

Paradoxical ictal EEG lateralization in children with unilateral encephaloclastic lesions

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Received February 21, 2009; Accepted July 8, 2009

ABSTRACT – Background. Describe an ictal EEG pattern of paradoxical lateralization in children with unilateral encephaloclastic hemispheric lesion acquired early in life. **Methods.** Of 68 children who underwent hemispherectomy during 2003-2005, scalp video-EEG and brain MRI of six children with an ictal scalp EEG pattern discordant to the clinical and imaging data were re-analyzed. Medical charts were reviewed for clinical findings and seizure outcome. **Results.** Age of seizure onset was 1 day-4 years. The destructive MRI lesion was an ischemic stroke in 2, a post-infectious encephalomalacia in 2, and a perinatal trauma and hemiconvulsive-hemiplegic syndrome in one patient each. Ictal EEG pattern was characterized by prominent ictal rhythms with either 3-7 Hz spike and wave complexes or beta frequency sharp waves (paroxysmal fast) over the unaffected (contralesional) hemisphere. Scalp video-EEG was discordant, however, other findings of motor deficits (hemiparesis; five severe, one mild), seizure semiology (4/6), interictal EEG abnormalities (3/6), and unilateral burden of MRI lesion guided the decision for hemispherectomy. After 12-39 months of post-surgery follow up, five of six patients were seizure free and one has brief staring spells. **Conclusion.** We describe a paradoxical lateralization of the EEG to the “good” hemisphere in children with unihemispheric encephaloclastic lesions. This EEG pattern is compatible with seizure free outcome after surgery, provided other clinical findings and tests are concordant with origin from the abnormal hemisphere.

Key words: epilepsy surgery, EEG, pediatric epilepsy, video-EEG in epilepsy

Unilateral hemispheric destructive lesions in children, such as perinatal or postnatal stroke, and post-infectious, iatrogenic or post-traumatic encephalomalacia, are commonly associated with infantile hemiparesis, epilepsy, mental retardation, impaired vision and hearing, language delay, and behavioral problems

(Uvebrant, 1988). Up to 32% of such children with epilepsy develop intractable seizures (Gaggero *et al.*, 2001), and surgical treatment is often considered (Carreno *et al.*, 2002). However, in addition to the predominant brain MRI finding of encephalomalacia involving one hemisphere, multi-regional bilateral or diffuse brain

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injury are possible due to the type of underlying etiologies. Scalp ictal EEG recording is one of the most useful tool for selecting children who are likely to benefit from surgery (Iida et al., 2005). Concordant lateralization of a seizure on ictal scalp EEG to the side of the encephaloclastic brain MRI lesion is usually considered to be a reliable predictor of seizure freedom after surgery (Kossoff et al., 2003; Tinuper et al., 1988). However, diffuse interictal abnormalities and ictal EEG patterns have been described in patients with infantile hemiplegia due to extensive hemispheric lesions (Tinuper et al., 1988) complicating their evaluation. Recently, ictal EEG paradoxical lateralization (contralateral) on scalp recordings has also been reported in three patients with mesial temporal lobe epilepsy due to gliotic lesions (Sammaritano et al., 1987) acquired early in life leading to more invasive evaluation before the surgery. In this case series, we report a distinctive ictal EEG pattern with paradoxical lateralization (contralateral to the MRI lesion) in six children who had unilateral hemispheric destructive lesions. The ictal EEG “paradoxically” lateralized to the “good” (contralateral) hemisphere despite correct lateralization of ictal semiology on video-EEG (4 of 6 children) and of other clinical exam findings concordant to the side of the encephaloclastic MRI lesion.

