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Electroencephalography in holoprosencephaly: findings in children without epilepsy

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Abstract

Objective: To evaluate the electroencephalographic characteristics of patients with holoprosencephaly (HPE) without epilepsy.

Methods: We evaluated the electroencephalograms (EEGs) of 18 children with HPE who lacked a history of seizures. Neuroimaging studies were assessed for severity of HPE and thalamic non-separation and the presence of dorsal cysts and cortical malformations.

Results: Hypersynchronous theta activity occurred in 50 and 60% of EEGs during wakefulness or drowsiness/sleep, respectively, and correlated with the grade of thalamic non-separation ($p < 0.05$). Hypersynchronous beta activity during sleep occurred in 41% of EEGs. Posterior amplitude attenuation occurred in 33% of EEGs and correlated with the presence of a dorsal cyst ($p \leq 0.0004$). Photic driving responses were seen in 50% of the EEGs. If a dorsal cyst was present, the responses were anteriorly displaced. Epileptiform activity was noted in EEGs of 5 patients and did not correlate with the incidence of clinical seizures.

Conclusions: Hypersynchronous activity was present frequently in EEGs of HPE patients, possibly attributable to incomplete separation of the thalami and hemispheres. Dorsal cysts were associated with posterior amplitude attenuation and anterior displacement of the photic response. In this selective cohort, the presence of epileptiform activity was not a risk factor for seizures.

Significance: To date, this is the largest study of EEGs in children diagnosed with HPE without seizures. This study complements our earlier clinical and neuroradiologic studies by providing neurophysiologic data that serves to enhance our understanding of this complex, rare disorder.

Keywords: Holoprosencephaly; Brain malformation; Electroencephalogram; Hypersynchrony

1. Introduction

Holoprosencephaly (HPE) is a complex developmental brain malformation in which the primary defect is the failure of the rostral neural tube to bifurcate into the two cerebral hemispheres. Based on the degree of hemispheric non-separation, HPE has traditionally been classified into 3 'classic' types: alobar, semilobar, and lobar (Fig. 1) (DeMyer et al., 1964). Classic HPE results from a primary defect in patterning of the basal forebrain during the first 4 weeks of embryogenesis (Golden, 1999). A fourth subtype, called the middle interhemispheric variant of HPE (MIH) or syntelencephaly, was first identified in 1993 (Barkovich and Quint, 1993). MIH consists of an abnormal midline continuity of the cerebral hemispheres in the posterior frontal and parietal regions, with separation of the basal forebrain, anterior frontal lobes, and occipital regions (Fig. 1) (Simon and Barkovich, 2001). The clinical characteristics of patients with classic HPE and MIH have recently been published (Lewis et al., 2002; Plawner et al., 2002).

As reported in a recent review, there have been few studies of electroencephalography in HPE (Clegg et al., 2002). Most of these studies have focused on children with the most severe form (alobar) of this malformation or those

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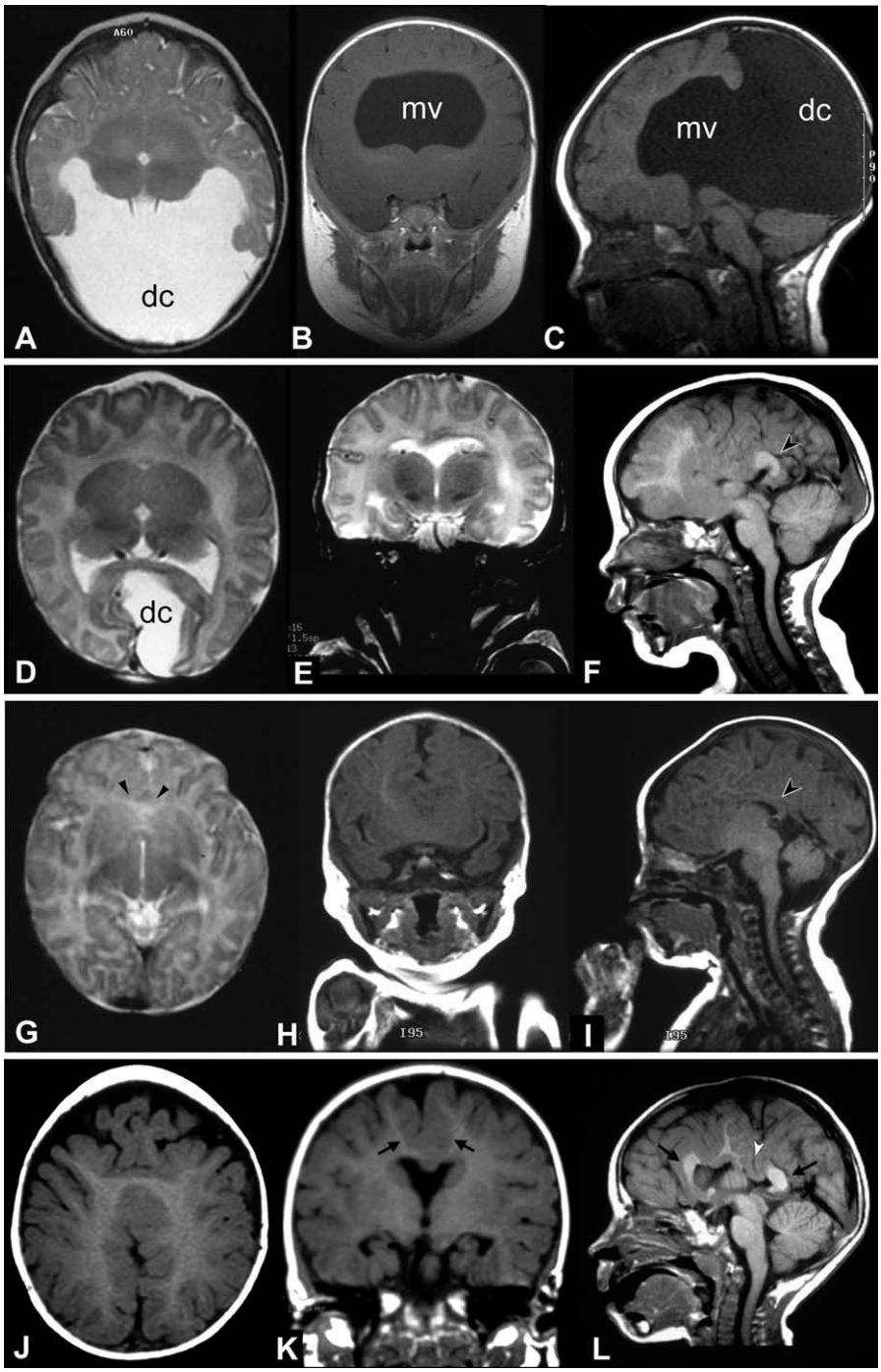

