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Review Article

Evaluation and Management of Children With Holoprosencephaly

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Recent advances in genetics and neuroimaging have greatly contributed to our understanding of the spectrum of midline brain and craniofacial malformations known as holoprosencephaly. Neuroradiologic studies have provided detailed characteristics of four major types of holoprosencephaly: alobar, semilobar, lobar, and middle interhemispheric variant. Clinical studies in children with these types of holoprosencephaly have revealed a wide range of survival and neurologic outcomes. Motor and developmental dysfunctions correlate with the severity of the brain malformation in holoprosencephaly. These findings have implications in the management of medical problems associated with holoprosencephaly and overall prognostication.

Hahn JS, Plawner LL. Evaluation and management of children with holoprosencephaly. Pediatr Neurol 2004;31: 79-88.

Introduction

Holoprosencephaly (HPE) is a complex congenital brain malformation characterized by failure of the forebrain to bifurcate into two hemispheres, a process normally complete by the fifth week of gestation [1]. It is the most common developmental defect of the forebrain and midface in humans, occurring in 1 in 250 pregnancies [2]. Because only 3% of fetuses with HPE survive to delivery [3], the live birth prevalence is only approximately 1 in 10,000 [4-6]. Two thirds of affected patients have been observed to have alobar HPE, the most severe form [7]. With advances in neuroimaging with magnetic resonance imaging, children with less severe forms who have gone undiagnosed in the past are being increasingly identified. Therefore the true live birth prevalence of HPE is likely to be higher than previously estimated, and the actual distribution of subtypes remains to be determined.

Holoprosencephaly has traditionally been classified according to DeMyer's division into three grades of severity: alobar, semilobar, and lobar. In addition, to these classic forms, there is another milder subtype of HPE, called middle interhemispheric variant (MIH) or syntelencephaly [8,9]. The sine qua non feature of HPE is an incomplete separation of the cerebral hemispheres. In the most severe form, *alobar* HPE, there is complete or nearly complete lack of separation of the cerebral hemispheres with a single midline forebrain ventricle (monoventricle), which often communicates with a dorsal cyst (Fig 1). The interhemispheric fissure and corpus callosum are completely absent. In *semilobar* HPE, there is a failure of separation of the anterior hemispheres, whereas some portion of the posterior hemispheres manifests separation. The frontal horns of the lateral ventricle are absent, but posterior horns are present. The corpus callosum is absent anteriorly, but the splenium of the corpus callosum is present. In *lobar* HPE, the mildest form, the cerebral hemispheres are fairly well separated, whereas only the most rostral/ventral aspects are nonseparated. The splenium and body of the corpus callosum are present, although the genu may be poorly developed. Rudimentary formation of the frontal horns may be present. In contrast to "classic" HPE, in *MIH* there is failure of separation of the posterior frontal and parietal lobes whereas the poles of the frontal and occipital lobes are well separated (Fig 1) [8,9]. More detailed characteristics of MIH are provided in the "Neuroimaging Studies" section.

It should be emphasized that the extent of hemispheral nonseparation falls in a spectrum and it is not always easy to categorize an individual case into the three classic forms. In addition, the deep gray nuclei are frequently abnormally separated in HPE, and this separation may be

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Received November 13, 2003; accepted March 1, 2004.