Methods

Of 68 children who underwent hemispherectomy at the Epilepsy Center, Cleveland Clinic Foundation during 2003-2005, six children (4 females) had intractable epilepsy due to unilateral hemispheric destructive lesions with ictal scalp EEG recordings showing paradoxical lateralization (ictal EEG onset contralateral to the brain MRI lesion or a generalized ictal EEG pattern with maximum amplitude contralateral to the brain MRI lesion). However, the children were operated based on their concordant clinical history, neurological deficits, interictal EEG (3/6), brain MRI and FDG-PET findings, all pointing to the correct side for hemispherectomy. All children underwent pre-surgical evaluation and were operated at the Cleveland Clinic Foundation. Medical charts of these patients were reviewed for pre-surgical and post surgical follow up data. Video-EEG and neuro-imaging data were restored and reanalyzed.

Results

Pertinent findings are summarized in *table 1*.

Demographic data, history and examination

In six children (4 females), age of seizure onset was 1 day-4 years (median 9.5 months). Age at surgery was 3-14 years (median 7.5 years). All patients had catastrophic epilepsy with almost daily seizures resulting in loss of

consciousness and/or falls. Five had severe and one had mild (impaired dexterity and mild weakness of distal upper and lower extremity) hemiparesis. All patients had severe cognitive impairment. Encephaloclastic lesions were sequels of remote perinatal and postnatal brain insults. Based on the history and brain MRI findings (*figures 1, 2*), two had middle cerebral artery strokes (1 spontaneous, 1 myocarditis), one each had perinatal hypoxia and trauma, bacterial meningo-encephalitis, hemiconvulsive-hemiplegia syndrome, and one had a possible viral encephalitis with status epilepticus.

Video-EEG review

VEEG data including interictal abnormalities and ictal semiology are summarized in *table 1*.

Four of the six patients had ictal lateralizing signs documented by video-EEG, and three patients had more than one lateralizing sign. Lateralizing ictal signs included unilateral tonic seizures involving extremities (4/6), head versive seizures (2/6), hemi-clonic seizures (1/6), and asymmetric epileptic spasm (1/6). Whenever, lateralizing signs were seen, these were concordant with the MRI lesion, even though, the ictal EEG pointed to ictal onset over the opposite hemisphere. In two patients (*table 1*, patients 3 and 4), no lateralizing features were present on history or on the video documented seizures. Interictal EEG showed generalized and bilateral multi-regional discharges in all patients. Only in 3/6 (*table 1*, patients 3, 5 and 6) patients, the interictal epileptiform abnormalities were predominantly seen concordant to the side of the brain MRI lesion. In the remaining three patients, interictal epileptiform abnormalities were either generalized (2/6) or lateralized (1/6) to the discordant (contralateral) side of the MRI lesion.

Samples of ictal scalp EEG recordings along with brain MRI are shown in *figures 1* and *2*.

In all the cases, the ictal EEG patterns on standard bipolar montage, whenever lateralized, were most predominant over the unaffected hemisphere (paradoxical lateralization) and mid line electrodes characterized by either a high amplitude spike or poorly defined sharp transient followed by 3-7Hz spike and wave complexes (patient 1 [*figure 1A, B*]; patient 2 [*figure 1C, D*]; patient 4 [*figure 2C, H*]) or a sharp wave or diffuse slow wave followed by a beta frequency ictal rhythms (patient 3 [*figure 1E, F*]; patient 5 [*figure 2I, J*]; patient 6 [*figure 2K, L*]). The hemisphere with the destructive MRI lesion only showed ictal EEG change characterized by low amplitude ictal rhythms in frontal or posterior electrodes or relative electrodecrement (patient 5, *figure I, J*).

We analyzed ictal EEG of every patient using reference montages (common average reference, Cz reference, and ipsilateral TP9 or TP10 reference), bipolar transverse montage, and bipolar hat band montage, and confirmed the scalp distribution of this characteristic ictal EEG pattern.

Table 1. Salient clinical, imaging, scalp EEG, and postoperative seizure outcome data in patients.

