CONDITION

Familial alobar holoprosencephaly

Familial alobar holoprosencephaly is an inherited condition in which the developing forebrain does not divide into two hemispheres.

WHAT IT IS
Severe inherited difference in early forebrain development

BODY SYSTEM
Brain and nervous system

MAIN SYMPTOMS
Profound developmental impairment, seizures, feeding problems, breathing difficulties

WHAT CAUSES IT
Inherited gene or chromosome changes

HOW IT IS DIAGNOSED
Prenatal ultrasound or brain MRI, plus genetic testing

MAIN TREATMENT
Multidisciplinary supportive and comfort-focused care

CAN IT BE CURED?
No - brain development cannot be reversed

IS IT AN EMERGENCY?
Sometimes - breathing pauses or prolonged seizures

LONG-TERM OUTLOOK
Severe disability with often shortened survival

Overview

Familial alobar holoprosencephaly is a severe condition affecting brain development before birth. "Holoprosencephaly" means that the forebrain does not divide in the usual way into right and left halves. "Alobar" describes the most complete form, in which this separation is largely absent.

The difference develops very early in pregnancy. There may be one large central fluid-filled space instead of separate brain ventricles, and deep brain structures may be joined.

"Familial" means that the condition has occurred in more than one family member or is linked to an inherited genetic change. Relatives carrying the same change may be affected very differently. One may have alobar holoprosencephaly, while another has subtle facial or dental differences or no obvious features.

The condition usually causes profound developmental disability and complex medical needs. It can affect feeding, breathing, movement, hormone control, temperature regulation and seizures. Survival is often shortened, although brain imaging cannot predict an individual's exact lifespan.

Symptoms

Signs may first be detected during a pregnancy ultrasound. After birth, effects depend partly on the associated genetic condition, facial development and other organ differences.

Common effects include:

Some babies have differences affecting the middle of the face, such as closely spaced eyes, a flattened nose, cleft lip or palate, or a single central upper tooth. Facial appearance does not always indicate the extent of the brain difference.

The pituitary gland, which controls several hormones, may not work normally. This can affect growth, blood sugar, thyroid function, stress responses, puberty or water balance. Excessive urination and dehydration may indicate diabetes insipidus, a hormone-related water-balance disorder unrelated to the more common form of diabetes.

Symptoms can change over time. Feeding or breathing problems may become more noticeable, and seizures may begin or change as the child grows.

- Profound delays in movement, communication and learning
- Seizures
- Difficulty coordinating sucking and swallowing
- Choking or food and liquid entering the airway
- Low or unusually high muscle tone
- Limited head control and movement
- Changes in breathing, heart rate or body temperature
- Vision or hearing impairment
- Poor growth

Causes and risk factors

Familial alobar holoprosencephaly is caused by changes affecting early brain and facial

development. Associated genes include SHH , ZIC2 , SIX3 and TGIF1 , among others.

Many familial cases follow an autosomal dominant inheritance pattern. A person can pass on the genetic change even if they have mild features or no obvious medical problems, known as reduced penetrance. Variable expression means that people with the same change can have different outcomes.

Less commonly, holoprosencephaly is part of a recessive or X-linked syndrome. It can also occur with chromosome differences, including trisomy 13 and structural chromosome changes that may affect several organs.

Sometimes testing does not identify a cause. This does not rule out an inherited condition because current tests cannot detect every relevant change.

Pre-existing diabetes in the pregnant parent is a recognized risk factor for holoprosencephaly overall, but it does not usually explain a pattern across several relatives. Nothing a parent did during pregnancy should be assumed to have caused a familial case without specific evidence.

The chance of recurrence depends on the genetic result, inheritance pattern and whether either parent carries the change.

Diagnosis

Alobar holoprosencephaly may be found before birth during ultrasound. The scan may show that the forebrain has not divided, along with differences in fluid spaces and central structures. Fetal MRI can provide more detail and help with care planning.

After birth, brain MRI is usually the clearest way to define the structure. The assessment may also include:

Genetic testing may include chromosome analysis, chromosome microarray, a holoprosencephaly gene panel, or exome or genome sequencing. Testing parents and sometimes other relatives can help determine whether a change was inherited.

A result may be disease-causing, uncertain or negative. An uncertain result does not confirm the cause, while a negative result does not exclude a genetic condition.

- Examination of facial, dental and other physical features
- Feeding, breathing, vision and hearing assessments
- Seizure testing, including an EEG when appropriate
- Blood and urine tests for pituitary hormone problems
- Heart, kidney or other imaging if a broader syndrome is suspected

Treatment and management

There is no treatment that can separate the brain after development. Care focuses on comfort, safety, symptom control and quality of life.

Feeding support is often central. A swallowing assessment can identify whether milk, food or saliva is entering the airway. Some children need modified feeding methods, tube feeding or a surgically placed feeding tube.

Anti-seizure medicines may be used for epilepsy. Treatment depends on seizure type, test findings, side effects and other medical needs.

Hormone deficiencies require endocrine assessment. Treatment may replace missing hormones or control abnormal water balance. Because some hormone problems become serious during illness, families may receive a written management plan.

Other care may include respiratory support, secretion management, physical and occupational therapy, positioning equipment, hearing and vision services, and treatment for muscle stiffness or joint problems. Cleft lip, cleft palate, hydrocephalus or other structural differences may sometimes be treated surgically if consistent with overall care goals.