doi:10.1016/j.pediatrneurol.2004.03.006 • 0887-8994/04/$—see front matter

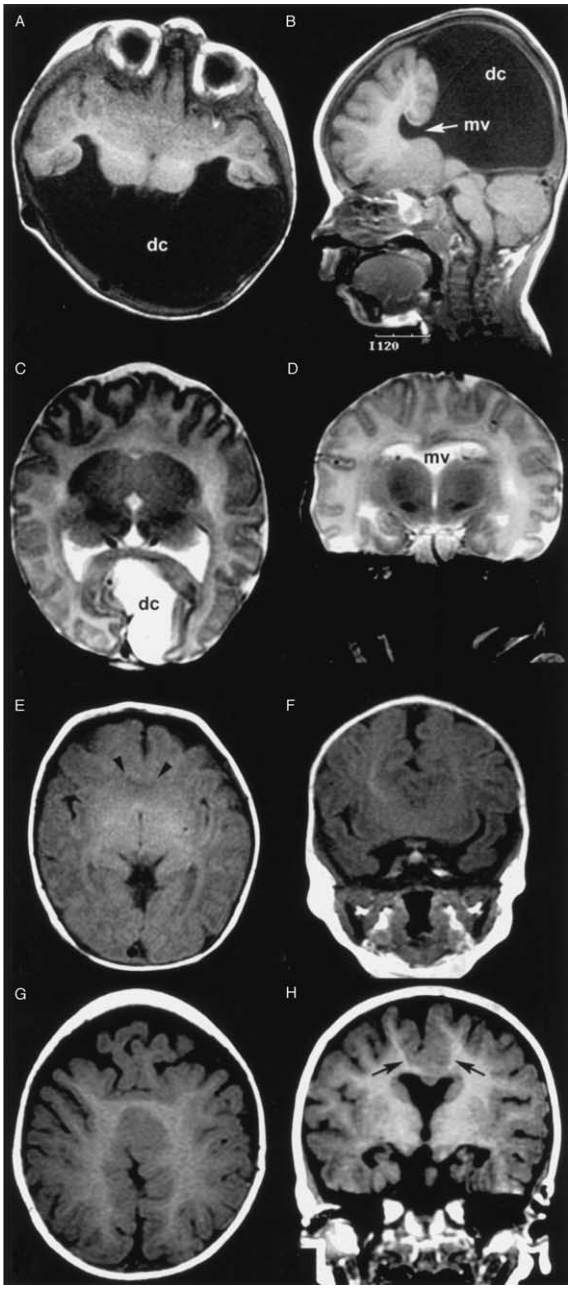

Figure 1. The spectrum of holoprosencephaly as demonstrated by magnetic resonance imaging. (A, B) Magnetic resonance images of a patient with alobar HPE. T_1-weighted axial image (A) reveals lack of separation of the two hemispheres and deep gray nuclei. Large dorsal cyst (dc) is observed posteriorly. T_1-weighted sagittal image (B) reveals a midline ventricle, a monoventricle (mv), that communicates posteriorly with the dorsal cyst (dc). (C, D) Magnetic resonance imaging of a patient with semilobar HPE. T_2-weighted axial image (C) indicates separation of the hemispheres posteriorly but not anteriorly. Anterior horns of the lateral ventricles are absent, whereas the posterior horns are well formed and separated. There is also an incomplete separation of the basal ganglia. T_2-weighted coronal image (D) reveals a lack of interhemispheric fissure and a monoventricle (mv). (E, F) Magnetic resonance imaging of a patient with lobar HPE. T_1-weighted axial image (E) reveals that two hemispheres are fairly well separated as manifested by the presence of an interhemispheric fissure both anteriorly and posteriorly. Note that the frontal horns of the lateral ventricles are only rudimentary (arrowheads). T_1-weighted coronal image (F) documents incomplete separation of the inferior frontal lobes near the midline. (G, H) Magnetic resonance imaging of a patient with the middle interhemispheric variant of HPE. T_1-weighted axial (G) and coronal (H) images demonstrate the continuity of gray matter in the posterior frontal lobes across the midline (arrows). For T_1-weighted images, TR of 600-630 ms and TE of 10-16 ms were used. For T_2-weighted images, TR of 3000 ms and TE of 120 ms were used.

just as important in predicting outcome and function [10,11].

The complex midline brain malformations in HPE are associated with various neurologic, craniofacial, and endocrine manifestations. The purpose of this article is to provide a framework for evaluating and managing children with various forms of HPE.

Assessment of Etiology

HPE is etiologically heterogeneous, and both environmental and genetic causes have been identified. *Chromosomal anomalies* including trisomies, duplications, deletions, and ring arrangements have played an important role in HPE. Approximately 40% of live births with HPE have a chromosomal anomaly, and trisomy 13 accounts for over half of these cases [4]. Of infants born with trisomy 13, 70% have holoprosencephaly [12]. The prognosis in HPE is much worse for those with cytogenetic abnormalities, with only 2% surviving beyond 1 year, compared with 30-54% for those without cytogenetic anomalies [4].

Several multiple malformation syndromes have been associated with HPE, with as many as 25% of HPE cases having a recognizable monogenic syndrome [4,13]. These include pseudotrisomy 13 [14], Pallister-Hall, Meckel, and velocardiofacial syndromes [15]. In addition, there is an increased incidence of HPE (~5%) in patients with Smith-Lemli-Opitz syndrome, in which affected children have a defect in 7-dehydrocholesterol reductase, the enzyme that catalyzes the final step of cholesterol biosynthesis [16]. Defective cholesterol synthesis may have a role in the pathogenesis of HPE through the sonic hedgehog signaling pathway because cholesterol is required for activation of the sonic hedgehog molecule.

In addition, to the association of HPE with chromosomal anomalies and monogenic syndromes, familial cases of nonsyndromic HPE with normal chromosomes have been described [7]. Based on nonrandom chromosomal rearrangements, at least 12 different loci on 11 different chromosomes have been implicated in HPE [17]. Mutations in eight genes have been associated with HPE in humans: *SHH*, *PATCHED1* (*PTCH*), *TGIF*, *TDGF1*, *ZIC2*, *SIX3*, *GLI2*, and *FAST1* [18]. Two of these genes (*SHH* and *PTCH*) encode members of the sonic hedgehog signaling pathway, which regulates ventral development in both the forebrain and spinal cord. Human mutations have been discovered in *SHH* [19] which encodes a secreted signaling ligand localized at early stages to ventral domains in the developing neural tube and *PATCHED1* (*PTCH*) [20] which encodes a receptor for *SHH*. The hedgehog signaling network and its role in holoprosencephaly has been recently reviewed in detail [21]. Three additional HPE mutations implicate the nodal signaling pathway, which plays a vital role in neural patterning. These include: transcriptional co-repressor TG-interacting factor (TGIF), which represses the activity of SMAD transcription factors and is activated by nodal signaling;