Patient/ Sex	Age at Onset of Sz (years)	Age at surgery (years)	Etiology/brain MRI	Preoperative neuro exam and cognitive evaluation	Sz freq /day	Interictal video-EEG with frequency of sharp waves	Ictal semiology (VEEG); # of sz type/ # total sz recorded	Type of Surgery	Postoperative exam and cognitive evaluation	Follow-up after Surgery (months)	Sz outcome
1/F	Day 1 of life	3	Vacuum delivery, perinatal HIE and L subdural hematoma/ L hemispheric EM	Severe R HP nonverbal, VF - NT, VABC 53	15-30	- 75% Gen max R HS - 25% MF R HS - 5% MF L HS	- *R versive → BAT; 10/12 - *R arm & leg tonic → BAT; 2/12	L HSY	Unchanged HP, better alertness, more social, speak simple words	39	Sz free 2 yrs, then starting spells (? epileptic), 2 AEDs
2/M	48 mo	8	Refractory SE at 4years of age/ R posterior quadrant EM	Mild L HP, normal language, VF - L HH	8-10	- 85% L posterior quadrant - 10% MR R HS - 5% vertex	- *L versive → *L body tonic clonic → BAT; 8/10 - GTCS or NCS; 2/10	R posterior quadrant resection	Transiently worse L HP, improved over 6 months	31	Sz free, on 1 AED
3/F	17 mo	7.25	Perinatal R MCA stroke noted at 9 months of age/ R MCA stroke	Severe L HP, Nonverbal, VF - NT, VABC 35	1 cluster (5-15 sz over 15 minutes)	- 70% MR R HS - 30% Gen	- Atypical absence; 5/9 - NCS; 3/9 - BAT; 1/9	R HSY	Unchanged HP, improved social interaction	25	Sz free, on 1 AED
4/M	8 wks	14.75	Bacterial meningitis at 8 weeks with complicated course/ R EM in MCA territory	Severe L HP, speak short sentences, not reading, VF - possible L HH, FSIQ 42,	3-5	- 75% Gen max bifrontal - 25% MF R HS	- Axial tonic; 8/8	R HSY	Unchanged HP, spasticity reduced, improved affect	14	Sz free, no AED
5/F	7 mo	12.5	Myocarditis complicated by embolic stroke/ Remote L MCA stroke	Severe L HP, speaks short sentences, VF - L HH	3-6	- 100% Gen max L HS	- *R arm tonic → Complex partial seizure; 20/20	L HSY	Unchanged HP	20	Sz free, no AED
6/F	12 mo	6.25	R HHE syndrome at 12 months/ R posterior quadrant & central EM	Severe L HP, speaks short sentences, VF - L HH, FSIQ 66	1-4 clusters (5-10 sz over 5-7 minutes)	- 65% MF R HS - 25% MF L HS - 10% vertex	- AES → *L arm & leg tonic; 9/9 clusters	R HSY	Spasticity reduced, remarkable alert, sociable	12	Sz free, no AED

AED: antiepileptic drug; AES: asymmetric epileptic spasm; BAT: bilateral asymmetric tonic seizure; EM: encephalomalacia; F: female; FSIQ: full scale IQ; Gen: generalized; GTCS: generalized tonic clonic seizure; HH: homonymous hemianopsia; HHE: hemiconvulsive hemiplegia epilepsy syndrome; HIE: hypoxic ischemic encephalopathy; HP: hemiparesis; HS: hemisphere; HSY: hemispherectomy; L: left; M: male; Max: maximum; MCA: middle cerebral artery; MF: multifocal; MO: months; NCS: no clinical signs (EEG seizure); NT: not testable objectively; R: right; SE: status epilepticus; Sz: seizure; VABC: Vineland Adaptive Behavior Composite scale; VEEG: video-EEG; VF: visual fields; Wks: weeks; * signifies lateralizing semiology on video-EEG.

