

# Holoprosencephaly (HPE)

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## Holoprosencephaly (HPE)

**Primary Disciplinary Field(s):** Neurology, Developmental Biology, Pediatrics, Genetics, Craniofacial Surgery

### 1. Core Definition and Pathogenesis

**Holoprosencephaly (HPE)** is a complex congenital brain malformation characterized by the incomplete separation of the developing embryonic forebrain (prosencephalon) into two distinct cerebral hemispheres. This fundamental failure in brain development occurs early in gestation, typically between the 18th and 28th days after conception, and results in a spectrum of structural abnormalities of the brain and face. The severity of HPE can vary dramatically, ranging from severe forms that are incompatible with life and often result in spontaneous fetal demise, to much milder forms that may present with only subtle facial anomalies and relatively normal neurological function. The condition underscores the intricate and precisely timed processes of early human embryogenesis, where even minor disruptions can have profound and widespread effects on central nervous system development.

The prosencephalon, or forebrain, is a critical precursor structure in the developing embryo that normally divides into two telencephalic vesicles, which eventually form the cerebral hemispheres, and the diencephalon, which develops into structures such as the thalamus and hypothalamus. In HPE, this crucial midline cleavage fails to occur completely, leading to a single, undivided cerebral ventricle and a variable degree of fusion or absence of deep brain structures. This structural anomaly directly impacts the formation of the skull and facial features, as the developing brain plays an inductive role in shaping the overlying craniofacial tissues. Consequently, the brain malformation is often accompanied by characteristic facial deformities that can serve as indicators of the underlying neurological severity, ranging from profound disfigurement to subtle variations in facial anatomy.

The spectrum of HPE is broadly categorized based on the degree of forebrain division. At one end lies **alobar HPE**, the most severe form, where there is a complete absence of forebrain division, resulting in a single ventricular cavity and often severe facial malformations. Intermediate forms, such as **semilobar HPE**, involve partial separation of the posterior cerebrum but fusion of the frontal lobes. The mildest forms, including **lobar HPE** and **middle interhemispheric variant (MIHV)**, exhibit nearly complete separation of the cerebral hemispheres with varying degrees of fusion in specific areas, such as the frontal lobes, or a localized failure of fusion across the midline. Understanding this spectrum is vital for diagnosis, prognosis, and counseling, as the clinical presentation and long-term outcomes are directly correlated with the extent of forebrain division.

## 2. Classification and Phenotypic Spectrum

The classification of HPE primarily reflects the anatomical extent of forebrain non-division. **Alobar holoprosencephaly** is the most severe manifestation, characterized by a single, common ventricular cavity, a fused thalamus, and the complete absence of the interhemispheric fissure, falx cerebri, and corpus callosum. The cerebral cortex is typically a rudimentary mantle surrounding this single ventricle. Patients with alobar HPE often present with the most extreme facial anomalies, including cyclopia (a single central eye), ethmocephaly (a proboscis located above hypotelorism), cebocephaly (a single-nostril nose located above hypotelorism), or severe hypotelorism with a flattened nose. The prognosis for alobar HPE is extremely poor, with most affected fetuses dying in utero or shortly after birth due to severe central nervous system dysfunction and respiratory failure.

**Semilobar holoprosencephaly** represents an intermediate form where the posterior aspects of the cerebral hemispheres are partially separated, but the frontal and parietal lobes remain fused. The lateral ventricles may be partially separated posteriorly, but they typically merge anteriorly into a single cavity. While the falx cerebri may be partially present posteriorly, it is absent anteriorly. Facial anomalies associated with semilobar HPE are less severe than those seen in the alobar form but are still significant. These can include hypotelorism, cleft lip and palate, and a flattened nasal bridge. Individuals with semilobar HPE often survive longer than those with alobar HPE, but they typically experience significant developmental delays, intellectual disability, seizures, and other neurological deficits.

**Lobar holoprosencephaly** is the mildest classical form, characterized by significant separation of the cerebral hemispheres with distinct frontal and temporal horns of the lateral ventricles. However, some degree of fusion may persist in the frontal lobes, particularly involving the corpus callosum and septum pellucidum, which are often absent or hypoplastic. The interhemispheric fissure and falx cerebri are usually present, distinguishing it from more severe forms. Facial anomalies in lobar HPE are often less pronounced and may include mild hypotelorism, a median cleft lip, or a single central incisor. Neurological outcomes are variable, with some individuals experiencing mild cognitive deficits, while others may have more significant developmental challenges, but survival into adulthood is more common.

