The roles of electroencephalography and neuroimaging in children with holoprosencephaly

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ABSTRACT – We analyze the respective roles of neuro-imaging and EEG in the assessment of 11 children with holoprosencephaly and epilepsy. Seizures were present in seven patients (64%); six were treated with antiepileptic drugs; five had intractable epilepsy. Two of the patients with intractable epilepsy became seizure-free under polytherapy. Fourteen EEG recordings were performed in eight patients. The abnormal EEG findings included slow waves, focal epileptiform discharges, slow spike-and-wave complexes, hypsarrhythmia, frontal fast activity, fronto-occipital gradients of amplitudes (posterior amplitude attenuation), lack of photic driving, periodic discharges, and extremely large amplitudes. A fronto-occipital gradient was found only in alobar and semilobar holoprosencephaly (HPE), while hypsarrhythmia only in lobar HPE. Lack of photic driving was found only in alobar HPE. All EEGs showed diffuse slow waves, and all patients had severe developmental delay. The Deep Gray Score (DGS) in neuroimaging studies, thought to predict clinical outcome, was irrelevant given the presence and intractability of the epilepsies. Patients with higher DGS, nonetheless, tended to have higher mortality rate. In conclusion, EEG evaluation provides additional functional information to neuroimaging studies in the assessment of neurological outcome in patients with HPE. With a more mature and well-formed cerebrum, as found in the lobar and semilobar types, the possibility of hypsarrhythmia and photic driving increased, while that of fronto-occipital gradients decreased.

KEY WORDS: holoprosencephaly, semilobar HPE, alobar HPE, epilepsy, hypsarrhythmia, EEG.

Holoprosencephaly (HPE) results from the failure of the embryonic forebrain, the prosencephalon, to separate into symmetric cerebral hemispheres during the first four weeks of embryogenesis [1, 2]. The deformities of HPE are categorized into three major types in order of decreasing severity: alobar, semilobar, and lobar [3]. The patients with HPE usually present with delayed development, spastic quadriplegia, failure to thrive and seizures [2]. However, the neurodevelopmental outcome cannot always be predicted ac-
accurately on the basis of DeMyer’s classification (lobar, semilobar, and alobar) [4]. The often-cited rule of “face predicts the brain” was found to be true in approximately 80% of cases [5]. Recently, the deep gray score (DGS), which measures the degree of involvement of the basal ganglia and thalami (see Methods section for details), was reported to correlate better with clinical performance and outcome [6].

The EEG, as a method of functional evaluation, has been found to be valuable in evaluating patients with CNS malformations [7, 8]. The peculiar EEG patterns in cortical dysplastic lesions, including type 1 lissencephaly and hemimegalencephaly, are of unusually high amplitude (150-3,000 µV) background activity and unusual alpha activity at 15-25 Hz, more or less continuous or in bursts [8]. In most patients, these unusual patterns are age-dependent. However, there are few EEG studies in children with HPE, and their relationship with the neurological outcome is rarely reported [9-13]. Therefore, in the present study, we analyzed the EEGs and neuroimaging, including DGS, in children with HPE in order to examine their value as predictors of the development and outcome of epilepsy.

Methods

We reviewed the medical records of all children diagnosed with HPE between 1993 and 2002 at three major medical centers in Taiwan. The functional status of each patient was updated by direct inquiry, either by interview or by phone. There were eleven patients with HPE enrolled in total. Their clinical manifestations, seizure pattern, EEG findings, neuroimaging studies, associated chromosome abnormalities and long-term prognosis were analyzed.

The epilepsies were classified according to the revised classification of epilepsies and epilepsy syndromes (ILAE, 1989) [14]. Fourteen EEGs were performed in eight patients (patients 1 to 8). Follow-up EEGs were available for three patients (patients 1, 2 and 6). All EEGs were reviewed by two child neurologists. Each record lasted at least 30-40 minutes. Each patient was exposed to photic stimulation of a 5-20 Hz flash. Special attention was given to high-amplitude (more than 50 µV) fast activities and fronto-occipital gradients. Fronto-occipital gradient (or ‘posterior amplitude attenuation’ ording some [15]) is defined as decreasing amplitudes of EEG tracing from the fronto-temporal leads to the occipital leads, instead of the occipital predominance observed in the normal population.

