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Neuroanatomy of holoprosencephaly as predictor of function

Beyond the face predicting the brain

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Abstract—*Background:* Despite advances in neuroimaging and molecular genetics of holoprosencephaly (HPE), the clinical spectrum of HPE has remained inadequately described. *Objective:* To better characterize the clinical features of HPE and identify specific neuroanatomic abnormalities that may be useful predictors of neurodevelopmental function. *Methods:* The authors evaluated 68 children with HPE in a multicenter, prospective study. Neuroimaging studies were assessed for the grade of HPE (lobar, semilobar, and alobar), the degree of nonseparation of the deep gray nuclei, and presence of dorsal cyst or cortical malformation. *Results:* In general, the severity of clinical problems and neurologic dysfunctions correlated with the degree of hemispheric nonseparation (grade of HPE). Nearly three-quarters of the patients had endocrinopathies, with all having at least diabetes insipidus. The severity of endocrine abnormalities correlated with the degree of hypothalamic nonseparation ($p = 0.029$). Seizures occurred in approximately half of the children with HPE. The presence of cortical malformations was associated with difficult-to-control seizures. The presence and degree of dystonia correlated with the degree of nonseparation of the caudate and lentiform nuclei and the grade of HPE ($p < 0.05$). Hypotonia correlated with the grade of HPE ($p < 0.05$). Mobility, upper extremity function, and language correlated with the degree of nonseparation of the caudate, lentiform and thalamic nuclei, and grade of HPE ($p < 0.01$). *Conclusions:* Patients with HPE manifest a wide spectrum of clinical problems and neurologic dysfunction. The nature and severity of many of these problems can be predicted by specific neuroanatomic abnormalities found in HPE.

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Holoprosencephaly (HPE) is a brain malformation that results from a primary defect in induction and patterning of the rostral neurotube (basal forebrain) during the first 4 weeks of embryogenesis.[1] This defect results in incomplete separation of the cerebral hemispheres. Based on the degree of hemispheric nonseparation, HPE traditionally has been classified into three types: alobar, semilobar, and lobar (figure 1).[2]

Advances in neuroimaging over the past decade have led to a better understanding of the pathogenesis of HPE and the variability of this condition.[3-6] A recent study highlighted the frequent involvement of deep brain structures in HPE, such as basal ganglia, thalamic nuclei, hypothalamic nuclei, and mesencephalon.[3] This study proposed a grading system based on the degree of nonseparation of these deep structures, to complement the traditional classification of HPE that depends on hemispheric nonseparation.[3]

Additional material related to this article can be found on the *Neurology* Web site. Go to www.neurology.org and scroll down the Table of Contents of the October 8 issue to find the title link for this article.

Children with HPE have many neurologic problems including mental retardation, spasticity, athetoid movements, seizure disorders, and endocrinologic dysfunction.[7,8] The degree of neurologic problems and delay generally correlates with the severity of the brain malformation.[8] Patients with the most severe type (alobar) make minimal developmental progress and have shortened life spans.[8] In contrast, our initial experience indicated that the developmental outcomes and prognosis appear more favorable in milder forms of HPE (semilobar and lobar). The clinical spectrum of HPE has been inadequately described in these milder forms. The goals of this study were to better characterize the clinical features for all types of HPE and to identify specific neuroanatomic abnormalities that may be used as predictors of neurodevelopmental function.

Methods. *Patient selection.* Our series details 68 children with HPE that were evaluated at one of the three Carter Centers for Brain Research in Holoprosencephaly and Related Brain Malformations (a national consortium funded by a nonprofit, private foundation). The patients

From Stanford University School of Medicine, Stanford, CA, and Lucile Packard Children's Hospital (Drs. Plawner and Hahn and V.T. Sweet), Palo Alto, CA; Texas Scottish Rite Hospital (Drs. Delgado, Miller, and Clegg), Dallas, TX; Kennedy Krieger Institute (Drs. Levey, Kinsman and Stashinko), Baltimore, MD; University of California at San Francisco (Dr. Barkovich); and Children's Hospital of Philadelphia (Dr. Simon), PA.

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were referred to the Centers through various sources, including pediatricians, neonatologists, geneticists, and neuroradiologists. Some patients were self-referred via the Carter Center Web site. The patients were enrolled prospectively from 1998 through 2001. Twenty-six patients were evaluated at Kennedy Krieger Institute, 21 at Texas Scottish Rite Hospital, and 21 at Stanford University Medical Center. The study was approved by the Institutional Review Boards at each of the Centers. Consent was obtained from the parents before enrollment.

Clinical evaluations. We evaluated clinical features of patients with HPE using a structured data form. The evaluations at the Carter Centers included obtaining a detailed medical history from direct questions and review of medical records, physical examination, and assessment of developmental achievements. If there was more than one clinical evaluation, the most recent one was used.

The seven clinical variables examined were the presence and severity of seizures, endocrinologic dysfunction, temperature dysregulation, craniofacial anomalies, sleep disorders, self-abusive behavior, and feeding or swallowing disorders. They were graded on a scale of 0 to 2, 0 to 3, or 0 to 4, depending on the variable (table 1). More detailed definitions of these categories are provided in the supplementary information on the *Neurology* Web site (go to www.neurology.org and scroll down the Table of Contents to find the title link for this article).

We also documented three basic developmental milestones, including degree of mobility, upper extremity or fine motor function, and language development. The grading scales are detailed in table 1.