Beyond these classic forms, a newer classification, the **middle interhemispheric variant (MIHV)**, sometimes referred to as syntelencephaly, describes a specific type where the posterior frontal and parietal lobes are fused across the midline, while the anterior frontal and occipital regions are separated. This variant often presents with a unique pattern of clinical findings, including significant motor and cognitive impairments. Additionally, "microforms" of HPE exist, where brain malformations are minimal or absent, but subtle facial features such as a single central incisor, microphthalmia (small eyes), or coloboma (a gap in part of the eye) indicate the underlying

developmental field defect. These microforms highlight the broad clinical spectrum and the variable penetrance of HPE-related genetic mutations, emphasizing that facial anomalies, even subtle ones, can be crucial diagnostic clues.

### 3. Etiology and Risk Factors

The etiology of holoprosencephaly is complex and multifactorial, involving a combination of genetic and environmental factors. While the source content correctly notes that there are "no exact causes" in all cases, significant progress has been made in identifying both genetic mutations and maternal risk factors that increase susceptibility to HPE. Genetic factors are now understood to play a predominant role, with up to 40% of cases having an identifiable genetic cause. Chromosomal abnormalities are frequently associated with HPE, particularly trisomy 13 (Patau syndrome) and, less commonly, trisomy 18 and trisomy 21 (Down syndrome). These aneuploidies disrupt numerous developmental pathways, including those critical for forebrain cleavage. Furthermore, specific microdeletions or duplications on various chromosomes have also been implicated, suggesting a dosage-sensitive mechanism in some instances.

Beyond chromosomal abnormalities, numerous single-gene mutations have been identified as causative for HPE. Among the most well-studied is the **Sonic Hedgehog (SHH)** gene, located on chromosome 7. Mutations in SHH or genes involved in its signaling pathway (e.g., PTCH1, GLI2) account for a significant proportion of monogenic HPE cases. SHH plays a critical role in patterning the ventral neural tube and midline structures of the developing brain. Other important genes implicated include **ZIC2** (zinc finger protein 2) on chromosome 13, **SIX3** (sine oculis homeobox homolog 3) on chromosome 2, and **TGIF1** (TGFB-induced factor homeobox 1) on chromosome 18. Each of these genes contributes to the intricate network controlling forebrain development, and mutations can lead to disruptions at various points, resulting in the HPE phenotype. The genetic heterogeneity of HPE suggests that many other genes, perhaps with smaller individual effects or in combination, likely contribute to the remaining unexplained cases.

Environmental risk factors, as highlighted in the source content, also contribute to the occurrence of HPE, often acting as teratogens during the critical period of forebrain development. **Gestational diabetes** in the mother is a well-established risk factor, with studies indicating a several-fold increased risk of HPE in infants born to diabetic mothers, particularly if the diabetes is poorly controlled during early pregnancy. The precise mechanism by which maternal hyperglycemia causes HPE is not fully understood but is thought to involve disruptions in metabolic pathways and cellular signaling important for embryonic development. Other maternal conditions, such as **first-trimester bleeding** and a history of **miscarriage**, may be indicators of underlying uterine or systemic issues that could impact fetal development, though their direct causal link to HPE is less clear and could also be correlative with other genetic or environmental factors.

Maternal exposure to certain substances during early pregnancy is also recognized as a significant environmental risk. The source mentions general **drug use**, which is a broad category. Specific teratogenic drugs include alcohol (leading to Fetal Alcohol Spectrum Disorders, which can sometimes include HPE-like features), retinoic acid (a potent teratogen used in acne medications like isotretinoin), and certain anticonvulsants. Exposure to toxins or infections, such as rubella or toxoplasmosis, although less commonly linked than genetic factors or diabetes, have also been investigated as potential contributors. The interplay between genetic predispositions and environmental exposures is a key area of ongoing research, as it is believed that a "two-hit" mechanism, where a genetic susceptibility is unmasked or exacerbated by an environmental insult, may explain many of the sporadic cases of HPE.