Fig. 1. MRI of a patient with alobar HPE (A–C). Axial T2-weighted image (A) demonstrates incomplete separation of the two hemispheres, basal ganglia, and thalami and a large dorsal cyst (dc). Coronal T1-weighted image (B) shows a continuity of gray matter over the two hemispheres without an interhemispheric fissure. A single midline ventricle, i.e. monoventricle (mv), is present. Sagittal T1-weighted image (C) shows absence of corpus callosum and a monoventricle that communicates freely with the dorsal cyst. MRI of two patients with semilobar HPE (D–F). Axial T2-weighted image (D) shows non-separation of anterior hemispheres, while the posterior hemispheres are well separated with development of posterior horns of the lateral ventricle. A small dorsal cyst is present (dc). The frontal horns are poorly developed (D) and posteriorly, there is a monoventricle demonstrated on a coronal T2-weighted image ((E), same patient as (D)). A sagittal T1-weighted image of another patient (F) demonstrates that the posterior corpus callosum is formed (arrowhead), but the anterior portion is not developed. MRI of a patient with lobar HPE (G–I). 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 image (H) shows incomplete separation of the frontal lobes. A sagittal T1-weighted image (I) demonstrates that the posterior corpus callosum is formed (arrowhead), but the anterior portion is not developed. MRI of two patients with MIH (J–L). Axial T1-weighted image (J) shows continuity of gray matter in the posterior frontal lobes across the midline. Coronal T1-weighted image ((K), same patient as (J)) through incompletely separated hemispheres at the level of the body of the lateral ventricle shows continuity of the gray matter (black arrows). In a different patient, sagittal T1-weighted image (L) through the midline shows the presence of genu and splenium of the corpus callosum (black arrows). The body of the corpus callosum is absent in the region of non-separated hemispheres (white arrowhead) (Parts A–I adapted from Plawner et al., 2002 and Parts J–L from Lewis et al., 2002; used with permission).

with epilepsy (DeMyer and White, 1964; Habedank and Thomas, 1970; Watanabe et al., 1976). Little is known about the electroencephalograms (EEGs) of HPE patients without epilepsy.

In the present study, we explore the electroencephalographic characteristics of a cohort of HPE patients evaluated through a nationwide clinical research consortium. The primary goal of this study was to identify characteristic electroencephalographic patterns in patients with HPE without seizures. The secondary goal was to determine if there were any findings on pre-seizure EEGs that might suggest an increased risk for seizures.

2. Methods

2.1. Patient selection

Eighteen children diagnosed with HPE without a previous history of seizures were prospectively enrolled between 1998 and 2002. This represented 17% of patients diagnosed with HPE enrolled at the Carter Centers (a national consortium funded by a non-profit private foundation). Inclusion criteria of the study were the diagnosis of HPE confirmed by review of imaging studies, neurological evaluation at one of the Centers, and an EEG prior to any seizures. Exclusion criteria included prior history of seizures or epilepsy. Each Institutional Review Board approved the study prior to initiation. Informed consent was obtained from the parents prior to enrollment.

2.2. Neuroimaging assessment

Neuroimaging studies of patients were evaluated by two pediatric neuroradiologists who were unaware of the clinical status. Available imaging included MRI or high-quality CT. When CTs were used, we required a slice thickness of ≤ 5 mm and adequate image quality to allow assessment of key structures (basal ganglia, thalami, and interhemispheric fissure). The grade of HPE (alobar, semilobar, lobar, and MIH in order of severity) was determined by previously published criteria (DeMyer et al., 1964; Barkovich, 2000; Simon and Barkovich, 2001; Simon et al., 2002). The degree of non-separation of the thalamic nuclei was graded (none, mild, moderate, or complete) using previously published criteria (Simon et al., 2000). The presence or absence of cortical malformation and dorsal cyst were also determined.

2.3. Clinical assessment and scoring

All 18 patients whose scans were scored as described above received complete evaluations at one of the centers. The evaluations included a review of past medical history with particular attention to seizure histories and treatments.

2.4. Electroencephalographs

EEGs were performed using a 24-channel digital recording technique. The international 10–20 system was used for electrode placements. For newborns or young infants, a modified reduced-array of electrodes was utilized. Most of the EEGs were performed without sedation. Chloral hydrate was used in 3 EEGs. Benzodiazepines were not used for sedation. The EEGs were independently assessed by two separate teams of pediatric electroencephalographers (J.S.H. and D.M.O. from Stanford University and M.R.D. and S.P.S. from Texas Scottish Rite Hospital). They were masked with respect to the clinical history and neuroimaging details at the time of EEG review. EEGs were reviewed with attention to specific patterns occurring in various states and the data were collected on a standardized data collection form. If there were disagreements in the interpretation of a pattern, a consensus was reached after discussions between the two teams. We initially examined patterns during wakefulness, drowsiness, and sleep. To simplify data analysis, drowsiness and sleep states were combined into a single state.