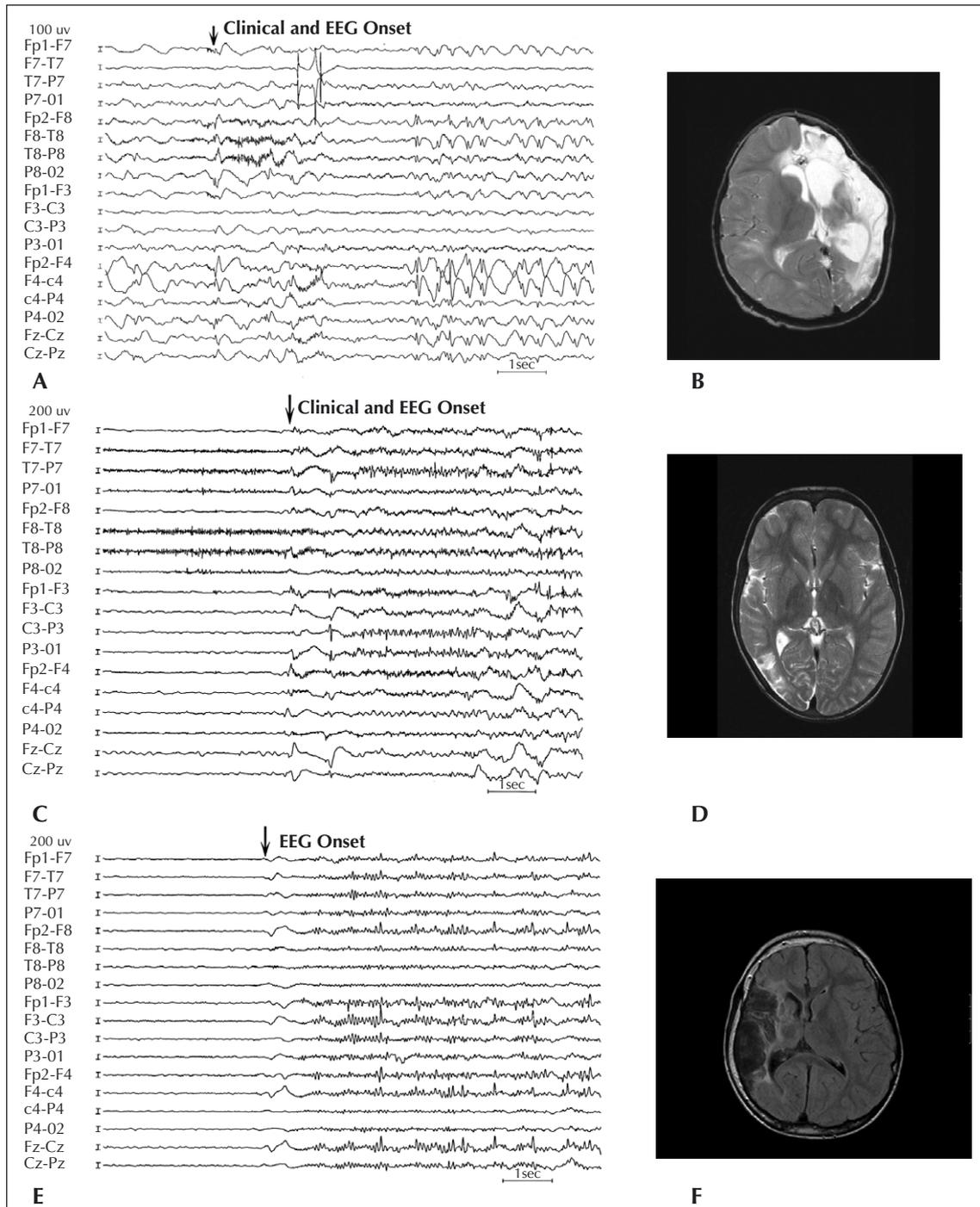


Figure 1. **A, B** Patient 1. Ictal EEG onset (**A**) in a patient with multicystic encephalomalacia of the left hemisphere (**B**, axial T2 MRI). It shows an initial spike at the right frontal and right mesial frontal electrodes (Fp2, F4, Fz) followed by slow waves and disappearance of background for 2 seconds before rhythmic ictal propagation occurs with high amplitude spike and wave complexes over the right hemisphere. The left hemisphere only shows low amplitude slow spike and wave in frontal electrodes (Fp1, F3). **C, D** Patient 2. Ictal EEG onset (**C**) in a patient with right occipito-temporal and parietal encephalomalacia with relative sparing of the frontal lobe (**D**, axial T2 MRI). It shows an initial poorly defined sharp transient of diffuse distribution followed in approximately 1 second by a spike and 6-7 Hz spike and waves maximum over the left posterior quadrant (P3, P7, and O1). **E, F** Patient 3. Ictal EEG onset (**E**) in a patient with remote right middle cerebral stroke (**F**, axial proton density MRI). It shows a diffuse slow wave followed by a beta frequency ictal rhythm that is generalized but of higher amplitude over the left hemisphere.