All patients, except patient 3, had an MRI, coupled or not with a CT scan examination. Patient 3 received only CT. The Deep Gray Score (DGS) was assessed by a neuroradiologist on the basis of CT and MRI findings, including the noncleavage of caudate nuclei, lentiform nuclei, thalami and hypothalamus and the spatial orientation of the thalami, according to the rating scale of Simon EM et al. [16]. The caudate nuclei, lentiform nuclei and thalami were graded on a scale of 0 to 3, with 0 = complete separation, 1 = less than 50% noncleavage or abnormal medial location, 2 = 50% to 99% noncleavage, and 3 = complete noncleavage. The degree of hypothalamic noncleavage was assessed using a scale of 0 to 2, with 0 = complete separation, 1 = partial (anterior) noncleavage, and 2 = complete noncleavage. The DGS score consisted of the sum of the grades of caudate nuclei, lentiform nuclei, thalami and hypothalami, with a maximum score of 11 [6]. The higher DGS indicated more severe noncleavage of forebrain.

Results

Among the eleven patients with HPE (table 1), four were female and seven were male. Ages at the last follow-up were from ten days (Patient 11), when she expired, to seven years. HPE was diagnosed by brain imaging studies taken from prenatally to 22 months old. Three patients had lobar HPE; four semilobar HPE; four alobar HPE (figure 1). Patients 7 and 8 were siblings, and patient 3 had a younger brother, who was terminated prenatally as the result of a malformation.

Seizures were noted in seven patients (patients 1-7), including three with a lobar type HPE, two with a semilobar type and two with an alobar type. The ages at seizure onset ranged from one day to two years of age. Patients 4 and 5, alobar type HPE, tended to have earlier seizure onset than the other patients. Of the seven patients who experienced seizures, six (patients 1-6) had epilepsy and were treated with antiepileptic drugs. The types of seizures in these six patients were: infantile spasms in two; neonatal seizures in two; generalized seizures in one; both generalized and partial seizures in one. The remaining patient, patient 7, had only one episode of generalized tonic-clonic seizures secondary to central diabetes insipidus with hypernatremia. Only one of the six patients with epilepsy, patient 3, had an easy-to-control seizure and was free of seizures under monotherapy with phenobarbital; the other five patients had intractable epilepsies. The risk of intractability was not related to HPE types, DGS, or age of seizure onset. Patients with earlier onset of seizures however, tended to have intractable epilepsy. Two of the five patients with intractable epilepsy (patients 1 and 6) became seizure free-under polytherapy. The remaining three patients still suffer from intractable epilepsies.

Fourteen EEG studies were performed in eight patients (tables 1 and 2). The characteristic EEG findings included slow background activity in all (8 patients), frontal fast activity in 5 out of 8 (figure 2), focal epileptiform discharges in 4 out of 8, modified hypersrrhythmia in two
Table 1. Clinical presentations in children with HPE.