A Composite Clinical Severity Score (CCSS) was calculated by adding the grades of clinical variables (except for craniofacial anomalies) and developmental variables (table 2). Patients missing values for any variable were excluded for analyses that involved CCSS.

Based on the neurologic examination, we also graded the severity of various motor abnormalities, including spasticity, dystonia, choreoathetosis, and hypotonia (see table 1). A Composite Motor Score (CMS) was calculated by adding the grades of the four motor variables.

Other clinical information gathered included head circumference, history of CSF shunting, and seizure history. Seizures were classified into three categories: none, moderate (i.e., <3 seizures or seizures that were easily controlled with antiepileptic medications), and severe (i.e., difficult-to-control, medically refractory seizures).

Neuroimaging assessment. Neuroimaging studies of these 68 patients were evaluated by two pediatric neuroradiologists (E.M.S. and A.J.B.) who were unaware of the clinical status. Available imaging included MRI (61) or high-quality CT (7). To be included in the study, the CT scans had to have a slice thickness of ≤ 5 mm and adequate image quality to allow assessment of key structures (basal ganglia, thalami, and interhemispheric fissure). The type of HPE (alobar, semilobar, or lobar) was determined based on the extent of the interhemispheric separation and ventricular morphology.

The degree of nonseparation of the deep gray nuclei, including the caudate nuclei, lentiform nuclei, thalamic nuclei, and hypothalamic nuclei, were graded using previously published methods.[3] Briefly, the neuroimaging studies were graded on the degree of separation on a scale of 0 (fully separated) to 3 (complete noncleavage) for all deep gray structures except for the hypothalamic nuclei, where a 0-to-2 scale was used. A composite nonseparation score, called the Deep Gray Score (DGS), was calculated by adding the grades of these four variables (see table 2). Patients missing values for any of these variables were excluded for analyses involving DGS. When imaging allowed, the pituitary gland was subjectively graded as normal or abnormal in size and signal intensity for age.

Other imaging variables examined were the presence or absence of a dorsal cyst and cortical malformation.

Statistical analyses. Analysis of ranked variables was performed using the Spearman rank correlation test. For example, when assessing the correlation between ranked clinical variables with the ranked neuroimaging variables, the Spearman rank correlation test resulted in a correlation coefficient (rho) and a p value for level of significance. Categorical variables were analyzed using a χ^2 test or Fisher's exact test (where appropriate). Comparisons between ranked and dichotomous variables were analyzed with Mann–Whitney U test. Group differences of continuous variables were evaluated using Student's t-test.

Results. *Patient demographics.* Of the 68 patients with HPE, 13 (19%) had alobar type, 43 (63%) had semilobar, and 12 (18%) had lobar. There were 35 males and 33 females. The mean age of evaluation was 0.86 years for alobar (range, 0.1 to 2.6 years), 3.8 for semilobar (range, 0.1 to 13.6 years), and 5.8 for lobar (range, 0.8 to 19 years). The mean age of alobar HPE patients was younger (alobar vs lobar, $p = 0.01$, and alobar vs semilobar, $p = 0.01$, t-test; table 3). Forty-six patients were 1 year of age or older at the time of evaluation (5 alobar, 30 semilobar, and 11 lobar).

Four of the 63 children with HPE (6%) in whom chromosomal analysis was performed had an abnormality (13q deletion, ring 13, mosaic 46XO, and 47XX plus marker). Although genetic mutation analysis has not been entirely completed, thus far only two patients have been identified with a mutation in one of the four known genes for HPE (*SHH, SIX3, ZIC2,* and *TGIF*); both of these patients had *ZIC2* mutation. Most of the patients had sporadic HPE without a positive family history. There was only one sibling pair in this cohort (a male with lobar HPE and female with semilobar HPE, who both had features of Pallister–Hall syndrome).

Seizures. For all HPE types, 33 of 68 (49%) of the patients had at least one seizure. Of the 33 patients with seizures, 17 (52%) had seizures that were considered difficult to control. The severity and frequency of seizures in the various subtypes of HPE are shown in table 4. The proportion of those patients with at least one seizure was approximately half for each subtype of HPE, i.e., there was no direct correlation of prevalence of seizures and the severity of HPE.

When we analyzed the 46 patients 12 months of age or older, the proportion with difficult-to-control seizures increased with the severity of HPE ($p = 0.012$, Mann–Whitney U test) (see table 4). The presence of cortical malformation did not correlate with the presence or absence of seizures. However, difficult-to-control seizures correlated with the presence of cortical malformations ($p = 0.014$, Fisher's exact test). Cortical malformations