3. Results

There were a total of 18 patients enrolled in the study. There were 4 with alobar type, 10 with semilobar, two with lobar, and two with MIH. Craniofacial malformations were present in 13 patients. These include 10 patients with mild malformations (e.g. mild hypotelorism, single central maxillary incisor), one with moderate malformations (e.g. moderate hypotelorism, midface hypoplasia), and two with severe malformations (e.g. premaxillary agenesis, flat nose, and median cleft). The frequency and severity of the malformations were distributed fairly evenly among the different subtypes of HPE. None had very severe malformations such as cyclopia, ethmocephaly, or cebocephaly. Chromosomal analysis was normal in all patients. The severity of clinical problems and neurodevelopmental function of these patients were measured by using the composite clinical severity score (CCSS) described in our previous study (Plawner et al., 2002). This score is the sum of the grades of several variables including seizures, endocrinopathies, temperature dysregulation, sleep disorders, self-abusive behavior, feeding problems, mobility, upper extremity function, and language. CCSS correlates with the severity of the neuroimaging abnormality (Plawner et al., 2002). For the present study, 3 patients had CCSS in the mild range, 10 in moderate range, and 5 in severe range. The distribution of the CCSS was similar to our previous studies which included a total of 83 patients (Lewis et al., 2002; Plawner et al., 2002).

Twenty EEGs were performed in the 18 patients (two patients had two EEGs each). Eleven EEGs were performed at Stanford University, 8 at Texas Scottish Rite Hospital,

and one at University of California, San Francisco. The mean age at the time of EEG was 35.6 months (range 12 days–17.5 years). This mean age was 14.7 months for the alobar group, 30.1 months for semilobar, 11.6 months for lobar, and 141.8 months for MIH. The mean duration of clinical follow-up after the initial EEG was 18.9 months. The EEG findings on 18 patients with HPE are described below.

3.1. Posterior dominant rhythm

A waking posterior dominant rhythm (PDR) was present in 11 of the 18 (61%) EEGs (Table 1). The frequency of this rhythm ranged from 4 to 6 Hz in alobar, 4 to 7 Hz in semilobar, 7 to 8 Hz in lobar, and 12 to 14 Hz in MIH (Table 1). The two alobar patients, ages 14 and 40 months, had a PDR of 4 and 6 Hz, respectively. The PDR frequency was considered slow for their age. The rhythm was also anteriorly displaced or asymmetric, most likely due to the presence of a dorsal cyst. In the 7 semilobar patients exhibiting a PDR (age range 11 months–10 years), the PDR was fragmentary and the frequency was slow for their age. The PDR was symmetric in all but one patient. For the two patients with less severe forms of HPE (19-month-old with lobar HPE and 17-year-old with MIH), the PDR was normal in frequency and topography (Table 1).

3.2. Hypersynchronous theta activity

The most common EEG characteristic was hypersynchronous theta activity (Fig. 2). This is a high-amplitude, monorhythmic (sinusoidal) theta activity that usually ranged 4–6 Hz in frequency. This activity was seen in 9/18 (50%) of EEGs during wakefulness and 12/20 (60%) of EEGs during drowsiness/sleep (Table 1). In some patients, this activity was nearly continuous in the drowsiness/sleep state. This pattern differed from normal hypnagogic hypersynchrony in that it was present during both wakefulness and drowsiness and had longer duration. There was a correlation between the presence of hypersynchronous theta activity during wakefulness and the grade of HPE ($p = 0.039$, Mann–Whitney U test), i.e. this activity was more likely to be present in the more severe types of HPE. There was also a correlation between the grade of thalamic non-separation and the presence of hypersynchronous theta activity during wakefulness ($p = 0.027$, Mann–Whitney U test) and drowsiness/sleep ($p = 0.0499$, Mann–Whitney U test).

3.3. Normal sleep patterns

Sleep spindles were present in 8/17 (47%) of EEGs (Table 1). The spindles ranged from 12 to 14 Hz in frequency and were located in the frontocentral regions. The durations were approximately 1–3 s. Vertex waves were seen in 8/17 (47%) of the EEGs. We did not include 3 EEGs that showed only drowsiness.

3.4. Hypersynchronous beta activity

Hypersynchronous beta activity was present in 7/17 (41%) of sleep recordings (Table 1). Fig. 3 shows an example of this activity. This activity was intermittent and generalized with frequencies of 12–25 Hz, amplitudes of 30–180 μV, and durations of 2–22 s. This pattern resembled sleep spindles, but was generally higher in frequency, longer in duration, and more diffusely distributed.

Table 1
EEG patterns in holoprosencephaly by type of HPE

	Alobar	Semilobar	Lobar	MIH	**Total**
Posterior dominant rhythm					
Present	2/5	7/10	1/2	1/1	11/18 (61%)
Range (Hz)	4–6	4–7	7–8	12–14	4–14
Hypersynchronous theta					
Wakefulness	4/5	5/10	0/2	0/1	9/18 (50%)
Drowsiness/sleep	3/5	8/11	1/2	0/2	12/20 (60%)
Sleep spindles[a]	0/4	5/10	2/2	1/1	8/17 (47%)
Vertex waves (sleep)[a]	2/4	4/10	1/2	1/1	8/17 (47%)
Hypersynchronous beta (sleep)[a]	0/4	6/10	0/2	1/1	7/17 (41%)
Hypersynchronous delta					
Drowsiness/sleep	2/5	3/11	0/2	0/2	5/20 (25%)
Episodic attenuation					
Wakefulness	1/5	4/10	0/2	0/1	5/18 (28%)
Drowsiness/sleep	1/5	4/11	0/2	0/2	5/20 (25%)
Posterior attenuation					
Wakefulness	5/5	1[b]/10	0/2	0/1	6/18 (33%)
Drowsiness/sleep	5/5	1[b]/11	0/2	0/2	6/20 (30%)
Epileptiform activity	3/5	2/11	0/2	0/2	5/20 (25%)

[a] Only 17 EEGs showed sleep activity, other than drowsiness.
[b] Unilateral posterior attenuation.