<table>
<thead>
<tr>
<th>No.</th>
<th>Sex</th>
<th>Age*</th>
<th>HPE type</th>
<th>DGS Presentation</th>
<th>Seizure onset</th>
<th>Epilepsy type</th>
<th>EEG findings</th>
<th>Chromosome</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
<td>#</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>M</td>
<td>6y9m</td>
<td>Lobar</td>
<td>Dyssymorphism</td>
<td>2m</td>
<td>Infantile spasms</td>
<td>+ + + + +</td>
<td>18p deletion</td>
<td>Bed-ridden Intractable then seizure-free with polytherapy</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>2y3m</td>
<td>Lobar, ACC</td>
<td>Dyssymorphism</td>
<td>2m</td>
<td>Infantile spasms</td>
<td>+ + + + +</td>
<td>N</td>
<td>Bed-ridden Intractable seizures</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>6y10m</td>
<td>Semilobar, meningocele</td>
<td>Meningocele (on scalp)</td>
<td>2y9m</td>
<td>Generalized seizures</td>
<td>+ + + + +</td>
<td>N</td>
<td>Bed-ridden Seizure-free with monotherapy</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>4m</td>
<td>Alobar (with dorsal cyst)</td>
<td>Prenatal echography</td>
<td>1d</td>
<td>Neonatal seizures</td>
<td>+ + + + +</td>
<td>N</td>
<td>Bed-ridden Intractable seizures</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>1y7m</td>
<td>Alobar</td>
<td>Seizures</td>
<td>3m</td>
<td>Neonatal seizures</td>
<td>+ + + + +</td>
<td>N</td>
<td>Expired Intractable seizures</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>7y7m</td>
<td>Lobar</td>
<td>Spastic posture Developmental delay</td>
<td>1y10m</td>
<td>Partial and generalized seizures</td>
<td>+ + + + +</td>
<td>N</td>
<td>Expired Intractable then seizure-free with polytherapy</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>2y4m</td>
<td>Semilobar</td>
<td>Seizures</td>
<td>3m</td>
<td>+ + + + + + + +</td>
<td>+ + + + + + +</td>
<td>N</td>
<td>Bed-ridden Seizure-free after control of DI</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>1m</td>
<td>Alobar (with dorsal cyst)</td>
<td>Congenital hydrocephalus</td>
<td>+</td>
<td>+ + + +</td>
<td>+ + + + + +</td>
<td>N</td>
<td>Expired</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>6y3m</td>
<td>Semilobar</td>
<td>Micropenis</td>
<td>+</td>
<td>+ + + + + + +</td>
<td>+ + + + + +</td>
<td>N</td>
<td>Bed-ridden No seizure</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>7m</td>
<td>Semilobar, ACC</td>
<td>Imperforate anus</td>
<td>+</td>
<td>+ + + + + + +</td>
<td>+ + + + + +</td>
<td>N</td>
<td>Loss follow-up No seizure</td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>10d</td>
<td>Alobar (with dorsal cyst)</td>
<td>Dyssymorphism</td>
<td>+</td>
<td>+ + + + + + +</td>
<td>+ + + + + +</td>
<td>18p deletion</td>
<td>Expired</td>
</tr>
</tbody>
</table>

ACC = agenesis of corpus callosum; AED = anti-epileptic drug; DGS = deep gray score (see methods for score evaluation); DI = diabetes insipidus; FFA = frontal fast activity; FOG = fronto-occipital gradient; FS = focal spikes; GTC = generalized tonic-clonic seizure; H = hypsarrhythmia; N = normal; PD = photic driving; SL = slow waves/ slow background activities; SSW = slow-spike-and-wave complexes. [U1] *Age: at the day of the last follow-up interview, phone, chart records. # Other EEG findings: In patient 4: periodic discharges, lack of normal organization, and in patient 6: extremely high amplitude.
(figure 2), slow spike-and-wave complexes in one (figure 3), periodic discharges and lack of normal organization in one, and extremely large amplitude in one (figure 3). Hypsarrhythmia was noted in two patients with lobar HPE. A fronto-occipital gradient of EEG amplitude was found in two patients with alobar HPE and one with semilobar HPE. Photic stimulation to 5-20 cps flickering lights revealed fundamental driving in all patients with lobar and semilobar HPE, apart from two patients with alobar HPE, aged four days and six months respectively.

Concerning age-dependent EEG manifestations (figure 4), slow background activity, focal epileptiform discharges, and frontal fast activity were noted in all kinds of HPE patients from birth to six years old. Hypsarrhythmia, noted only in patients with lobar type HPE, appeared before two years old. Conversely, slow spike-and-wave complexes appeared after two years old in patient 3 (semilobar type) and patient 6 (lobar type). A fronto-occipital gradient of EEG amplitude and lack of photic driving, mostly in patients with alobar HPE, were noted before one year old.