TDGF1, which encodes a membrane-associated protein that serves as a co-receptor for nodal signaling [22]; and *FAST1* [21]. The other known HPE genes do not play an obvious role in either of the above pathways. *ZIC2* encodes a zinc-finger transcription factor and is homologous to odd-paired gene in *Drosophila* [23]. It is unique among HPE genes in that it is expressed in dorsal and ventral midline regions of the telencephalon, rather than predominantly in ventral regions as other identified HPE genes. *GLI2* mutations, also present in human HPE, may cause defective translocation of Gli proteins to the nuclei by coexpressed Zic proteins [21]. *SIX3* encodes a homeodomain transcription factor expressed in ventral forebrain [24].

Although progress has been made in identifying gene mutations associated with HPE, the current known mutations have been identified in only 15% to 20% of the HPE cases in a cohort with normal karyotypes [18]. In a recent population-based study, screening for five HPE genes resulted in identification of a mutation in less than 5% of sporadic cases [25]. In the *autosomal dominant* form of HPE, *SHH* is the most frequently identified gene defect, with 37% of families having *SHH* mutations [26].

Evidence from many human studies and animal models implicate multiple environmental factors in the pathogenesis of HPE [27]. Maternal diabetes, including gestational diabetes, is a well-established risk factor [28]. A diabetic mother's risk of having a child with HPE is approximately 1%, a greater than 100-fold increase over the general population. Prenatal exposures to a variety of toxins, medications, and infections have also been reported in cases of HPE. These include alcohol [29], antiepileptic drugs [30-32], retinoic acid [33], cigarette smoking [29], and congenital cytomegalovirus infection [34]. Some teratogens may interfere with the sonic hedgehog signaling pathways by perturbing cholesterol biosynthesis or the ability of target tissue to sense or transduce the sonic hedgehog signal [27]. Although relatively low doses of these teratogens by themselves may not be sufficient to cause HPE, they may act synergistically with other genetic or environmental factors to produce the HPE phenotype [18]. Likewise, although a single HPE gene mutation by itself may not be sufficient to produce HPE in a patient, another factor, such as teratogens, may work in concert to generate the HPE phenotype.

In familial HPE, such as that caused by *SHH* mutation, variable penetrance has been observed [35,36]. Some individuals are severely affected, whereas others with the same mutation or deletion are only mildly affected with "microforms" of HPE and may be neurologically normal. These microforms include microcephaly, hypotelorism, single maxillary central incisor, iris coloboma, absent frenulum, and hyposmia [37]. Because these individuals are still at an increased risk for having children with HPE, it is important to carefully look for these signs in family members of children with HPE.

When evaluating a child with HPE, we recommend high-resolution chromosome studies and HPE gene mutation analysis (Table 1). These genes currently include *SHH*, *TGIF*, *SIX3*, and *ZIC2* (available commercially at GeneDx, Gaithersburg, MD). Other candidate genes that are being tested on a research basis at the National Institutes of Health (Dr. Max Muenke's laboratory) include *PTCH*, *DKK1*, *GLI2*, *TDGF1*, and *FAST1*. In certain circumstances, a genetic evaluation to assess for syndromic HPE may be warranted. We also recommend a detailed prenatal exposure history to possible teratogens. The parents should be examined for possible features of HPE microforms.

Neuroimaging Studies

Advances in neuroimaging have improved our understanding of the pathogenesis of HPE. Our group has published several neuroimaging studies of a large cohort of HPE patients (over 100) [9,10,38-40]. These studies have provided a new grading system for various components of HPE, which allowed correlation studies of imaging findings and clinical characteristics [11,41]. The studies have also led to a better understanding of the embryologic derangements that lead to HPE. Examples of neuroimaging in classic HPE and MIH are provided in Figure 1.

Table 2 summarizes the assessments made on a neuroimaging study of an HPE by our neuroradiologists. High-resolution magnetic resonance imaging scans that include thin-section image sequences in three orthogonal planes (axial, sagittal, and coronal) are preferred. The study should also include a volumetric data set (three-dimensional spoiled gradient-echo sequences), which displays good gray-white matter differentiation and permits reformatting in other planes and volumetric analyses [42]. To determine the type of HPE, careful assessment of the telencephalon is required. Close attention is paid to the presence of anterior and posterior interhemispheric fissures and the localization of nonseparation of the two hemispheres. In addition, the deep gray nuclei are also analyzed systematically as they are often involved in HPE. In our neuroimaging study of 57 classic HPE patients, we observed that the hypothalamus and caudate nuclei were the most commonly nonseparated deep-gray structures in HPE [10], 99% and 96%, respectively. The thalami were least frequently involved of the deep gray nuclei, revealing noncleavage in 67%. In 11% of the HPE cases a single deep gray nuclear mass without discrete basal ganglia, thalami, and mesencephalon was observed. The pattern of deep gray nuclei abnormalities supports the theory that a lack of induction of the most rostral aspects of the embryonic floor plate is the cause of classic HPE. A dorsal cyst is often present in HPE, and its presence is an important risk factor for hydrocephalus and cerebrospinal fluid shunting (see section on dorsal cyst).