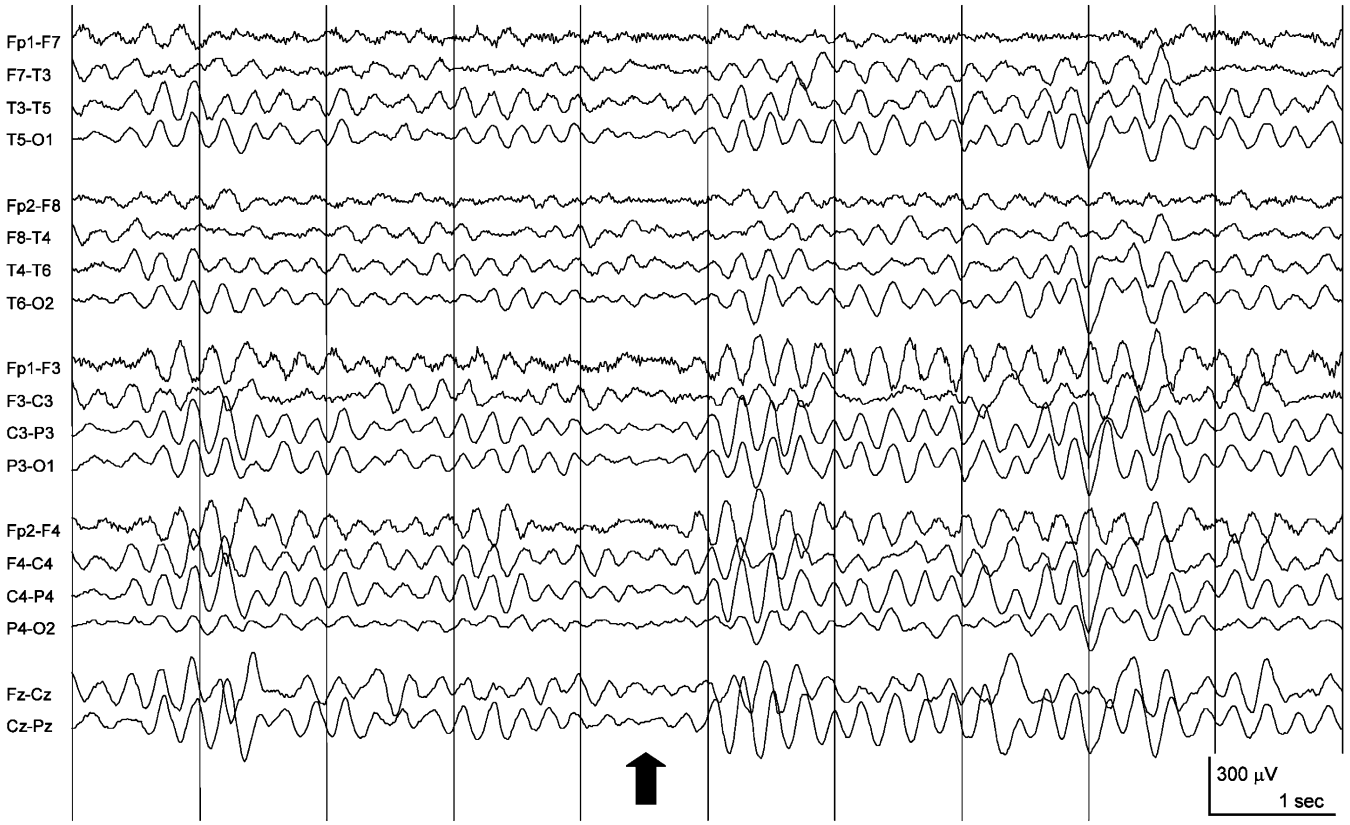

Fig. 2. Hypersynchronous theta activity (4.5 Hz, 100–300 μV) during drowsiness seen in an EEG of a 15-month-old girl with semilobar HPE. A brief episode of attenuation is present during this epoch (arrow).

3.5. Hypersynchronous delta activity

Hypersynchronous delta activity was noted in 5/20 (25%) of EEGs during drowsiness/sleep (Table 1). This activity was high-amplitude, generalized, and monorhythmic with a frequency of 2–3.5 Hz. It often evolved from hypersynchronous theta activity seen during drowsiness/sleep. This activity was not noted during wakefulness.

3.6. Episodic attenuation

Episodic attenuation of cerebral activity was also seen in 5 EEGs, both during wakefulness and drowsiness/sleep (Table 1). This consisted of sudden attenuation of background amplitudes lasting 1–30 s, with the intervals being composed of low amplitude theta activity (Fig. 2). These episodes occurred during both states, but were generally longer in duration during drowsiness/sleep state.

3.7. Posterior amplitude attenuation and dorsal cyst

Bilateral amplitude attenuation in the posterior head regions was present in 5 EEGs during wakefulness and drowsiness/sleep (Fig. 4), all in patients with alobar HPE. In one EEG (of a semilobar HPE patient), the attenuation was present unilaterally in the posterior head region. The presence of posterior attenuation correlated with the presence of a dorsal cyst ($p = 0.0004$ during wakefulness and $p = 0.0002$ during drowsiness/sleep, Fisher exact test). All the patients, whose EEGs displayed posterior attenuation, had a dorsal cyst (5 alobar and one semilobar) (Table 2). In contrast, none of the cases without a dorsal cyst had posterior amplitude attenuation.

3.8. Photic driving responses

Driving responses to intermittent photic stimulation were present in 8/16 (50%) of the EEGs. Photic stimulation was omitted in 4 EEGs. Photic responses occurred in 1/4 alobar, 4/8 semilobar, 2/2 lobar, and 1/2 MIH patients. In 4 patients, the responses were considered normal in amplitude and topography. Two EEGs contained photic driving responses that were anteriorly displaced toward the central–parietal regions (Fig. 5). Both these patients had a dorsal cyst. Two other EEGs displayed asymmetric photic driving responses. None showed epileptiform activity induced by photic stimulation.