Follow-up EEGs were performed in patients 1, 2 and 6 with lobar HPE. Evolutionary changes were noted in patients 1 and 2, who initially had hypsarrhythmia. Patient 1 presented with infantile spasms and hypsarrhythmia at two months of age. Following adrenocorticotropic hormone therapy, the EEG at seven months showed diffuse slow waves and the pattern of hypsarrhythmia disappeared. Frontal fast activities and focal spikes on the EEG were noted at five months. Hypsarrhythmia developed. Vigabatrin was given initially but changed for topiramate at nine months because of lack of efficacy. At that time the EEG showed only mild frontal fast activities and diffused slow waves. The EEG at one and a
half years old evolved to slow waves with multifocal spikes, when the seizure pattern was mainly focal seizures with eye blinking. EEGs of patient 6 showed no apparent changes.

Only seven neuroimaging investigations were available for DGS grading (Table 1). Two out of three patients who had a DGS greater than seven expired, and the remaining one is currently four months old [U2], with marked hypotonia and developmental delay. Three out of four patients with DGS less than seven lived up to six years old; all had developmental delay and were bed-ridden.

For the 11 patients we imposed a follow-up from ten days to seven years. Four died between the age of ten days and seven years. One patient was lost to follow-up. Among the six remaining patients (two with a lobar type, three with a semilobar type, and one with alobar type), motor development was severely delayed in all. A high or low DG score made no difference.

Chromosome studies (karyotyping) were performed in all patients. Two were found to have an 18p deletion.

### Discussion

Plawner et al. [6] reported that about half (49%) of the patients with HPE have at least one seizure and about half (52%) of them have difficult-to-control seizures. In the present study, 3 patients (43%), among the seven with seizures, had intractable seizures. As previously reported, our study showed that the severity of the cortical malformation did not correlate with the presence or absence of seizures [6]. Nonetheless, in alobar HPE (as in our patients 4 and 5), epilepsy was an early and severe manifestation, while patients with semilobar and lobar HPE usually had a later onset of seizures. However, late onset of seizures has also been reported in children with alobar HPE [17, 18]. The causes of epilepsy in HPE may be related to the cortical abnormalities [19-21]. The variations in seizure severity may be due to a mediolateral gradient in cortical abnormalities, sparing the lateral cortex relatively [6]. This is in contrast with other brain malformations, such as classic lissencephaly.

Some characteristic EEG findings in patients with HPE, related to their underlying embryogenic abnormalities,
have been reported in the literature. The characteristic EEG abnormalities in alobar HPE include random or repetitive intermixed spikes and slow waves, periodic discharges, and isoelectric or relatively flat leads, reflecting the poor organization of cerebral cortex in HPE [10]. It was suggested that because of the poor connections between

Figure 3. The EEG of patient 6 at two years four months old shows intermittent, high-voltage generalized spike-slow wave complexes during sleep. The EEG at six years old shows more frequent high-voltage generalized spike-slow wave complexes. In addition, frontal fast activities and central alpha rhythm are noted.

Figure 4. Age distribution of abnormal EEG findings in HPE patients. Although there was slow background activity, focal epileptiform discharges, and frontal fast activity were noted all ages, hypsarrhythmia, fronto-occipital gradient of EEG amplitudes and lack of photic driving were noted below two years old. Slow spike-and-wave complexes appeared after two years old. FFA: frontal fast activity; FOG: fronto-occipital gradient; FS: focal spikes; H: hypsarrhythmia; PD-: lack of photic driving; SL: slow waves/ slow background activities; SSW: slow-spike-and-wave complexes.
the bilateral cortices and poor connections between the cortex and the subcortical structures, the seizures in patients with alobar HPE may also present with a Jacksonian-type propagation without secondary generalization [22]. In the present study, however, diffuse slow waves on the EEG were found in all patients with HPE, while hypersynchrony and focal epileptiform discharges were also occasionally found. Our data suggest that the abnormalities in HPE are not just the result of non-separation of the midline structures, but also of the presence of cortical dysplasia.