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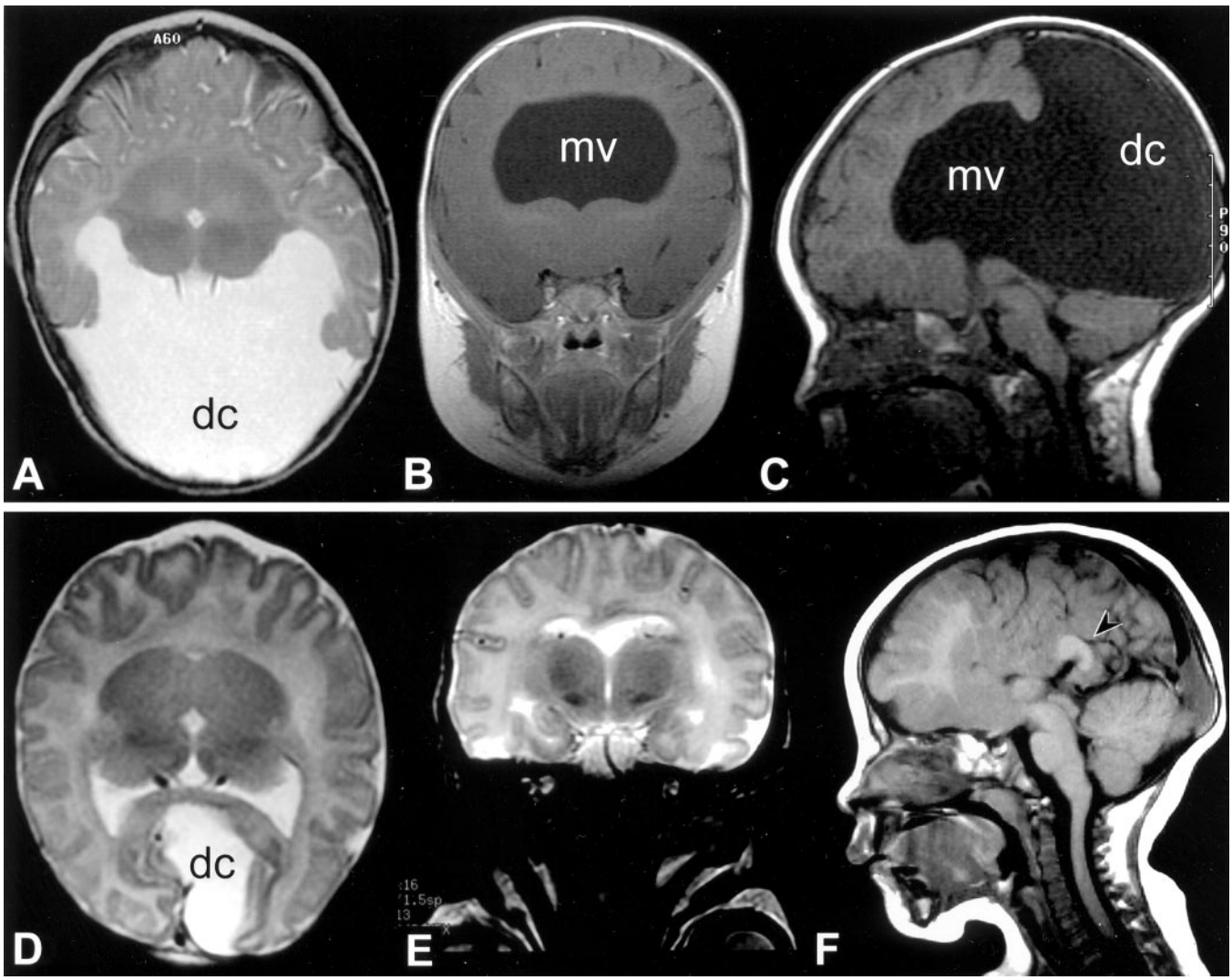

were present in eight of 12 patients with difficult-to-control seizures, but in only 11 of 44 without difficult-to-control seizures.

Endocrinopathies. Endocrinologic dysfunctions were classified into four categories of severity, as shown in table 1. Forty-nine of the 68 HPE patients (72%) had endocrine abnormalities. Of the 49 patients with endocrine abnormalities, 13 (26.5%) had mild abnormalities, 28 (57.1%) moderate, and eight (16.3%) had severe. All 49 had at least a sodium balance problem in the form of diabetes insipidus.

The severity of endocrine abnormalities correlated with the degree of hypothalamic nonseparation ($p = 0.029$, Spearman rank correlation) but not with the degree of pituitary abnormality ($p = 0.61$, Spearman rank correlation). The abnormality of the pituitary could not be assessed on neuroimaging studies in 13 of the cases.

Temperature dysregulation. Temperature dysregulation problems were compared to hypothalamic morphology. The severity of temperature dysregulation was classified into three categories: none, mild, and severe. Twenty-two of 68 (32%) had temperature regulation problems (16 mild and 6 severe). There was a correlation between the severity of temperature regulation problem and the degree of hypothalamic nonseparation ($p = 0.0013$, Spearman rank correlation).

Craniofacial malformations. Midline craniofacial malformations were classified into five categories as detailed in table 1, ranging from normal to very severe. Forty-six of 68 (68%) had at least some degree of midline craniofacial abnormality. Twenty-two patients (32.3%) had mild craniofacial malformations, nine (13.2%) moderate, 13 (19.1%) severe, and two (2.9%) very severe. There was a correlation between the severity of the midline craniofacial malformation and the severity of HPE ($p = 0.034$, Spearman rank correlation). However, a minority of the patients did not follow this trend. For example, three patients with alobar HPE had no craniofacial malformation, while two patients with lobar HPE had severe craniofacial malformations.