Palliative care can help at any stage and does not prevent other treatment. It supports comfort, decision-making, family communication and planning for medical crises.

Complications

Swallowing difficulties can allow food, liquid or saliva to enter the lungs. This aspiration can contribute to breathing problems or pneumonia.

Some unusual movements are not epileptic. An EEG, which records the brain's electrical activity, can help distinguish seizures from other movements.

Possible complications include:

Complex care can place substantial practical and emotional demands on families. Social work, respite services, home nursing and bereavement support may help when available.

- Repeated chest infections
- Poor growth or dehydration
- Breathing pauses
- Difficult-to-control seizures
- Pituitary hormone deficiencies

- Abnormally low or high body temperature
- Constipation and reflux
- Joint stiffness, hip problems or spinal curvature
- Skin injury from limited movement or equipment

Prevention

Familial alobar holoprosencephaly usually cannot be prevented. An inherited change affecting early brain formation cannot be reversed through diet, supplements or activity during pregnancy. Folic acid supports general pregnancy health but has not been shown to prevent an inherited familial form.

Genetic counselling can explain the likely inheritance pattern and chance of another affected pregnancy. If the specific change is known, options may include testing during pregnancy or in vitro fertilization with preimplantation genetic testing. Some people consider donor eggs or sperm, adoption, or pregnancy without testing. These are personal choices, not required steps.

Managing diabetes before and during pregnancy supports general health but does not remove a risk caused by an inherited change.

Living with it and what to expect

The structural brain difference is permanent. Children who survive usually have severe or profound developmental disability and need full assistance with daily activities. Development may continue at an individual pace, but independent walking, speech and self-care are often not achieved.

Needs may change over time. Feeding may become less safe, seizures may begin or alter, and muscle stiffness or spinal curvature may increase. Hormone problems can also appear later, so ongoing monitoring remains important even if early tests were normal.

Survival is often shortened. Some affected pregnancies end in miscarriage or stillbirth, and some babies die around birth or during infancy. Others survive into childhood or longer. Chromosome conditions, breathing difficulty, infections, seizures and hormone problems may influence the course, but no scan or genetic result can predict an exact lifespan.

Regular care may involve neurology, clinical genetics, endocrinology, nutrition, respiratory or feeding specialists, rehabilitation services and primary care. Appointments review growth, comfort, seizures, breathing, feeding, equipment and family priorities.

Care goals may change. Some families choose hospital-based treatment for complications, while others emphasize care at home and avoiding burdensome procedures. Either approach may be appropriate when it reflects the person's comfort and the family's informed goals.

When to get medical help

Use routine appointments to discuss gradual changes in growth, muscle tone, sleep, constipation, development, equipment needs or seizure control. Report new feeding difficulty or possible hormone symptoms promptly.

Seek urgent medical advice for:

Call emergency services for severe breathing difficulty, blue or grey skin, unresponsiveness, or a seizure that continues beyond the person's emergency plan. Repeated seizures without recovery between them also require emergency help.

Families caring for someone at risk of seizures or breathing pauses should have an individual emergency plan explaining what can be managed at home and what requires immediate help.

- More coughing, choking or distress during feeds
- Repeated vomiting or inability to keep feeds down
- Much less urine, a very dry mouth or other signs of dehydration
- A new seizure or a clear change in seizure pattern
- Fever with unusual sleepiness or worsening breathing
- Sudden excessive thirst and urination

Common questions

Is familial alobar holoprosencephaly always inherited from a parent?

Not always. A change may be inherited from a parent with mild or no obvious features, or it may occur for the first time in the affected child. Testing the child and parents can help clarify this.

Can a baby survive with alobar holoprosencephaly?

Some do, but survival is often shortened and profound disability is expected. Some babies die before or soon after birth, while others live for months, years or longer.

Can ultrasound diagnose it before birth?

Prenatal ultrasound can often identify the characteristic brain structure. Fetal MRI may clarify the details. Genetic testing may look for the cause but does not always find one.

Could this happen again in another pregnancy?

Yes. The chance varies because it depends on the gene or chromosome change and whether a parent carries it. Genetic counselling provides the most relevant estimate.

Does the face always look different?

No. Midline facial differences are common but inconsistent. Severe brain involvement can occur without the most recognizable facial features.

Is holoprosencephaly the same as anencephaly?

No. In holoprosencephaly, the forebrain forms but does not separate normally. In anencephaly, large parts of the brain and skull do not develop.

Sources

- Solomon BD, Gropman A, Muenke M. "Holoprosencephaly Overview." GeneReviews , University of Washington, Seattle.
- Levey EB, Stashinko E, Clegg NJ, Delgado MR. "Management of Children with Holoprosencephaly." American Journal of Medical Genetics Part C: Seminars in Medical Genetics . 2010;154C(1):183-190.
- Dubourg C, Bendavid C, Pasquier L, Henry C, Odent S, David V. "Holoprosencephaly." Orphanet Journal of Rare Diseases . 2007;2:8.
- Kruszka P, Muenke M. "Syndromes Associated with Holoprosencephaly." American Journal of Medical Genetics Part C: Seminars in Medical Genetics . 2018;178(2):229-237.
- National Library of Medicine. "Nonsyndromic Holoprosencephaly." MedlinePlus Genetics .
- Raam MS, Solomon BD, Muenke M. "Holoprosencephaly: A Guide to Diagnosis and Clinical Management." Indian Pediatrics . 2011;48(6):457-466.