3.9. Epileptiform activity and cortical malformations

Epileptiform activity was present in 5 patients. The epileptiform activity included sharp waves and sharp-

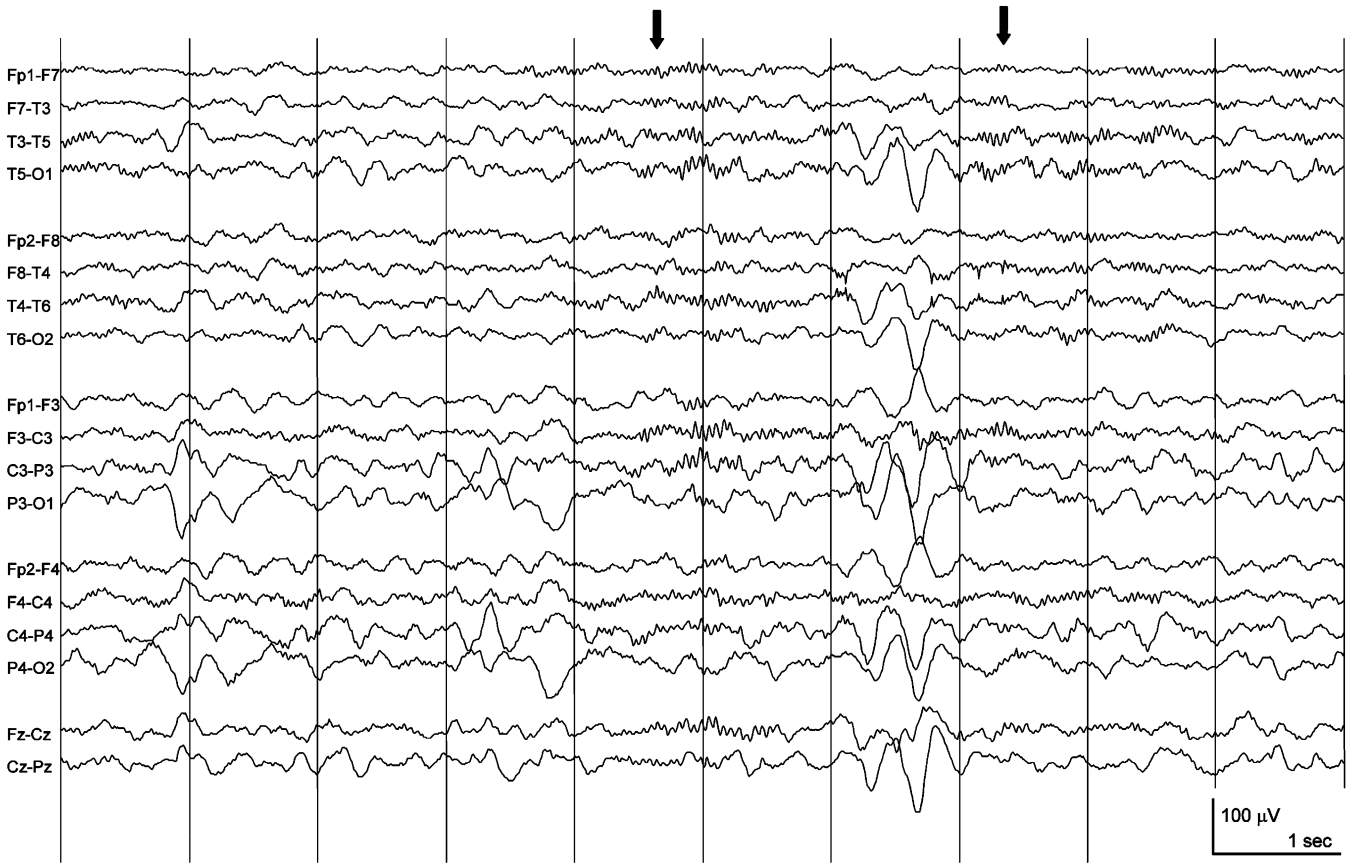

Fig. 3. Hypersynchronous beta during sleep (arrows) in a 4-year-old boy with semilobar HPE.

and-slow wave discharges. The localization was focal in 3 EEGs and multifocal in two EEGs. None of the EEGs performed for the study showed hypsarrhythmia. There was no correlation between presence of severe cortical malformations and epileptiform activity. However, there was a correlation between the presence of epileptiform activity and grade of HPE ($p = 0.038$, Mann–Whitney U test, see Table 1).