Cranial size and shunting. Forty-eight of the 68 patients (74%) had microcephaly. Table 3 shows the observed frequencies for microcephaly depending on the type of HPE. Microcephaly was present in a greater proportion of the patients with lobar HPE (83%) and semilobar HPE (81%) when compared with patients with alobar HPE (38%) ($p = 0.0062$, χ^2 test). This difference may be due to the fact that a greater proportion of patients with alobar

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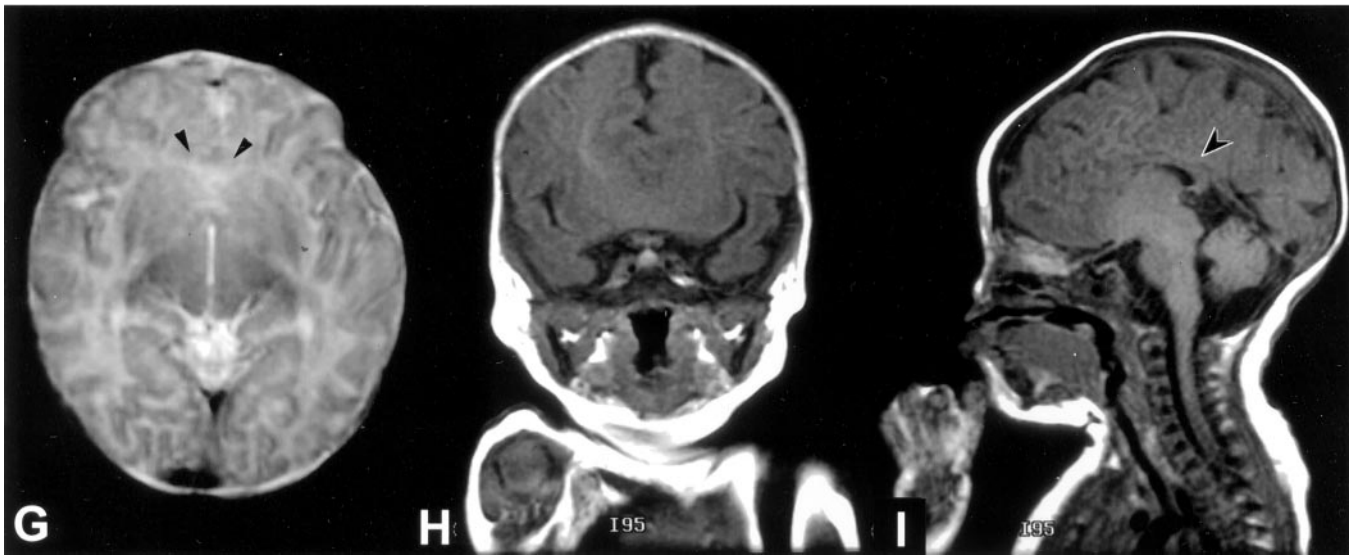

Figure 1. (A, B, and C) MRI of a patient with alobar holoprosencephaly (HPE). Axial T2-weighted image (A) demonstrates incomplete of separation of the two hemispheres, striatum, and thalami, and a large dorsal cyst (dc). Coronal T1-weighted image (B) shows a continuity of gray matter over the two hemispheres without an interhemispheric fissure. The ventricular system is composed of a single midline ventricle, monoventricle (mv). Sagittal T1-weighted image (C) shows absence of corpus callosum and a monoventricle that communicates freely with the dorsal cyst. (D, E, and F) MRI of two patients with semilobar HPE. Axial T2-weighted image (D) shows posterior portions of the hemispheres are well separated, but the anterior cerebral hemispheres are not cleaved. A dorsal cyst (dc) is present. The posterior horns of the lateral ventricles are well formed. The frontal horns are poorly developed (D) and posteriorly there is a monoventricle demonstrated on a coronal T2-weighted image (E, same patient as in D). A sagittal T1-weighted image of a different patient (F) demonstrates that the posterior portion of the corpus callosum is formed, butthe anterior portion is not developed (arrowhead). This finding is highly characteristic of semilobar or lobar HPE. (G, H, and I) MRI of a patient with lobar HPE. Axial T2-weighted image (G) shows that the cerebral hemispheres are fairly well separated both anteriorly and posteriorly. There is some development of the frontal horns (arrowheads). Coronal T1-weighted images (H) shows failure of complete cleavage of the frontal lobe. A sagittal T1-weighted image (I) demonstrates that the posterior portion of the corpus callosum (arrowhead) is formed but the anterior portion is not developed.

HPE required CSF shunting for hydrocephalus (62%) compared to patients with other types of HPE (7% in semilobar and 9% in lobar; $p < 0.0001$, χ^2 test).

The need for CSF shunting also correlated with the presence of a dorsal cyst (a midline structure that occupies the dorsocaudal aspect of the diencephalon). In the neuroimaging studies in which the presence of a dorsal cyst could be evaluated, nine of 23 (39%) patients with a dorsal cyst required shunting, whereas only two of 41 (5%) patients without a dorsal cyst required shunting. There was a higher incidence of dorsal cyst in patients with alobar HPE (11/12, 92%) compared with patients with semilobar HPE (12/43, 28%) and lobar HPE (1/11, 9%). The need for shunting paralleled this trend.

Motor abnormalities. Four motor variables were evaluated: spasticity, dystonia, hypotonia, and choreoathetosis. The classification of these variables is detailed in table 1. Because we were examining developmental and neurologic abnormalities that might not appear in young infants, we restricted the analysis in this part to those 46 patients who were 12 months of age or older.

The extent of nonseparation of the deep gray nuclei and the grade of HPE were correlated with the motor variables for statistical association using Spearman rank correlations. Table 5 shows the results of these analyses. Among the motor variables, only dystonia correlated with the degree of nonseparation of the caudate and lentiform nuclei, as well as the grade of HPE. Hypotonia correlated with grade of HPE but not with the grade of nonseparation of the deep gray nuclei. None of the other motor variables showed significant correlation with the degree of nonseparation of deep gray nuclei.

