomes, which contain the genetic material (DNA). The most common chromosomal abnormality associated with HPE is when there are 3 copies of chromosome 13 (trisomy 13), although a number of other chromosomal changes can also cause holoprosencephaly.

In other children, holoprosencephaly is due to a change in a specific gene. These changes cause the genes and their proteins to function abnormally, and this affects the development of the brain, resulting in holoprosencephaly. Some of these genes are SHH, SIX3, TGIF, ZIC2, PTCH1, FOXH1, NODAL, CDON, and GLI2. Holoprosencephaly can also occur in certain genetic syndromes in which there are other medical issues besides those mentioned in this report that affect organs in addition to the brain and face (e.g., Smith-Lemli-Opitz syndrome).

Despite the above understanding of the causes of holoprosencephaly, the exact cause of the condition is not identified for many individuals. There are likely to be additional genetic causes other than those already known and mentioned above.

Affected Populations

Holoprosencephaly affects males and females in equal numbers before birth and has been reported in many ethnic groups. The incidence of holoprosencephaly has been estimated at 1 in 250 during early embryonic development, and approximately 1 in 16,000 live births.

Related Disorders

Holoprosencephaly can also occur in association with malformations in other organ systems that are not directly related to holoprosencephaly.

Smith-Lemli-Opitz syndrome (SLOS) is a variable genetic disorder that is characterized by slow growth before and after birth, small head (microcephaly), mild to moderate intellectual disability and multiple birth defects including particular facial features, cleft palate, heart defects, fused second and third toes, extra fingers and toes, and underdeveloped external genitals in males. SLOS is caused by a deficiency in the enzyme 7-dehydrocholesterol reductase that results in an abnormality in cholesterol metabolism. SLOS is inherited as an autosomal recessive genetic disorder. (For more information about this condition, choose “SLOS” as your search term in the Rare Disease Database.)

Other genetic syndromes that have been reported in association with holoprosencephaly include Hartfield syndrome (ectrodactyly, cleft lip/palate), agnathia-otocephaly complex (very small chin, ear anomalies), and Pallister-Hall syndrome (extra fingers/toes, hypothalamic hamartoblastomia, anal anomalies).

Standard Therapies

The diagnosis of holoprosencephaly is usually made by MRI or CT of the brain. Holoprosencephaly can sometimes be detected prenatally through ultrasound or MRI, though mild forms may not be reliably detected prenatally.

Treatment and care for the issues associated with holoprosencephaly are supportive and based on the specific medical issues present for an individual child.

An endocrinology evaluation should be performed to assess for pituitary abnormalities. A neurologist should also be involved in the child’s care and can guide treatment for seizures if they are present. Plastic reconstructive surgery of cleft lip and palate or other facial features may be needed if indicated. A developmental pediatrician can help direct developmental therapies. Other treatments can be instituted as appropriate.

A clinical genetics evaluation and genetic counseling should be obtained for patients and their families once the diagnosis is made. Relatives of a child with holoprosencephaly may have an increased risk of having a child with holoprosencephaly, and this should be assessed and discussed by the child's physicians, especially the neurologist and/or clinical geneticist. There are specific features that suggest an increased risk for having another child with holoprosencephaly (e.g., a single central upper incisor), and these should be carefully assessed in parents and family members. A chromosome analysis and gene testing is often performed.

Pediatricians, neurologists, dentists, special education teachers, surgeons, therapists, psychologists, developmental pediatricians, and others must systematically and comprehensively plan the child's treatment for holoprosencephaly.

Investigational Therapies

Information on current clinical trials is posted on the Internet at www.clinicaltrials.gov. All studies receiving U.S. government funding, and some supported by private industry, are posted on this government web site.

For information about clinical trials being conducted at the NIH Clinical Center in Bethesda, MD, contact the NIH Patient Recruitment Office:

Tollfree: (800) 411-1222
TTY: (866) 411-1010
Email: prpl@cc.nih.gov

For information about clinical trials sponsored by private sources, contact:
www.centerwatch.com

For more information about clinical trials conducted in Europe, contact: https://www.clinicaltrialsregister.eu/

Resources

Holoprosencephaly Resources

Supporting Organizations

- Carter Centers for Brain Research in Holoprosencephaly and Related Malformations
  Texas Scottish Rite Hospital for Children, Department of Neurology
  2222 Welborn Street
  Dallas, TX 75219-3993
  Phone: (214) 559-8411
  Toll-free: (800) 421-1121
  Email: hpe@tsrh.org
  Website: http://www.carterdatabase.org/hpe

- Genetic and Rare Diseases (GARD) Information Center
  PO Box 8126
  Gaithersburg, MD 20898-8126
  Phone: (301) 251-4925
  Toll-free: (888) 205-2311
  Website: http://rarediseases.info.nih.gov/GARD/

- MyFace
  333 East 30th Street, Lobby Unit
  New York, NY 10016

Phone: (212) 263-6656
Email: info@myface.org
Website: http://www.myface.org

- NIH/National Institute of Child Health and Human Development
  31 Center Dr
  Building 31, Room 2A32
  Bethesda, MD 20892
  Toll-free: (800) 370-2943
  Email: NICHDInformationResourceCenter@mail.nih.gov
  Website: http://www.nichd.nih.gov/

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Years Published

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National Organization for Rare Disorders (NORD)
55 Kenosia Ave., Danbury CT 06810 • (203)744-0100