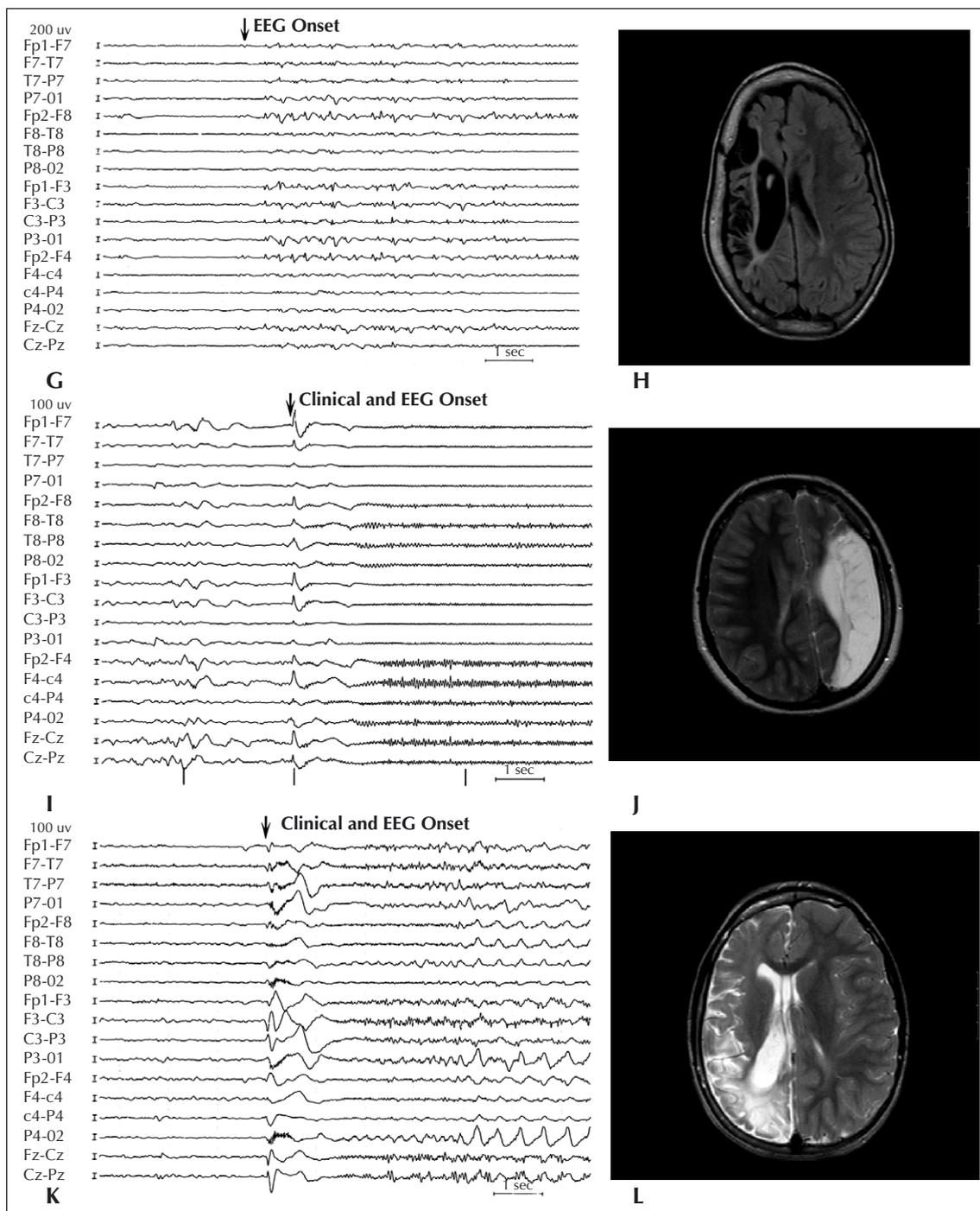


Figure 2. **G, H** Patient 4. Ictal EEG onset (**G**) in a patient with remote history of meningo-encephalitis and right hemispheric encephalomalacia (**H**, axial proton density MRI). It shows high amplitude spike and wave ictal rhythm maximum over the left parasagittal chain. Right hemisphere shows ictal rhythms confined to fronto-polar electrode (Fp2). **I, J** Patient 5. Ictal EEG (**I**) in a patient with remote left middle cerebral artery ischemic stroke (**J**, axial T2 MRI). It is characterized by a bi-frontal sharp wave followed by fast ictal rhythms lateralized to the right hemisphere and midline electrodes (maximum F4, Fz). The ictal pattern seen over the left hemisphere consists of electro-decrement from baseline and subtle low amplitude ictal rhythms over the frontal electrodes (Fp1, F3). **K, L** Patient 6. Ictal EEG onset (**K**) in a patient with right posterior quadrant encephalomalacia (**L**, axial T2 MRI) as a sequel of remote hemiclusive-hemiplegia syndrome. It shows an initial left central (C3 > T7, Cz) sharp wave followed by beta frequency ictal rhythms over the entire left hemisphere for 4 seconds before a diffuse ictal pattern is seen.

Neuroimaging and other pre-surgical considerations

Brain MRI images are shown in *figures 1* and *2* (2 panels, A-L). The brain MRI of these six children did not show any abnormality in the unaffected (contralateral) hemisphere. Brain PET in all patients showed regions of hypometabolism in and around the areas of the MRI lesion.