Developmental abnormalities. Three developmental variables were evaluated: mobility, upper extremity function, and language. The classification of these variables is detailed in table 1. Again, because we were assessing developmental outcomes, we restricted the analysis to those 46 patients who were 12 months of age or older. In general, the degree of the developmental disability paralleled the severity of HPE. Detailed figures of the developmental outcomes by HPE type are provided in the supplementary data on the *Neurology* Web site (go to www.neurology.org).

In terms of mobility, none of the patients with alobar HPE was able to sit independently. Patients with semilobar HPE had slightly better mobility, although the majority could not sit independently. Approximately half of the patients with lobar HPE were walking independently or with assistance.

Upper extremity function in patients with alobar HPE was very poor. At best, these patients were able to reach and bat at objects, but could not attain them. In contrast, normal upper extremity function or mild fine motor dysfunction was achieved by four of the 30 patients with semilobar HPE and half of the patients with lobar HPE.

Language development was also limited in patients with HPE. Patients with alobar HPE were only able to

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Table 1 *Grading scheme for variables*

Variable/score	Definition
Clinical	
Seizures	
0/1/2	None/Moderate Severe
Endocrinopathies	
0/1/2/3	None/Mild/Moderate/Severe
Temperature dysregulation	
0/1/2	None/Mild/Severe
Craniofacial malformation	
0/1/2/3/4	None/Mild/Moderate/Severe/Very severe
Sleep disorder	
0/1/2	None/Mild/Severe
Self-abuse	
0/1/2	None/Mild/Severe
Feeding/swallowing	
0/1/2	Normal/Mild/Severe
Developmental	
Mobility	
0	Walks independently
1	Walks with support
2	Stands independently
3	Crawls
4	Sits independently
5	None of the above
Upper extremity	
0	Normal for age
1	Mild fine motor difficulties
2	Able to reach and attain objects
3	Able to grossly reach or bat at objects
4	Able to hold objects when placed in hands
5	None of the above
Language	
0	Normal
1	Sentences (short)
2	Single words
3	Consonant sounds
4	Vowel sounds
Motor	
Spasticity	
0/1/2/3	None/Mild/Moderate/Severe
Dystonia	
0/1/2	None/Mild/Severe
Choreoathetosis	
0/1/2	None/Mild/Severe
Hypotonia	
0/1/2	None/Mild/Severe

More detailed definitions of clinical variables are provided in the supplementary data on the *Neurology* Web site (go to www.neurology.org).

vocalize vowel sounds. Again, the patients with milder HPE types achieved better language function. Two patients each from the semilobar and lobar HPE groups were able to speak multiword sentences or better.

These developmental variables highly correlated with the degree of nonseparation of the caudate nuclei, lentiform nuclei, thalami, as well as the grade of HPE (see table 5). This correlation was also seen with the swallowing/feeding variable. In general, there was a much higher statistical correlation between the grade of HPE and deep gray nuclei nonseparation and the developmental variables as compared to the motor variables.

Deep gray nuclei nonseparation and outcome. We performed statistical analyses of the composite scores on the 46 patients 12 months of age or older. Table 2 provides the formulas for the DGS, CMS, and CCSS.

For motor dysfunction, we examined the group differences of the CMS. There was a higher mean CMS in alobar (4.2) and semilobar (4.1) HPE when compared with lobar (1.8) HPE ($p = 0.037$ alobar vs lobar and $p = 0.001$ semilobar vs lobar; see table 3). There was no significant difference in the CMS between alobar and semilobar HPE groups.

For clinical problems and developmental disabilities, we examined the group differences for the CCSS. The mean CCSS was highest for alobar the HPE group (20.4), followed by semilobar (15.7), then lobar (9.9) (see table 3; $p = 0.0004$ alobar vs lobar, $p = 0.0016$ semilobar vs lobar, and $p = 0.041$ alobar vs semilobar).

We also performed simple linear regression analyses between the DGS and CMS and between the DGS and CCSS. There was a no significant correlation between the DGS and CMS (figure 2). However, there was a high correlation between the DGS and the CCSS ($p < 0.0001$; figure 3).

Figure 3 shows that there is a clustering of the alobar group in the high CCSS and the high DGS. Most in the lobar group cluster in the low DGS (with one exception, v.i.), although there is a wider variability in the CCSS. The semilobar group clusters broadly in between these two groups. The scattergram demonstrates that none of the alobar patients had a CCSS less than 18.

One exception to the clustering of types of HPE seen in figure 3 was the patient who was diagnosed with lobar HPE based on the presence of interhemispheric separation and ventricular morphology (figure 4). The brain was very complex, with infolding of dysplastic cortex in the right hemisphere. The degree of nonseparation of the deep gray nuclei was high in this case, resulting in a high DGS. Therefore, in this case, the high DGS would be expected to have a high CCSS (as was the case), but her category of HPE is lobar, which made the patient an "outlier."

Discussion. Advances in neuroimaging have provided a better understanding of the pathogenesis and variability of HPE. With detailed morphologic analyses of the neuroimaging features of HPE, we have been able to move beyond "the face predicts the brain" dictum forwarded by DeMyer et al.[2] Through a systematic analysis of the neuroimaging findings and neurodevelopmental problems in children with HPE, we have been able to provide a modern schema for a more precise prognostication on the nature and severity of neurodevelopmental disorders associated with HPE.