#### 4. Clinical Presentation and Diagnosis

The clinical presentation of holoprosencephaly is as diverse as its underlying pathology, ranging from severe manifestations detectable prenatally to subtle findings observed only postnatally. In the most severe forms of HPE, such as alobar and severe semilobar, the condition is often diagnosed during routine prenatal ultrasound examinations in the first or second trimester. Sonographic findings indicative of HPE include the absence of a midline falx, a single monoventricle, fused thalami, and severe facial anomalies like cyclopia, proboscis, or severe hypotelorism with cleft lip and palate. Fetal magnetic resonance imaging (MRI) is often utilized to confirm the diagnosis and provide more detailed anatomical information about the extent of brain malformation, which is crucial for prognostication and counseling.

For fetuses diagnosed with HPE, particularly the severe forms, the prognosis is often grim, with a high incidence of spontaneous abortion or fetal demise. If live-born, infants with severe HPE typically exhibit profound neurological dysfunction, including severe hypotonia, respiratory distress, seizures intractable to medication, and feeding difficulties. The facial deformities are usually immediately apparent and often require surgical correction, though the underlying neurological deficits remain the primary determinant of quality of life and survival. These infants often require intensive medical support from birth and rarely survive beyond infancy, emphasizing the profound impact of this developmental anomaly on the central nervous system's ability to sustain vital functions.

In cases of milder HPE, such as lobar forms or microforms, diagnosis may not occur prenatally or even immediately after birth. Infants with milder HPE might initially present with less dramatic symptoms, such as subtle facial anomalies (e.g., a single central incisor, mild hypotelorism, or a median cleft lip), developmental delay, seizures that emerge later in infancy, or endocrine dysfunction. Endocrine abnormalities, particularly central diabetes insipidus or pituitary hormone deficiencies (e.g., growth hormone deficiency, hypothyroidism), are common due to the involvement of the hypothalamus and pituitary gland, which are located at the base of the

forebrain. These children may require thorough postnatal evaluation, including physical examination, brain imaging (MRI or CT scan) to precisely delineate the extent of brain malformation, and genetic testing to identify specific chromosomal or gene mutations. Early and accurate diagnosis is critical for guiding management strategies and providing families with realistic expectations regarding their child's developmental trajectory and potential challenges.

## 5. Management and Prognosis

The management of holoprosencephaly is primarily supportive and multidisciplinary, as there is currently no cure for the underlying brain malformation. Treatment focuses on alleviating symptoms, managing associated complications, and improving the quality of life for affected individuals. Given the wide spectrum of severity, management plans are highly individualized. For infants with severe forms, palliative care may be the most appropriate approach, focusing on comfort, pain management, and support for the family. Decisions regarding aggressive medical interventions are made in close consultation with parents, considering the expected prognosis and potential for suffering. Respiratory support, nutritional management (often via gastrostomy tube due to feeding difficulties), and seizure control are critical components of care in these most fragile cases.

For individuals with milder forms of HPE who survive beyond infancy, long-term management involves a comprehensive team of specialists. Neurologists manage seizures with anticonvulsant medications and monitor for hydrocephalus, which may require shunt placement. Endocrinologists are essential for evaluating and treating pituitary hormone deficiencies, which can impact growth, metabolism, and fluid balance. Developmental pediatricians, physical therapists, occupational therapists, and speech-language pathologists provide crucial interventions to address developmental delays, improve motor skills, enhance communication, and support cognitive development. These therapies are vital for maximizing functional abilities and promoting participation in daily activities, helping children reach their full potential despite their neurological challenges.

Craniofacial surgeons and plastic surgeons may be involved in correcting facial deformities such as cleft lip and palate, which can improve feeding, speech, and aesthetic appearance. Ophthalmologists may address eye abnormalities, and audiologists can assess hearing. The prognosis for individuals with HPE is highly variable and directly correlated with the extent of brain involvement. While most cases, particularly alobar HPE, result in fetal death or death shortly after birth, those with lobar HPE or microforms have a much better chance of survival, often into adulthood. However, surviving individuals frequently face lifelong challenges, including varying degrees of intellectual disability, motor deficits, epilepsy, and endocrine dysfunction. Ongoing research aims to better understand the molecular mechanisms underlying HPE, which may eventually lead to targeted therapies or preventive strategies, offering a glimmer of hope for future

interventions.