Ictal single photon emission computed tomography (SPECT) was not done due to practical limitations including high seizure frequency, brief seizure duration, multiple seizure types, and difficulty in accurately pinpointing the clinical seizure onset. Chronic or intra-operative subdural recordings were not done because it was felt unlikely that it would help in localizing ictal onset, salvaging any eloquent regions (location, technical limitations due to age or patient's inability to cooperate) or change the surgical plan of complete resection of the lesion/hemisphere.

Surgery and post-surgical follow-up

Each patient was presented in the patient management conference. In the presence of dis-concordant (paradoxical lateralization) ictal scalp EEG (ictal onset zone), the decision for surgery was based on a combination of other findings such as clinical history and examination (functional deficit zone), interictal EEG abnormalities (irritative zone), and ictal semiology of the recorded seizures (symptomatogenic zone) that were concordant with the side of the brain MRI and PET (epileptogenic lesion) abnormality. Benefits and risks of surgery were reviewed in each case, and hemispherectomy was considered due to extent of MRI lesions, and pre-existing motor (hemiparesis), visual, and cognitive deficits. In one patient (*table 1*, patient 2) with a lesion restricted to the posterior temporal, occipital and parietal regions with preexisting left homonymous visual field deficit and mild hemiparesis, a tailored posterior quadrant resection posterior to the central sulcus was done preserving the sensory motor function. Noninvasive mapping with functional MRI (fMRI) was not considered due to a low risk for any new motor and language deficits, and lack of cooperation in a developmentally delay child. Subdural grid evaluation was also discussed in the patient management conference, however, such an invasive procedure would have required bilateral posterior quadrant grids placement in a developmentally delayed child with low chances of altering the surgical strategy.