Table 1. Etiologic and genetic factors associated with holoprosencephaly

Categories	Factors
Genetic factors	Familial holoprosencephaly
Chromosomal abnormalities	Trisomy 13
	Trisomy 18
	Duplication, deletions, ring arrangements of chromosome 13
Monogenic syndromes	Pseudotrisomy 13
	Pallister-Hall syndrome
	Meckel syndrome
	Velocardiofacial syndrome
	Smith-Lemli-Opitz syndrome
HPE gene mutations	*SHH*
	PTCH
	TGIF
	TDGF1
	ZIC2
	SIX3
	GLI2
	FAST1
Environmental exposures during gestation	Antiepileptic drugs
	Retinoic acid
	Alcohol
	Smoking
	Statin drugs
	Gestational diabetes
	Cytomegalovirus infection
	Maternal hypocholesterolemia

In a neuroimaging study of 96 classic HPE patients, the cortical thickness was normal in all patients and gyral/sulcal sizes were normal in 83% [39]. Gyral/sulcal abnormalities were documented in a diffuse distribution in eight patients and limited to the anteromedial cortex in four lobar patients. Surprisingly, only four of 96 patients with classic HPE had subcortical heterotopia, which were also located anterior to the interhemispheric fissure in the noncleaved region.

The neuroimaging features of the subtype MIH are different from classic HPE (Fig 1). Unlike classic HPE where the most severely nonseparated region of the hemispheres is the basal forebrain, in MIH the posterior frontal and parietal lobes are affected. The anterior portions of the frontal lobes and the occipital lobes are well separated in MIH. The genu and splenium of the corpus callosum appear normally formed, but the callosal body is absent. The hypothalamus and lentiform nuclei appeared normally separated in all MIH patients, but the caudate nuclei and thalami were incompletely separated in many cases [9]. The sylvian fissures in most patients were oriented nearly vertically and were abnormally connected across the midline over the vertex of the brain [9]. Approximately two thirds of the MIH patients had either subcortical heterotopic gray matter or cortical dysplasia.

Neuroimaging evaluation of the brain in HPE may be difficult in young infants with microcephaly because of the small brain size and immature myelination. A follow-up imaging after a period of brain growth may be required. Difficulties in assessment also occur when hydrocephalus distorts underlying brain structures [42]. Definitive diagnosis in these cases often requires repeat magnetic resonance imaging after decompression.

It is also important that imaging studies be reviewed by a pediatric neuroradiologist with experience in brain malformations. Approximately one fifth of the imaging studies referred to our centers for HPE fail to meet the HPE neuroimaging criteria [43]. The ultimate diagnoses given to these studies include septo-optic dysplasia, agenesis of corpus callosum, or interhemispheric cyst. The dorsal cyst of HPE is similar in appearance to the interhemispheric cyst associated with agenesis of the corpus callosum (type 1b) [44,45]. The latter is frequently misdiagnosed as HPE, but is distinguished by normal cleavage of the basal forebrain structures.

Clinical Manifestations of HPE

When faced with a child with HPE, it is important to establish whether the HPE is an isolated brain malformation or part of a syndrome with other systemic manifestations. From the neurologist's point of view, the care of the child with HPE requires a multidisciplinary management, especially when they have multiple problems.

Children with HPE experience many medical and neurologic problems, including mental retardation, epilepsy, weakness, spasticity, dystonia, choreoathetosis, and endocrine disorders [11,46]. Developmental disability affects virtually all patients with HPE. The degree of delay and neurologic problems generally correlate with the severity of the brain malformation. Barr and Cohen have previously reported a poor survival and performance in a large group of patients with alobar HPE [46]. To better characterize the clinical characteristics of all types of HPE and their correlation with neuroimaging findings, a prospectively collected case series from the Carter Centers for

Table 2. Neuroimaging assessment of holoprosencephaly

Deep gray nuclei abnormalities (nonseparation)	Thalamic nuclei (degree of nonseparation and orientation)
	Caudate nuclei
	Lentiform nuclei
	Hypothalamus
	Pituitary*
	Mesencephalon
Ventricular system	Presence of a monoventricle
	Presence of dorsal cyst
	Aqueductal abnormalities
	Hydrocephalus
Cerebral cortex	Gyral and sulcal abnormalities (thickness and numbers)
	Subcortical heterotopias
	Sylvian fissure abnormalities
White matter maturation	Delayed or appropriate
Other malformations	Dandy-Walker malformation
	Encephalocele
	Myelomeningocele

* Pituitary gland is assessed as to whether it is normal or abnormal based on location, morphology, and signal intensity.