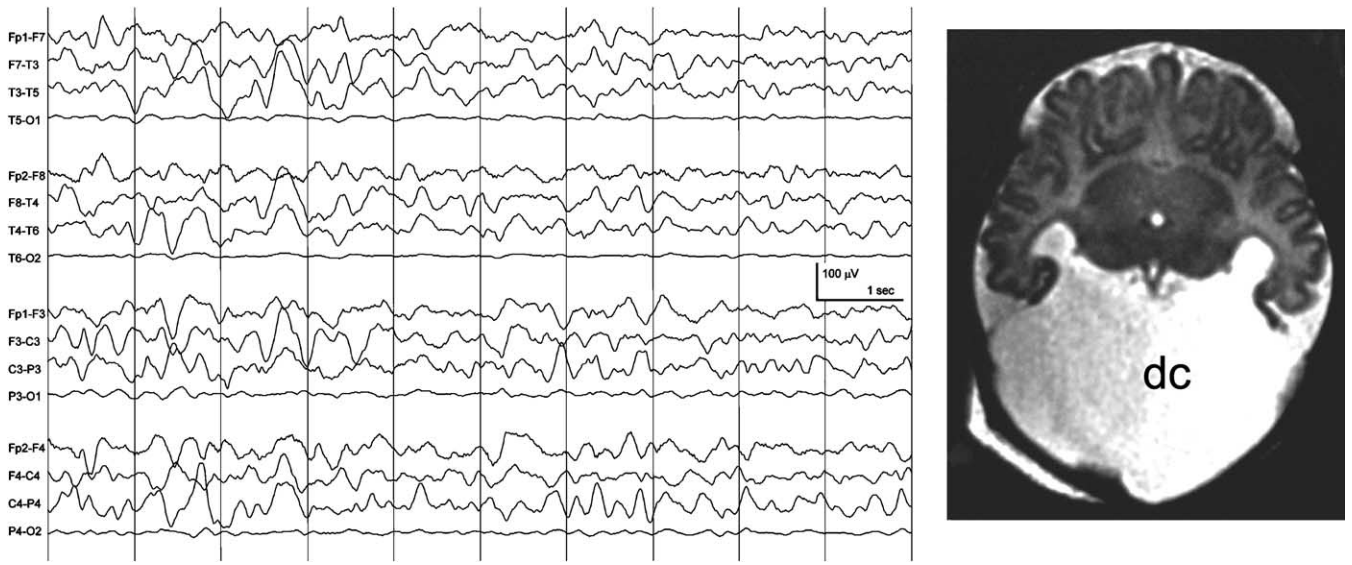

Fig. 4. EEG (left) shows amplitude attenuation in the parietal, posterior temporal, and occipital regions during sleep in a 4-month-old female with alobar HPE and a large dorsal cyst. Her T2-weighted axial MRI (right) at the level of basal ganglia shows completely non-separated hemispheres consistent with alobar HPE. A large dorsal cyst is present posteriorly (dc).

Table 2
Posterior amplitude attenuation and dorsal cyst

	Dorsal cyst	
	Present	Absent
Posterior attenuation (wakefulness)		
Present	6	0
Absent	1	11
Posterior attenuation (drowsiness/sleep)		
Present	6	0
Absent	1	13

3.10. Epileptiform activity and seizures

Only 3 of 18 (17%) patients developed seizures during the follow-up period (mean duration 18.9 months). One patient with semilobar HPE had a single seizure at 3 years of age during a febrile illness. The pre-seizure EEG did not show epileptiform activity. The post-seizure EEG revealed midfrontal epileptiform activity. However, the patient has not had another seizure during a 5 year follow-up period.

Another patient with alobar HPE had a single seizure at 16 months of age associated with hyponatremia. There were no recurrences during a 14 month period of follow-up. Her EEG, performed before the seizure, showed occasional focal sharp wave activity.

A third patient, a three and half-year-old with lobar HPE, developed infantile spasms at 14 months of age and was

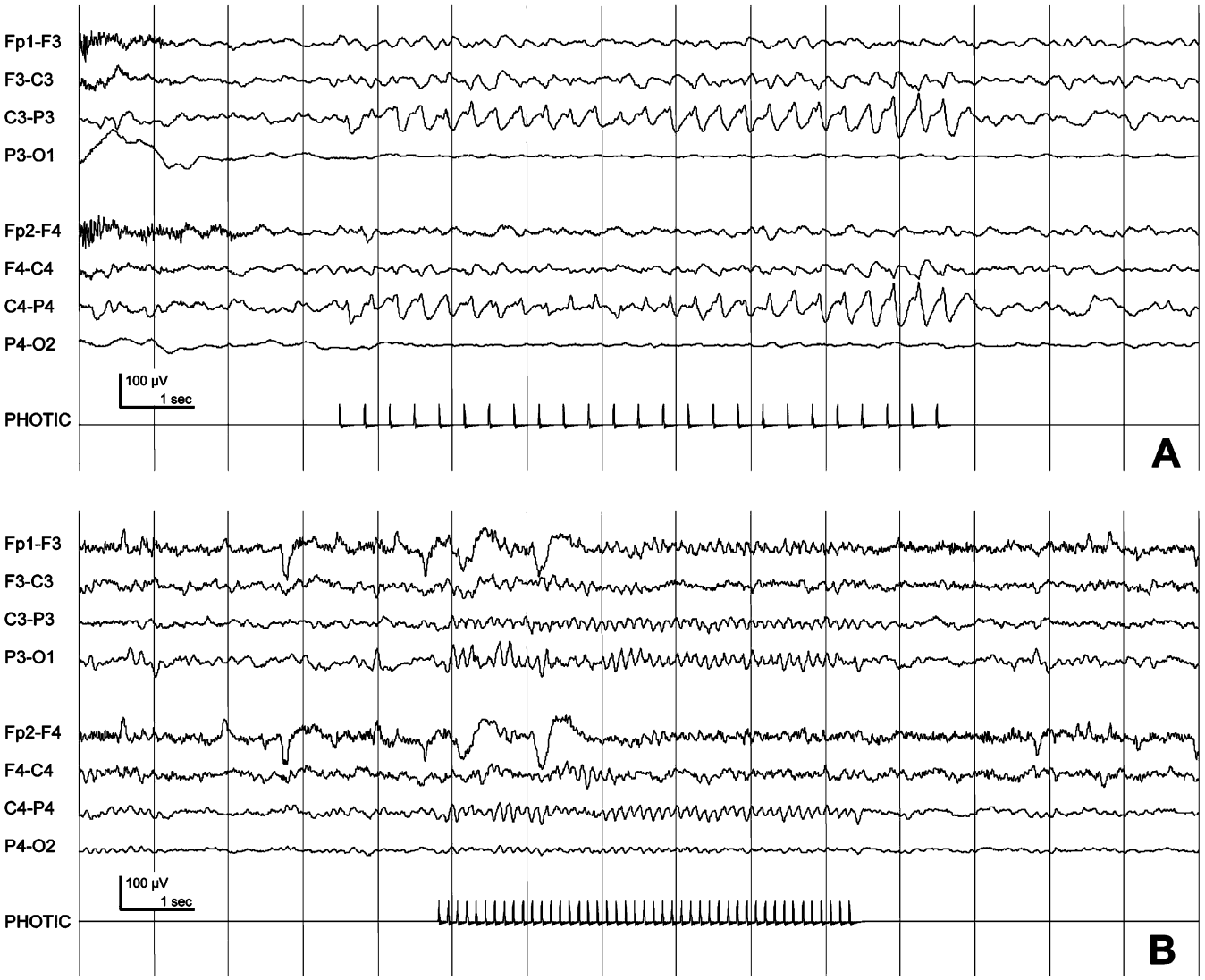

Fig. 5. (A) EEG during intermittent photic stimulation (3 flashes per second) shows photic driving response located maximally in the centro-parietal region in a 4-month-old female with alobar HPE (same patient as in Fig. 4). This patient has a large dorsal cyst. (B) EEG during photic stimulation (8 flashes per second) shows an asymmetric driving response in the posterior head region. The driving response is more anteriorly displaced in the right hemisphere. This patient had semilobar HPE with a dorsal cyst.