After 12-39 months of follow-up, 5/6 patients are seizure free. In one patient (*table 1*, patient 1), the family reported spells of behavior arrest which were not associated with EEG seizure pattern. These spells occurred 26 months after surgery, lasted only for a few seconds, and occurred 2-3 times a week. All parents reported remarkable improvement in children's behavior and affect. Only one patient (*table 1*, patient 2), showed immediate post-

surgical worsening of motor deficit. However, motor function improved to the baseline over six months after surgery. No other perioperative or postoperative complications were encountered.

Discussion

We report a distinctive pattern of ictal scalp EEG in six children with extensive unilateral encephaloclastic lesion that confounded the presurgical evaluation. The ictal EEG pattern consists of prominent ictal rhythms (paradoxical lateralization with sharp or slow wave followed by high amplitude spike and wave complexes or beta frequency ictal rhythms) over the unaffected (normal) hemisphere. This ictal EEG pattern despite being discordant (contralateral) to the side of the MRI lesion does not contraindicate surgery, provided other clues (as in each of our patient) are concordant to the hemisphere with the MRI lesion. These clues may include presence of focal neurological deficits on examination, predominance of concordant interictal abnormalities (seen in 3/6 in our series), ictal semiology, and absence of brain MRI and PET abnormalities in the unaffected hemisphere. Generalized interictal abnormalities and diffuse ictal EEG patterns have been described (Tinuper *et al.*, 1988; Gupta *et al.*, 2007; Wyllie *et al.*, 2007) in infants and children with extensive congenital or early onset acquired lesions; but exclusively lateralized ictal EEG patterns to the contralesional hemisphere appear to be unique to the children with encephaloclastic or destructive lesions as described in our series. Paradoxical lateralization has been reported in three patients with unilateral atrophic temporal lobe lesions (Sammaritano *et al.*, 1987), however, predominance of concordant interictal spikes and background disturbance on scalp EEG, and recordings from bilateral temporal depth electrode clarified the correct side of seizure origin in these patients.

Three hypotheses, likely interdependent, may explain paradoxical lateralization of ictal EEGs in our series. One hypothesis assumes that the hemisphere with the encephaloclastic lesion is able to generate interictal epileptiform abnormalities that may synchronize to generate a seizure, but a rapid spread to the "good" hemisphere must occur to produce a clinical seizure as the damaged hemisphere is unable to sustain and ipsilaterally spread ictal rhythms due to lack of a critical mass of cortical and subcortical connections. The rapid spread to the "good" hemisphere would then lead to an EEG pattern expressed predominantly over the "normal" hemisphere. This hypothesis, however, does not explain the correct semiology seen in these seizures that still implicate the hemisphere with the lesion being the hemisphere of seizure origin.

Second possible hypothesis is the deep location of the epileptogenic zone between the atrophied and injured cortex (and subcortical white matter) and scalp electrodes leading to an asymmetric ictal pattern with reduced amplitude ipsilateral to the lesion. It is also possible that very high frequency low amplitude ictal rhythms that preceded this pattern were not captured by the sampling and filter settings that are routinely used in the video-EEG laboratories.

Third possible explanation could be the spatial orientation of the ictal onset rhythms as dipoles (oriented oblique or parallel to the surface) in the mesial frontal or mesial parieto-occipital head regions. An oblique dipole causing paradoxical lateralization of parasagittal waves was found in patient with epilepsy partialis continua involving the right leg (Adelman *et al.*, 1982). Paradoxical lateralization of cortical generators of evoked potentials has also been described for evoked potentials generated in mesial brain regions (Adelman *et al.*, 1982; Cruse *et al.*, 1982). This seems to be an unlikely explanation in our cases since the location of the ictal potentials was rather diffuse over the contralateral normal side.

We conclude that, in patients with early onset encephaloclastic unihemispheric lesions, the ictal scalp EEG may paradoxically lateralize contralateral to the destructive lesion (epileptogenic) seen on the brain MRI. Even the interictal scalp EEG abnormalities may be bilaterally multiregional or generalized. Such constellation of findings should not preclude surgical option for treatment of epilepsy provided other tests (motor deficits, seizure semiology, and PET examination) are concordant to the side of the brain MRI lesion. □

Disclosures.

None.

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