Other characteristic EEG changes in HPE are frontal fast activities and fronto-occipital gradients of EEG amplitudes (posterior amplitude attenuation). Frontal fast activities and fronto-occipital gradients may be related to the sequence of embryogenesis, caudal to rostral and dorsal to ventral. Because the frontal forebrain is the last to be formed and is most commonly involved, fast activity is more apparent over the frontal areas. Frontal fast activity was noted in five of our patients (two in the lobar type, one in the semilobar and two in the alobar type), including two during the neonatal period. The peculiar EEG for neonates with semilobar HPE consisted of high-amplitude rhythmic fast activity, which was continuous during wakefulness and became discontinuous during sleep [13], and a fronto-occipital gradient. In comparison, continuous high-voltage (more than 50 µV) rhythmic fast activities in other cortical dysplasias, such as type I lissencephaly, are seldom observed in the neonatal period [8, 23], do not show asynchronous discontinuity in sleep and have no anterior-posterior voltage gradient. Frontal fast activity beyond the neonatal period appeared intermittently.

Fronto-occipital gradients or posterior amplitude attenuation were noted in alobar HPE [10], as was the case for our patients 4 and 8, and was correlated with the presence of a dorsal cyst [15]. However, patient 7, with semilobar HPE not associated with a dorsal cyst, also showed a fronto-occipital gradient. In our patients, a fronto-occipital gradient of EEG amplitudes was noted only in alobar or semilobar HPE, indicating that the more mature the brain, the less the fronto-occipital gradient or the less high-amplitude frontal activities.

In our study, only patients 1 and 2 with lobar type HPE showed evolutionary EEG changes. They both presented with infantile spasms, but only patient 2 suffered from difficult-to-control seizures. In Watanabe’s series, only one of the three patients with semilobar HPE presented with a generalized seizure during the neonatal period, evolving to a West syndrome and later a Lennox-Gastaut syndrome [24]. The age of onset of infantile spasms in our patients was earlier than what had been previously reported in Taiwan [25]. Furthermore, other studies [12, 13] showed that the hypersynchrony on the EEG usually develops in a more mature brain, such as lobar or semilobar HPE, and disappears after the age of one year. In our study, only patients with lobar HPE had hypersynchrony, showing alobar HPE no hypersynchrony. Furthermore, evolutionary EEG changes in the present study were only found in more mature type HPE and correlated with the maturation of brain, a finding compatible with previous studies [12, 13, 26].

DGS was suggested to have a better correlation with the severity of clinical problems and developmental outcomes in patients with HPE, compared to the simpler classification by DeMyer [6]. In the present study, DGS was not closely related to the developmental outcome of the patients: motor development of all patients, whether their DGSs were high or low, was less than three months. The DGS, nonetheless, correlated with the severity of the brain malformation, and a higher DGS may indicate earlier mortality in patients with HPE (table 1). In addition, although DGS may be useful for the prediction of clinical performance and outcome, in the present study neither the DeMyer’s classification nor the DGS could be used to predict the occurrence and severity of seizures (table 1). Conversely, abnormal non-epileptiform EEGs, such as triphasic waves or focal polymorphic delta activities, may be helpful in determining the severity and, hence, the prognosis of cerebral dysfunction [27]. As shown in the present study, despite their DGS, all our patients with developmental delay had diffuse delta activities. It indicated that the severity of non-separation of deep gray nuclei cannot be used as the only factor for predicting neurological outcome in patients with HPE. Functional investigations such as EEG may be of some help.

**Conclusion**

Characteristic EEG findings, including a fronto-occipital gradient, frontal fast activities and lack of photic driving, could be found in patients with HPE and were related to the severity of the brain malformation. With a more mature and well-formed cerebrum, as found in the lobar and semilobar type, the possibility of hypersynchrony and photic driving increases, while that of a fronto-occipital gradient decreases. EEG evaluation gives additional functional information to neuroimaging studies in the assessment of neurological outcome in patients with HPE.

**References**