Table 3
Epileptiform activity in initial EEG and development of seizures

	Seizures		
	Present	Absent	Total
Epileptiform activity			
Present	1	3	4
Absent	2	12	14
Total	3	15	18

The p value is non-significant (Fisher exact test).

treated with ACTH. Spasms recurred at 20 months of age and were treated with topiramate. The EEG at 4 months of age did not show epileptiform activity. EEGs done at a local hospital revealed hypsarrhythmia at 14 months of age and generalized sharp-and-slow waves at 20 months. We were not able to review these EEGs. The patient has been seizure-free on topiramate since 22 months of age.

Table 3 shows the relationship between the presence of epileptiform activity on the initial EEG (before any seizures, if any) and the development of seizures. Three additional patients had epileptiform activity on their EEG but did not develop seizures during the follow-up period. In this small group of patients, there was a lack of correlation between the presence of epileptiform activity and development of seizures (Fisher exact test).

4. Discussion

HPE is a congenital malformation of the central nervous system in which there is a failure of the rostral neural tube to bifurcate into the two hemispheres. This results in incomplete cleavage of the cerebral hemispheres and deep brain structures. There is a spectrum in the severity of these malformations. Given the abnormal development of the cerebral hemispheres and the deep gray nuclei, including the thalami, we would expect to find electroencephalographic abnormalities.

There have been several previous reports of EEGs in HPE patients (DeMyer and White, 1964; Habedank and Thomas, 1970; Watanabe et al., 1976; Clegg et al., 2002). Most of these have focused on patients with epilepsy. We studied a cohort of HPE patients who did not have a history of seizures at the time of enrollment. In this select population, we found many typical EEG patterns. For example, a PDR was present in 61% of the EEGs (although often slow in frequency). Sleep spindles and vertex waves were present in approximately half of the EEGs.

The key abnormal electroencephalographic findings in our cohort included hypersynchronous theta and beta activities, episodic attenuation, and posterior attenuation. The most common abnormal pattern was the presence of 'hypersynchronous theta' activity during wakefulness and drowsiness/sleep. This pattern differs from hypnagogic hypersynchrony seen in normal children during drowsiness, by its predominance as the main background pattern. Hypersynchronous slow rhythmic activity has been reported previously in patients with HPE (Habedank and Thomas, 1970; Watanabe et al., 1976; Veneselli et al., 1999). Watanabe et al. (1976) conducted serial EEGs on 3 semilobar HPE patients. The interictal background showed abundant high amplitude rhythmic alpha–theta activities. This pattern gradually disappeared with increasing age, being replaced by non-specific irregular slow waves. Habedank and Thomas (1970) noted an accelerated frontal activity and 'hypersynchronous discharges' in 3 children (two semilobar HPE and one lobar HPE). However, because the descriptions of the EEGs were brief and no EEG figures were provided, it is difficult to compare with the present study.

We also noted 'hypersynchronous beta' activity during sleep in many EEGs. This pattern may be related to normal sleep spindles since they were noted during sleep. However, the topographic distribution was more widespread and durations were longer than typical spindles.

We hypothesize that these hypersynchronous activities may be due to the non-separations of the thalamic nuclei and cerebral hemispheres in HPE. This is supported by our findings that hypersynchronous theta activity (awake) correlated with the grades of HPE (which represents hemispheric non-separation) and thalamic non-separation. The EEGs displaying hypersynchronous theta activity were associated with more severe HPE with a higher degree of thalamic non-separation.

Previous studies have described 'paroxysmal hypersynchrony' that appears to be evolving ictal patterns (DeMyer and White, 1964; Watanabe et al., 1976). DeMyer and White (1964) reported a study of EEGs in 10 children (mostly infants) with autopsy-confirmed HPE (8 alobar and two lobar). All the patients in their cohort had mixed seizures. They also reported what they described as 'paroxysmal hypersynchrony' which consisted of patterns beginning with low-amplitude fast (beta) activity and evolved to generalized rhythmic high-amplitude 1 Hz slow waves. Based on the figures in the study, these could well represent electroencephalographic seizure activity. This type of pattern was not noted in our patients. Similarly, Watanabe et al. (1976) described ictal EEG rhythms as rapid synchronous fast activity (alpha–theta) followed by slowing to 1–2 Hz. The patients in these two studies are not comparable with ours since they all had frequent seizures, whereas we selected a population that initially did not have a history of seizures. We did not find any ictal patterns similar to those described in these two studies.

We found a correlation between 'posterior amplitude attenuation' and the presence of a dorsal cyst. All patients with bilateral posterior attenuation had alobar HPE and a large dorsal cyst. This is not surprising since dorsal cysts are more commonly found in alobar HPE, and when found, the cysts are likely to be large (Plawner et al., 2002). With regard to the topographic distribution of EEG activity,

DeMyer and White (1964) also found a correlation between patients with alobar HPE and posterior dorsal cysts. In these cases, there was a posterior attenuation, corresponding to the large dorsal cyst where there was no functional cortex. However, if the holotelencephalic structures were retroverted (i.e. displaced posteriorly), the distribution and amplitude of EEG activity did not necessarily correlate with the location of the holotelencephalon. Habedank and Thomas (1970) also found posterior attenuation of EEG amplitudes in two semilobar HPE patients with dorsal cysts.

In a larger population of HPE patients with epilepsy, we have observed that many patients with a dorsal cyst do not demonstrate a posterior attenuation (unpublished observation). There are many factors that might be responsible for this. When patients with dorsal cysts undergo ventriculoperitoneal shunting, the dorsal cysts often collapse. Moreover, posterior attenuation may be limited to HPE patients with a relatively large dorsal cyst. Our routine EEG techniques may not be sensitive enough to detect the attenuation if the dorsal cyst is relatively small.