Brain Research in Holoprosencephaly and Related Malformations (a national consortium funded by a not-for-profit foundation) was recently completed [11,41]. These studies included 83 children (41 male and 42 female) with HPE evaluated at one of the Centers (Kennedy Krieger Institute, Texas Scottish Rite Hospital, or Stanford University Medical Center) between 1998 and 2001. Just over half had semilobar, and approximately 15% each had alobar, lobar, and MIH types. The age range for each type was broad: alobar from 0.1 to 2.6, semilobar 0.1 to 13.9, lobar 0.8 to 19, and MIH 0.5 to 14 years at the time of evaluation. The following summarizes some of the clinical problems and neurologic disorders in these children disclosed in our studies [11,41], as well as those of the series from Barr and Cohen [46].

Craniofacial Malformations

It has been long recognized that patients with HPE have various midline craniofacial malformations. In our studies, we evaluated these malformations (Table 3) and graded them according to severity [11,41]. Very severe abnormalities, such as cyclopia, ethmocephaly (a proboscis between severely hypoteloric eyes), and cebocephaly (hypotelorism with a single nostril), were observed in 2% of the patients. Severe defects including midline cleft lip and palate and flat nose occurred in 16%. Moderate defects including midface hypoplasia and moderate hypotelorism occurred in 14%. Mild malformations including single maxillary central incisors and iris colobomas were observed in 36%. The grade of HPE correlated with the severity of craniofacial malformation, although there were many exceptions [11]. The craniofacial malformations in MIH were usually mild and often manifested as hypertelorism [41].

Infants with craniofacial malformations in the more severe range often die during infancy. Those with less severe malformations, such as cleft palates, will require special attention with regard to their feeding. Special cleft palate nipples may assist with feeding difficulties. Surgical repair of the cleft is often performed if the infant survives beyond infancy.

Oromotor Dysfunction

Feeding and swallowing difficulties may be observed in HPE with or without cleft lip/palate. These include choking episodes and gagging during feedings, slowness in eating, and vomiting [46]. In classic HPE the severity of the feeding difficulties correlated with the grade of HPE [11]. For example, all the patients with alobar HPE (12 months or older) had severe feeding problems, whereas only 9% to 13% of the patients with milder HPE types (lobar and MIH) had such problems (Table 4). Approximately two thirds of patients with alobar and semilobar HPE required a gastrostomy tube. Gastrostomy tubes may help ensure sufficient caloric intake for growth. They may also help achieve sufficient free-water intake when patients have diabetes insipidus (see endocrinopathies section below). When significant feeding problems arise, gastroenterology and occupational therapy consultations should be obtained.

Table 3. Congenital malformations associated with holoprosencephaly

Region	Malformation
Head	Microcephaly
	Hydrocephalus
	Synophrys
	Encephalocele
Eye	Hypotelorism
	Hypertelorism
	Anophthalmia
	Microphthalmia
	Fused orbits
	Cyclopia
	Coloboma
	Epicanthal folds
	Ptosis
	Ethmocephaly
	Visual impairment
Nose	Flat nose
	Philtrum pit
	Single nares (cebocephaly)
	Septal defect/obstruction/deviation
	Pyriform sinus stenosis
	Proboscis
	Maxillary agenesis
Teeth	Single maxillary central incisor
	Fused teeth
	Missing teeth
Lip	Unilateral cleft lip
	Bilateral cleft lip
	Median cleft lip
Palate	Unilateral cleft palate
	Bilateral cleft palate
	Median cleft palate
Others	Spina bifida
	Digit anomalies
	Club feet
	Supernumerary nipples
	Cardiac defect
	Scoliosis
	Abnormal genitalia

Seizures and Epilepsy

Approximately one half of the children with HPE in this cohort had at least one seizure [11,41]. The seizure occurrence by type of HPE is provided in Table 4. Of patients with classic HPE, approximately one half had difficult-to-control seizures. In this latter group, there was higher incidence of cortical malformations. Approximately 30% had complex partial seizures with or without generalization, 9% generalized tonic-clonic seizures, 12% other generalized seizures (tonic, atonic, myoclonic, or infantile spasms), and 20% had mixed seizures (unpublished data on 56 patients with seizures and HPE). Detailed seizure type was not available in 29%.

It is important to realize that the majority of patients with HPE will not develop seizures or epilepsy. Only

Table 4. Clinical manifestations of HPE by type

	Alobar	Semilobar	Lobar	MIH
Seizures, any % (n/N)	53 (7/19)	46 (27/58)	64 (9/14)	40 (6/15)
Endocrinopathies % (n/N)	85 (11/13)	74 (32/43)	50 (6/12)	0 (0/15)
Microcephaly % (n/N)	38 (5/13)	81 (35/43)	83 (10/12)	47 (7/15)
CSF shunting % (n/N)	62 (8/13)	7 (3/42)	9 (1/11)	27 (4/15)
Dorsal cyst % (n/N)	92 (12/13)	28 (12/43)	9 (1/11)	40 (6/15)
Spasticity* % (n/N)	80 (4/5)	90 (27/30)	64 (7/11)	87 (13/15)
Hypotonia* % (n/N)	80 (4/5)	72 (21/29)	45 (5/11)	60 (9/15)
Dystonia* % (n/N)	80 (4/5)	80 (24/30)	36 (4/11)	47 (7/15)
Involuntary movements* % (n/N)	0 (0/5)	41 (12/29)	10 (1/10)	0 (0/15)
Severe feeding problems* % (n/N)	100 (5/5)	57 (17/30)	9 (1/11)	13 (2/15)