## 6. Historical Context and Research Directions

The recognition of congenital malformations affecting the brain and face has roots in ancient observations, but the scientific understanding of holoprosencephaly as a specific developmental anomaly began to take shape with advances in embryology and neuroanatomy. Early descriptions were often based on severe anatomical specimens, highlighting the dramatic facial disfigurement. The term "holoprosencephaly" itself, emphasizing the "whole" or undivided forebrain, reflects a more precise understanding of the underlying developmental failure. Over the past century, particularly with the advent of advanced imaging techniques like ultrasound and MRI, the ability to diagnose HPE prenatally and characterize its spectrum has vastly improved, moving from mere observation to detailed classification and etiological investigation.

Current research into HPE is multifaceted, spanning genetics, developmental biology, and clinical neurosciences. A major focus is the identification of novel genetic causes, as a significant proportion of HPE cases remain without a clear genetic diagnosis. This involves utilizing advanced genomic technologies, such as whole-exome sequencing and whole-genome sequencing, to discover new gene mutations and complex genetic interactions. Understanding the precise roles of these genes in forebrain patterning is crucial for unraveling the intricate molecular pathways involved. For instance, studies continue to elucidate how signaling pathways like the **Sonic Hedgehog pathway** orchestrate midline development, and how disruptions to these pathways lead to HPE phenotypes.

Another promising area of research involves the use of animal models (e.g., mouse, zebrafish) and induced pluripotent stem cells (iPSCs) to model HPE in vitro. These models allow scientists to investigate the effects of specific gene mutations or environmental insults on early brain development in a controlled environment. Such studies aim to pinpoint the critical time points and cellular mechanisms disrupted in HPE, offering insights into potential avenues for intervention. While a cure remains elusive, a deeper understanding of the pathogenesis could pave the way for novel therapeutic strategies, perhaps involving gene editing techniques or pharmacological interventions that could mitigate the severity of the malformation if applied very early in development. Furthermore, research into improving diagnostic accuracy, prognostication tools, and long-term supportive care continues to enhance the quality of life for individuals and families affected by HPE.

## 7. Ethical Considerations

The diagnosis of holoprosencephaly, particularly in its more severe forms, presents a myriad of profound ethical dilemmas for prospective parents, healthcare providers, and society at large. One

of the most significant challenges arises with prenatal diagnosis. When HPE is identified early in gestation, parents are faced with difficult decisions regarding pregnancy management, including the option of termination. These decisions are deeply personal and are influenced by individual moral, religious, and cultural beliefs, as well as the perceived severity of the condition and the potential for a child to experience significant suffering. Healthcare providers have an ethical obligation to provide comprehensive, unbiased information about the prognosis, potential treatments, and long-term care requirements, enabling families to make informed choices that align with their values.

Furthermore, for infants born with severe HPE, ethical considerations extend to end-of-life care and the extent of medical intervention. In cases where the condition is deemed incompatible with sustained life or is associated with profound and intractable suffering, discussions about palliative care versus aggressive life-sustaining measures become paramount. These discussions require sensitive communication between the medical team and the family, focusing on the child's best interests, comfort, and dignity. The ethical principle of non-maleficence (doing no harm) guides decisions to avoid prolonging suffering, while beneficence (acting in the child's best interest) informs efforts to provide comfort and support. Such situations often necessitate input from ethics committees to navigate the complex moral landscape and ensure that decisions are made with the utmost care and consideration.

Beyond the immediate medical decisions, HPE also raises broader societal and research ethics questions. The identification of genetic causes and risk factors can lead to discussions about genetic screening, counseling, and reproductive choices. There is an ongoing ethical debate surrounding the balance between preventing genetic disorders and respecting individual autonomy and diversity. For research, ethical oversight is crucial, especially in studies involving human embryonic development or genetic manipulation, ensuring that research advances are pursued responsibly and with appropriate safeguards. Ultimately, the presence of HPE compels a continuous ethical reflection on life, disability, suffering, and the responsibilities of medicine to both treat and care for those with profound congenital conditions, underscoring the importance of compassionate and holistic approaches to care.

## Further Reading

[Holoprosencephaly on Wikipedia](#)

[Holoprosencephaly Information Page - National Institute of Neurological Disorders and Stroke \(NINDS\)](#)

[Holoprosencephaly - National Organization for Rare Disorders \(NORD\)](#)

[Holoprosencephaly - Genetics Home Reference \(MedlinePlus\)](#)

[Holoprosencephaly - Children's Hospital of Philadelphia \(CHOP\)](#)