Watanabe et al. (1976) did not find posterior amplitude attenuation in their 3 patients with semilobar HPE. There are several possible explanations. First of all, their patients did not have alobar HPE, which is usually associated with large dorsal cysts. Their neuroradiologic studies were limited to pneumoencephalograms and cerebral angiography. A description of dorsal cysts is mentioned in only one of 3 patients. Secondly, they frequently used a reduced array of electrodes (typical neonatal montage) in a bipolar montage that may have obscured posterior amplitude attenuation. Finally, volume conduction from remote generators could make it possible to detect electroencephalographic activity overlying fluid-filled cysts. In patients with brain malformations such as HPE, it is important to use a full-array of electrodes whenever possible and analyze the EEG in referential and bipolar montages (Iinuma et al., 1989).

In a study by DeMyer and White (1964), none of the 8 patients with alobar HPE had a 'photic driving response'. They noted that these patients had what appeared to be an intact calcarine cortex and hypothesized that the abnormality may be in the geniculocalcarine pathways. Watanabe et al. (1976) were able to find visually evoked potentials in 3 of their semilobar HPE patients. Our study differs in that we found photic driving responses in all types of HPE. We also found that our alobar HPE patients tended to lack photic driving responses, although the case depicted in Fig. 5A is a notable exception. Interestingly, two of the patients with a dorsal cyst had anteriorly displaced photic responses (in the central–parietal regions). This is most likely due to anterior displacement of the visual cortex caused by the dorsal cyst formation.

We did not detect a correlation between presence of 'epileptiform activity' and the development of seizures. However, we do not claim that epileptiform activity is not predictive of seizures in HPE. Our study was limited by the small sample size, which most likely lacked the statistical power to detect a correlation. In addition, the relatively short follow-up period in this study may also underestimate the number that would eventually develop seizures. Further studies with more patients and longer follow-up periods are needed. Such studies are currently being performed at the Carter Centers.

It is interesting that a small number of HPE patients without seizures exhibited epileptiform patterns on EEG (Table 3). Despite the complex hemispheric abnormalities seen in HPE, the majority of our patients with HPE and no history of seizures lack epileptiform activity. Our previous studies showed that less than half of HPE patients had seizures and only a quarter had difficult-to-control seizures (Lewis et al., 2002; Plawner et al., 2002). Conversely, more than half of the patients will not have seizures and can be expected to have the type of EEG patterns found in this study.

There was a wide variability in the proportions of EEGs that contained various EEG patterns for each type of HPE (Table 1). The EEGs of children with more severe forms of HPE (alobar and semilobar) were more likely to exhibit posterior amplitude attenuation, episodic attenuations, and hypersynchronous theta and delta activities. Conversely, the EEGs of children with less severe forms of HPE (lobar and MIH) tended to exhibit sleep spindles more frequently. Although there was a sense that the EEGs in less severe forms of HPE were more likely to exhibit fewer abnormalities, the small numbers in these groups made it difficult to find statistical correlations. A larger EEG study evaluating a wider range of patients in HPE is presently underway and may provide better statistical power to detect these associations.

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References

Barkovich AJ. Congenital malformations of the brain and skull. Pediatric neuroimaging. Philadelphia, PA: Lippincott Williams and Wilkins; 2000. p. 251–382.

Barkovich AJ, Quint DJ. Middle interhemispheric fusion: an unusual variant of holoprosencephaly. AJNR Am J Neuroradiol 1993;14: 431–40.

Clegg NJ, Gerace KL, Sparagana SP, Hahn JS, Delgado MR. Holoprosencephaly: a review. Am J Electroneurodiagnostic Technol 2002; 42:59–72.

DeMyer W, White PT. EEG in holoprosencephaly (arhinencephaly). Arch Neurol 1964;11:507–20.

DeMyer W, Zeman W, Palmer CG. The face predicts the brain: diagnostic significance of median facial anomalies for holoprosencephaly (arhinencephaly). Pediatrics 1964;34:256–63.

Golden JA. Towards a greater understanding of the pathogenesis of holoprosencephaly. Brain Dev 1999;21:513–21.

Habedank M, Thomas E. Clinical and neuropathological investigations of four cases of holoprosencephaly with arhinencephaly. Neuropädiatrie 1970;2:144–63.

Iinuma K, Handa I, Kojima A, Hayamizu S, Karahashi M. Hydranencephaly and maximal hydrocephalus: usefulness of electrophysiological studies for their differentiation. J Child Neurol 1989;4:114–7.

Lewis AJ, Simon EM, Barkovich AJ, Clegg NJ, Delgado MR, Levey E, et al. Middle interhemispheric variant of holoprosencephaly: a distinct cliniconeuroradiologic subtype. Neurology 2002;59:1860–5.

Plawner LL, Delgado MR, Miller VS, Levey EB, Kinsman SL, Barkovich AJ, et al. Neuroanatomy of holoprosencephaly as predictor of function: beyond the face predicting the brain. Neurology 2002;59:1058–66.

Simon EM, Barkovich AJ. Holoprosencephaly: new concepts. Magn Reson Imaging Clin N Am 2001;9:149–64.

Simon EM, Hevner R, Pinter JD, Clegg NJ, Miller VS, Kinsman SL, et al. Assessment of the deep gray nuclei in holoprosencephaly. AJNR Am J Neuroradiol 2000;21:1955–61.

Simon EM, Hevner RF, Pinter JD, Clegg NJ, Delgado M, Kinsman SL, et al. The middle interhemispheric variant of holoprosencephaly. AJNR Am J Neuroradiol 2002;23:151–5.

Veneselli E, Biancheri R, Di Rocco M, Fondelli MP, Perrone MV, Donati PT. Unusually prolonged survival and childhood-onset epilepsy in a case of alobar holoprosencephaly. Childs Nerv Syst 1999;15:274–7.

Watanabe K, Hara K, Iwase K. The evolution of neurophysiological features in holoprosencephaly. Neuropädiatrie 1976;7:19–41.