* The percentage of patients with clinically significant motor dysfunctions by HPE type (number of patients 12 months of age or older: alobar 5, semilobar 30, lobar 11, MIH 15). Motor function in each area was graded and dichotomized such that presence of any degree of spasticity, hypotonia, dystonia, and involuntary movements was considered to be positive.

Abbreviations:
CSF = Cerebrospinal fluid
HPE = Holoprosencephaly
MIH = Middle interhemispheric variant
n/N = Number affected/total number in that category

about a quarter of the patients in our cohort had chronic seizures. Many patients may have isolated or rare reactive seizures. Therefore we do not recommend routine prophylactic treatment with antiepileptic medications. In patients who are suspected of having seizures, an electroencephalogram and a high-quality magnetic resonance imaging should be obtained. Magnetic resonance imaging should include imaging in three planes and should include thin-sliced three-dimensional acquisitions to assess for cortical malformations. Patients should also have routine electrolytes testing with special attention to sodium concentrations. Sodium imbalance is a common cause of acute reactive seizures in HPE patients.

Electroencephalographic studies have revealed a variety of abnormalities. In a prospective study of 18 HPE patients who had an electroencephalogram before any seizures, sharp transients were documented in 5 (28%) [47]. Sharp transient activity occurred only in patients with alobar or semilobar HPE. Three patients experienced seizures subsequently, but only one developed epilepsy. Other electroencephalographic studies in HPE patients with frequent seizures have reported abundant paroxysmal activity consisting of low-amplitude fast activity that evolves into generalized rhythmic high-amplitude delta activity [48,49]. Common background abnormalities include hypersynchronous theta and beta activity [47,50].

Endocrinopathies

Children with HPE are at risk for endocrine disorder because the midline malformation also affects the development of the hypothalamus and the pituitary gland. Endocrinopathies contribute significantly to the morbidity and mortality in HPE [51]. Diabetes insipidus, owing to posterior pituitary dysfunction, is a common problem in HPE [52-55]. Anterior pituitary dysfunction, such as growth hormone deficiency, hypocortisolism, and hypothyroidism, are also observed, but less frequently.

Consistent with previous reports, endocrinopathies were observed in nearly three quarters of our patients with classic HPE, with all affected children having at least diabetes insipidus (Table 4) [11]. Posterior pituitary dysfunction was much more common in HPE than anterior dysfunction. The severity of endocrine dysfunction correlated with the grade of hypothalamic abnormality (degree of nonseparation), but not with imaging abnormalities of the pituitary gland [11]. One possibility is that this may reflect the difficulty in imaging of the pituitary, especially in young infants. In contrast to classic HPE, none of the patients with MIH had either anterior or posterior pituitary dysfunction [41]. This finding may reflect the relative sparing of the hypothalamic nuclei in MIH [41]. These findings raise the possibility that the hypothalamus rather than the pituitary is the primary source of the endocrinopathy in HPE.

Currently when we evaluate children with HPE, we obtain electrolytes including sodium. Serial sodium concentrations (i.e., every 6 months during the first few years) may be necessary because the diabetes insipidus usually evolves slowly, and many children seem to remain asymptomatic. We have diagnosed diabetes insipidus in several asymptomatic children on routine screening that revealed sodium concentrations greater than 160 mEq/L. For mild diabetes insipidus, fluid management may be the only intervention required. If they develop clinically significant diabetes insipidus, desmopressin (DDAVP) is an effective treatment. For assessment of anterior pituitary function, we recommend cortisol, adrenocorticotropin hormone,

thyroid-stimulating hormone, free T4, and insulin-like growth factor 1 (Table 5). Others have observed growth delay to be common in children with alobar HPE [46]. However, it is unknown whether this is a result of growth hormone deficiency as no systematic studies have been performed in patients with HPE.

Microcephaly

Three quarters of patients with classic HPE had microcephaly, whereas approximately half of the patients with MIH had microcephaly. As Table 4 indicates, microcephaly was present in a greater proportion of patients with semilobar and lobar HPE when compared with alobar HPE, because when microcephaly was not present, hydrocephalus was usually the underlying problem [11] and hydrocephalus was more common in alobar patients. Our findings were similar to those of Barr and Cohen [46], who demonstrated that the brain in a child with HPE was small unless there was excess of cerebrospinal fluid around the brain. Hence, if a child with classic HPE does not have microcephaly, neuroimaging studies for hydrocephalus should be considered and the child should be closely monitored for signs of elevated intracranial pressure.