We found that, in general, the severity of developmental delay and motor abnormalities correlated with the grade of the HPE. The correlations of the motor and developmental variables to specific deep gray nuclei abnormalities were not as strong, although a few associations were found. The degree of nonseparation of the caudate and lentiform nuclei correlated with dystonia and feeding/swallowing problems, but not with spasticity, choreoathetosis, or

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Table 2 *Composite score definitions*

Composite score	Components	Maximum score
Deep Gray Score (DGS)	Caudate grade + lentiform grade + thalamic grade + hypothalamic grade	11
Composite Motor Score (CMS)	Spasticity grade + dystonia grade + choreoathetosis grade + hypotonia grade	9
Composite Clinical Severity Score (CCSS)	Seizure grade + endocrine grade + temperature dysregulation grade + sleep disorder grade + self-abuse grade + feeding/swallowing grade + mobility grade + upper extremity function grade + language grade	31

hypotonia. The lack of correlation of spasticity with the grades of deep gray nuclei nonseparation may be because these grades reflect the extent of lack of induction of the rostroventral midline structures. Motor pathways are more lateral and caudal in the developing brain and thus are relatively spared in HPE.[3]

There was a high degree of correlation between the nonseparation of deep gray nuclei (caudate, lentiform nuclei, and thalamus) and the developmental variables (mobility, upper extremity function, and language). Likewise, similar correlation was seen between the grade of HPE (which is based solely on the extent of hemispheric separation) and the developmental variables. This probably reflects the tight correlation found between the grade of HPE and grades of nonseparation of caudate, lentiform, and thalamic nuclei. This is not surprising given our current understanding of the pathogenesis of HPE, i.e., that the defects in ventral patterning involved in HPE affect not only the hemispheres but also the deep gray structures.

One of the goals of this study was to improve the classification system of HPE, one that would be more flexible and accurate in predicting outcome. Rather than using the three classic types of HPE, we incorporated other neuroanatomic features of HPE into the grading scheme. We found that the DGS, which takes into account the abnormalities in various deep gray nuclei, gave us a good correlation with the severity clinical problems and developmental outcomes (as reflected in the CCSS). Compared to the traditional classification of HPE, the DGS seemed to give a more precise prognostication about the clinical severity in some cases. For example, our study included a patient whose disorder would have been classified as lobar HPE (mildest form), but the patient was severely retarded and had intractable epilepsy as a result of an accompanying large cortical malformation (see figure 4). In this case, the DGS was a better indicator of the severity of brain malformation and thus, clinical dysfunction.

Other cliniconeuroanatomic correlations found in the study included seizure disorders, endocrinopathies, and the need for CSF shunting. These correlations provided some insights into the pathogenesis of these conditions.

Approximately half of our patients with HPE had at least one seizure. About half of these patients had difficult-to-control seizures. The presence of cortical malformations and alobar HPE were associated with

Table 3 *Frequency and percentage of clinical features by HPE type (total n = 68)*

Features	Alobar HPE, n = 13	Semilobar HPE, n = 43	Lobar HPE, n = 12
All patients			
Age, y, mean (median)	0.86 (0.72)	3.8 (3.9)	5.8 (6.3)
Age, y, range	0.1–2.6	0.1–13.9	0.8–19
Seizures, any, % (n/N)	54 (7/13)	43.5 (20/43)	50 (6/12)
Endocrine dysfunction, % (n/N)	84.6 (11/13)	74.4 (32/43)	50 (6/12)
Microcephaly, % (n/N)	38 (5/13)	81 (35/43)	83 (10/12)
Shunting, % (n/N)	62 (8/13)	7 (3/42)	9 (1/11)
Patients aged ≥12 mo, n	5	30	11
CMS, mean (SD)	4.2 (2.3)	4.1 (1.8)	1.8 (1.7)
CCSS, mean (SD)	20.4 (1.5)	15.7 (4.9)	9.9 (4.8)

HPE = holoprosencephaly; CMS = Composite Motor Score; CCSS = Composite Clinical Severity Score.

Table 4 *Seizure severity vs type of HPE*

Seizure category	Alobar HPE, n = 13	Semilobar HPE, n = 43	Lobar HPE, n = 12
All patients			
None	6 (46)	23 (53)	6 (50)
Moderate	1 (8)	11 (26)	4 (33)
Severe, difficult-to-control	6 (46)	9 (21)	2 (17)
Patients aged ≥12 mo	5	30	11
None	1 (20)	15 (50)	6 (55)
Moderate	0 (0)	11 (37)	4 (36)
Severe, difficult to control	4 (80)	4 (13)	1 (9)

Values are expressed as n or n (%).

HPE = holoprosencephaly.

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Table 5 *Correlation matrix for motor and developmental variables vs neuroimaging variables*

Clinical variables	Grade of HPE	Caudate	Lentiform nuclei	Thalamus
Spasticity	0.363	0.357	0.285	0.088
Dystonia	0.530†	0.431*	0.384*	0.255
Hypotonia	0.491*	0.246	0.188	0.237
Choreoathetosis	0.360	0.258	0.179	0.098
Mobility	0.619†	0.517†	0.493*	0.472*
Upper extremity function	0.559†	0.502†	0.494†	0.471†
Language	0.616‡	0.690‡	0.663‡	0.690‡
Feeding problems	0.645‡	0.574‡	0.557†	0.541†

Values represent rho (Spearman rank correlation coefficient).

* $p < 0.05$; † $p < 0.01$; ‡ $p < 0.001$.

HPE = holoprosencephaly.

difficult-to-control seizures. It is interesting to note that some patients with HPE have severe epilepsy, whereas others do not have a history of seizures. This variation may be due to a mediolateral gradient in cortical architecture abnormalities in HPE in which the medial parts of the forebrain are more disorganized than the lateral parts.[9] Some authors have postulated that the relative sparing of the lateral cortex may explain why some patients with HPE do not have seizures or severe mental retardation.[9] They also hypothesize that the variation in seizure severity may be due to the differences in sequential maturation of axonal terminals. This is quite a contrast to other malformations such as classic lissencephaly (a primary migrational defect involving entire cerebral cortex), in which epilepsy and severe mental retardation are universal.[10]

Endocrinologic dysfunctions were common in HPE and correlated with the degree of hypothalamic nonseparation. This is not surprising, as the hypothalamus is located very medial and rostral in the early fate maps and therefore is more frequently noncleaved than structures located further from the midline or more caudally. Defects in ventral patterning in HPE may cause hypothalamic dysfunction,[11] abnormalities in the hypothalamic–pituitary axis, or pituitary hypoplasia.[12-14]

Other reports have noted diabetes insipidus as a common problem in HPE.[14-18] Our study confirms previous findings of posterior pituitary dysfunctions being more common than anterior ones.[14] Because of the abnormal hypothalamic–infundibular region in HPE, diabetes insipidus could be caused by a defect in the supraoptic and paraventricular nuclei of the hypothalamus or in release of vasopressin via the infundibulum and posterior pituitary.[11] Some authors have postulated that this is due to abnormal hypothalamic osmoreceptors, as seemingly normal posterior pituitary was visualized with MRI.[16,17] Better imaging of the pituitary gland and hypothalamus with detailed, high-resolution MRI through the region may answer these questions.

Another hypothesis for the occurrence of diabetes insipidus in HPE is that the genes involved in the cerebral malformation of HPE have secondary genetic effects on the development of the hypothalamic neurons.[9] Recent evidence suggests that secondary downregulation of the *OTP* gene (or of its downstream genes) is important in the differentiation of magnocellular neurons of the supraoptic and paraventricular nuclei of the hypothalamus.[19] Therefore, failure of terminal differentiation of magnocellular neurons may cause a lack of vasopressin secretion.

Abnormalities of the pituitary gland did not correlate with endocrine problems. We believe this is may be because few of the neuroimaging studies included detailed images of the pituitary gland and therefore

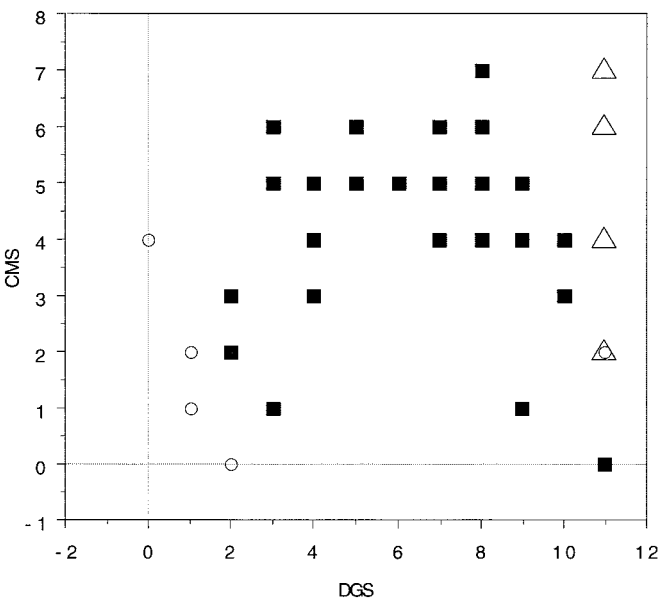

Figure 2. Composite Motor Score (CMS) vs Deep Gray Score (DGS) for patients 12 months of age or older by holoprosencephaly type. See table 2 for definitions of these composite scores. Circles = lobar; squares = semilobar; triangles = alobar.

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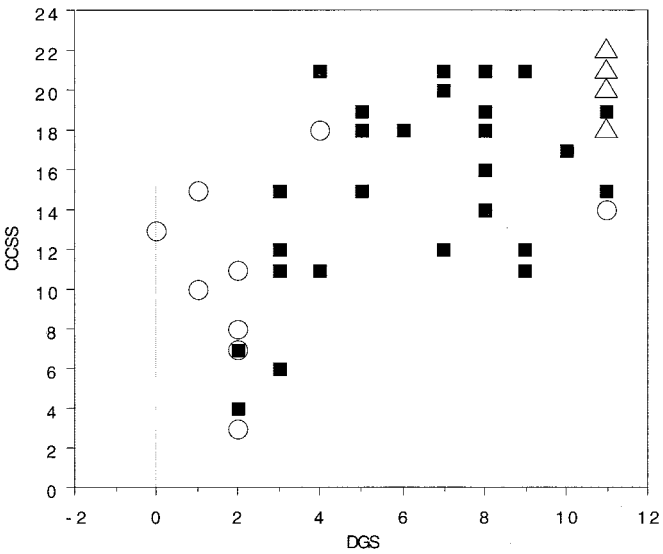

Figure 3. Composite Clinical Severity Score (CCSS) vs Deep Gray Score (DGS) for patients 12 months of age or older by holoprosencephaly type. See table 2 for definitions of these composite scores. Circles = lobar; squares = semilobar; triangles = alobar.

did not allow adequate assessment of the pituitary size or morphology. Alternatively, the primary endocrinologic defect in HPE may be in the hypothalamus, not the pituitary gland.