Dorsal Cyst and Hydrocephalus

The presence of a dorsal cyst strongly correlated with nonseparation of the thalami and hydrocephalus [11,38]. The more severely the thalami are nonseparated, the higher are the probabilities of finding a dorsal cyst and developing hydrocephalus. We hypothesized that during development thalamic nonseparation causes blockage of cerebrospinal fluid egress from the third ventricle. This blockage, especially in conjunction with aqueductal anomalies, would lead to an expansion of the posteriordorsal portion of the third ventricle and formation of the dorsal cyst [38]. This condition would then lead to expansion of the ventricular system proximal to the obstruction. Supporting this theory, hydrocephalus is often observed in association with dorsal cysts, and the cysts frequently disappear after ventriculoperitoneal shunting [42].

One sixth of classic HPE patients required cerebrospinal fluid shunting because of hydrocephalus. There was a much higher proportion of cerebrospinal fluid shunting in alobar type (nearly three quarters) and patients with a dorsal cyst (approximately two fifths). Therefore when a dorsal cyst is present, the child is at risk for developing symptomatic hydrocephalus and requires close follow-up for possible cerebrospinal fluid shunting. When significant hydrocephalus is present, shunting should be considered even in severe HPE. Deferring the procedure will only lead to progressive head enlargement and make caring for the child more difficult [46].

Table 5. Diagnostic evaluations in HPE

Laboratory	Electrolytes and osmolarity
	Cortisol
	ACTH
	TSH
	Free T4
	IGF1
Genetic	High-resolution chromosome
	HPE gene mutations (see Table 1)
Radiograph	If bony and spine abnormalities, skeletal radiographs of affected regions
Neuroimaging	MRI is preferred
	High-quality CT if MRI is unavailable
	Serial imaging if there is microcephaly, large dorsal cyst, or rapidly enlarging head size
Electrophysiology	Electroencephalogram if there is a history of seizures

Abbreviations:
ACTH = Adrenocorticotropin hormone
CT = Computed tomography
HPE = Holoprosencephaly
IGF1 = Insulin-like growth factor 1
MRI = Magnetic resonance imaging
TSH = Thyroid-stimulating hormone

Motor Dysfunction

Abnormalities of tone and movement are present in all forms of HPE [11,41,46]. In our cohort, the proportion of patients having significant motor dysfunction (hypotonia, dystonia, spasticity, and abnormal movements) varied considerably by type of HPE (Table 4). Patients with lobar HPE generally had milder motor abnormalities than those with the more severe alobar and semilobar forms. The MIH group displays significant problems with hypotonia, dystonia, and spasticity, but not with involuntary movements [41]. Many of the children with classic HPE had a typical distribution of upper limb dystonia and lower limb spasticity. In alobar HPE, others have observed hypertonia and spasticity that increase with stimulation or excitement [46]. This condition may represent a form of dystonia, because the hypertonicity varies with time.

HPE patients with motor dysfunction usually receive physical and occupational therapy. For symptomatic dystonia, which often has a predilection for the upper limbs, we treat our patients with trihexyphenidyl. This treatment can be commenced at low divided doses (usually 1 mg three times daily in all but infants), and titrated to effect (up to 2 mg/kg/day). The usual side effects include constipation, dry mouth, and other anticholinergic effects. This medication may improve upper limb dystonia, thus permitting better fine motor function of hands and arms. Trihexyphenidyl sometimes improves oromotor function by decreasing secretions and improving swallowing.

Developmental Dysfunction

Severe to profound developmental delay and mental retardation are common in more severe forms of HPE [46].

However, these problems are not universal in all types of HPE. The neurodevelopmental function in less severe forms of HPE (such as lobar and MIH) was better than previously reported [11,41]. In our study of classic HPE patients over 12 months of age (n = 46), we demonstrated an inverse correlation between the grade of HPE and developmental functions including mobility, hand/arm function, and expressive language (Fig 2) [11]. We found that alobar HPE patients (n = 5) were severely affected and made minimal developmental progress, whereas patients with semilobar (n = 30) and lobar (n = 11) HPE achieved better function. None of the children with alobar HPE were able to walk, able to reach and attain objects, or utter words. Only 4 of 30 patients with semilobar HPE had normal or mildly abnormal hand/arm function, and only two could speak in multiword sentences. In contrast, approximately one half of the lobar HPE patients were able to walk independently or with assistance, use their hands/arms normally or with mild dysfunction, and speak single words or multiword sentences.

Compared with the lobar group, the functional levels of the MIH group were similar in mobility, but somewhat better in hand/arm function and speech [41]. In our study of 15 patients with MIH, six were able to ambulate with support and 11 were able to use their hands/arms with only mild dysfunction. Three were able to speak in multiword sentences, and eight uttered single words.

We also performed detailed neuropsychological testing in most of the patients. These included the Bayley Scales of Infant Development (BSID-II) and the Stanford-Binet Intelligence Scale (SB-IV). The older participants were given the Wechsler Adult Intelligence Scale (WAIS-III). The parents completed the Vineland Adaptive Behavior Scales. A small study of nine patients with HPE (16 months to 17 years) suggested a pattern of relative strengths in receptive language and socialization skills, and weaknesses in visual reasoning and nonverbal problem skills [56]. Because of significant expressive language and motor impairments observed in HPE, a novel assessment tool (the Carter Neurocognitive Assessment) was developed at Rutgers University. The Carter Neurocognitive Assessment has been utilized for the past 3 years and a study assessing its usefulness is ongoing.

Prognostication

When giving prognostic information to families with a child affected by HPE, caution should be exercised. There is a correlation between the severity of HPE and outcome. Therefore it is clear that one should not give the same anticipatory counseling in regard to neurodevelopmental outcome to parents of children with alobar, semilobar, lobar, and MIH forms. The wide spectrum of outcomes underscores the importance of accurate neuroradiologic classification of HPE.

A common misperception is that children with HPE do not survive beyond infancy. Although early mortality is

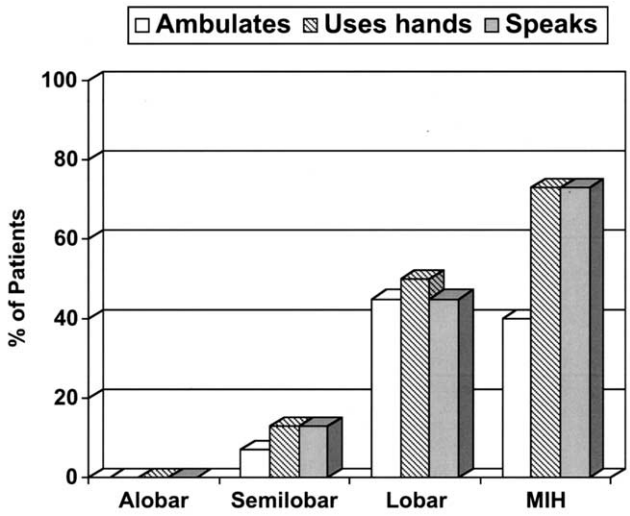

Figure 2. The percentage of patients with various developmental characteristics by type of HPE. The functional abilities in the patients with the classic HPE types (alobar, semilobar, and lobar) correlate inversely with severity of HPE. Patients with the middle interhemispheric variant (MIH) had functional abilities that were similar or better than those with lobar HPE. "Ambulates" is defined as ability to walk with or without assistance, "Uses hands" is defined as using hands/arms normally or with mild dysfunction, and "Speaks" is defined as the ability to say single words or multiword phrases. Children less than 1 year of age were excluded.

common in severe forms of HPE (especially when accompanied by severe craniofacial anomalies or chromosomal abnormalities), many patients with mild to moderate forms will survive into childhood and beyond. Of the 104 children with HPE evaluated at the Carter Centers, the mean age was 4 years and 15% were between 10 and 19 years of age [43]. The oldest patient in our studies, who has lobar HPE, was 19 years of age at the time of evaluation.

Prenatal Diagnosis and Genetic Counseling

The recurrence risk of HPE is estimated to be 6% [57]. Because recurrence risks are higher in familial forms of HPE, a thorough family history is essential. Special attention should be paid to microforms of HPE, such as a single central incisor or anosmia. Families concerned about recurrence in future pregnancies should receive genetic counseling from an experienced center. Prenatal ultrasound has been used to detect the central nervous system and facial abnormalities of severe HPE as early as the first trimester [58-60]. The sensitivity of ultrasonography for detection of milder forms of HPE (lobar and MIH) may be low. In our study of 104 HPE patients (weighted toward less severe types), despite the fact that prenatal ultrasound was performed in 93%, prenatal diagnosis was made in only 22% [43]. Nevertheless, if any central nervous system abnormalities are detected on prenatal ultrasound tests, fetal magnetic resonance imaging may provide better characterization of the malformations [61].

Conclusion

Holoprosencephaly is a complex developmental brain malformation. From the advances in neuroimaging and genetics, our understanding of the etiology and pathogenesis of this condition has advanced dramatically. The details of the complex interplay of genetic and environmental factors involved in HPE are just emerging. Our growing understanding and recognition of the wide clinical spectrum of HPE should enable us to provide more accurate diagnoses and prognoses. This advance should lead to improved management of common medical complications and more optimal family counseling. Careful assessment of each affected individual and neuroimaging studies are vital when dealing with cases of severe brain malformations such as HPE. With advanced magnetic resonance imaging, we are no longer dependent on the evaluation of the face to predict the brain. As pointed out in an editorial by Patterson [62], "the face predicts the brain; the image predicts its function."

The authors thank A. James Barkovich, M.D. and Erin M. Simon, M.D. for reviewing the neuroimaging studies, Nancy J. Clegg, Ph.D. and Elaine E. Stashinko, Ph.D. for assistance with the research database, and Eric B. Levey, M.D. for reviewing the manuscript. This research was supported by the Carter Centers for Brain Research in Holoprosencephaly and Related Malformations and the Don and Linda Carter Foundation.

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