The head size in most patients with HPE is in the microcephalic range.[20] Exceptions occur when there is a large dorsal cyst or other forms of hydrocephalus. Previous studies indicated that hydrocephalus is nearly always present in HPE with a dorsal cyst.[20,21] Our study confirms that the presence of a dorsal cyst is a risk factor for requiring CSF shunting due to hydrocephalus. In our previous study the presence of a dorsal cyst correlated strongly with the presence of nonseparation of the thalamus.[4] We speculated that the unseparated thalamus physically blocks egress of CSF from the third ventricle, resulting in expansion of the posterodorsal portion of the ventricle to form the cyst. This blockage of CSF egress, possibly in conjunction with dysgenesis of the cerebral aqueduct, may then cause hydrocephalus.

The correlation of the severity of craniofacial abnormalities with the severity of the brain malformation in HPE led to the dictum: "the face predicts the brain."[2] Although this was generally true in our series, a minority of patients did not follow this rule. This is not surprising, as even in familial HPE with a single defined mutation in the *SHH* gene, the spectrum of clinical and neuroanatomic characteristics within one family is broad.[22] Furthermore, there are several gene mutations that have been found in HPE,[23] which may account for the dissociation of craniofacial and CNS malformations.

The proportion of patients with the various types of HPE in our series differs from what has been previously described in the literature. Epidemiologic studies reported that two-thirds of patients had alobar HPE, one-quarter had semilobar, and the remainder had the lobar form.[24,25] In our study, we had a greater proportion of less-severe HPE (nearly two-thirds had semilobar and one-fifth had lobar HPE). This is likely due to the selection bias of patients clinically evaluated at the Carter Centers. This difference has allowed us to provide a detailed picture of a large number of patients with semilobar and lobar HPE, in addition to alobar HPE.

Overall, the clinical characteristics of our patients with alobar HPE were comparable to those previously reported in the literature by Barr and Cohen.[8] Similar to their experience, we also found that patients with alobar HPE were severely affected and developed minimal motor and language skills. However, the outcomes and prognosis in patients with semilobar and lobar HPE were not as dismal and were much more variable. Some of these patients survived into the teenage years and were able to speak and function with mild cognitive impairment.

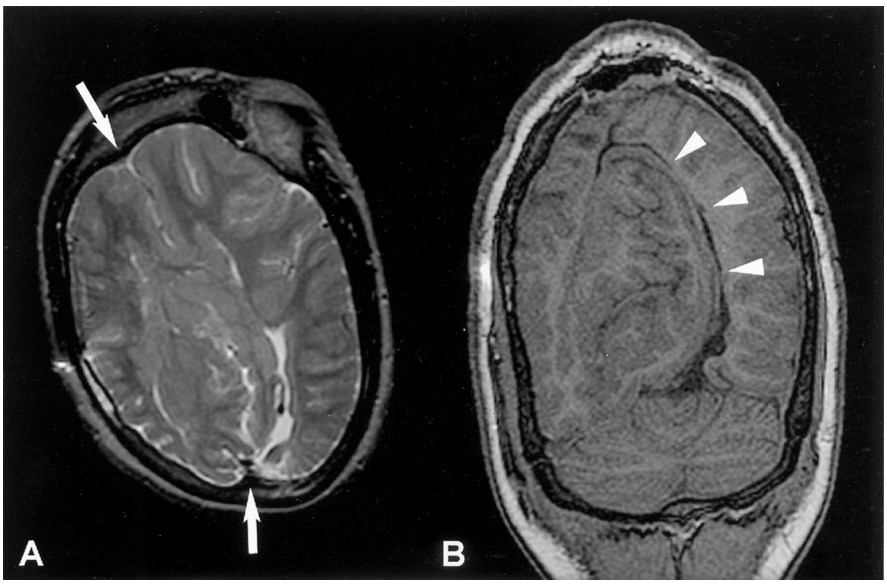

Figure 4. MRI of a patient with lobar holoprosencephaly (HPE). Axial T2-weighted image (A) shows the presence of a nearly complete interhemispheric fissure (arrows) and lateral ventricles. Therefore, this patient was classified as lobar HPE. Coronal three-dimensional spoiled gradient-recalled image (B) shows a large infolding of dysplastic cortex (arrowheads) in the right hemisphere. This patient was severely affected and had intractable epilepsy.

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This spectrum of outcomes in HPE is particularly important when counseling families.

There is a common misperception that children with HPE do not survive beyond infancy.[26] Although with some exceptions, severely affected infants may only live for hours, days, or months, many patients with milder forms of HPE will survive into childhood and beyond. Life span is generally shorter if there are chromosomal abnormalities. Of patients with HPE with known cytogenetic abnormalities, only 2% were alive at 1 year, compared with 30 to 54% without cytogenetic anomalies.[24,25] When counseling families of patients with isolated forms of HPE, it is important to recognize the relatively long survivals, particularly in milder forms.

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