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Spectrum of Congenital CNS Malformations in Pediatric Epilepsy

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This study was conducted in a tertiary pediatric epilepsy clinic to ascertain the spectrum of development malformations in children, with seizures. Seventy Six Children (0-12 yr) with seizures and CNS malformations based on neuroimaging were included. Observed anomalies included dysgenetic corpus callosum (DCC), lissencephaly, focal cortical dysplasia (FCD), pachygyria, polymicrogyria, heterotopia, schizencephaly, holoprosencephaly, hemimegalencephaly, and phakomatoses like tuberous sclerosis, Sturge Weber syndrome and linear cutaneous nevus syndrome. Seizure semiology varied in all categories. Microcephaly, developmental delay and tone abnormalities were common clinical findings. 60.5% cases presented in infancy. The characteristic EEG features provided a clue to the diagnosis of anomalies like lissencephaly, agenesis of corpus callosum and alobar holoprosencephaly.

Key words: *CNS malformations, EEG, Epilepsy, Neuroimaging.*

Developmental CNS malformations are a complex group of congenital malformations often presenting with variable neuro-developmental dysfunction and seizures(1). Computed tomography (CT) scan and magnetic resonance imaging (MRI) have revolutionized our understanding of these malformations, providing a good anatomic

diagnosis. However, accurate pathological diagnosis can be done by histopathology alone. We conducted a study to evaluate the entire spectrum of CNS malformations in children with seizures, as diagnosed by neuroimaging.

Subjects and Methods

Over a 5 year priod from 1996 to 2001, 1330 children were enrolled from the epilepsy clinic of a tertiary care pediatric hospital. These children were evaluated for age of seizure onset, sex, risk factors, family history, developmental delay, dysmorphic features, seizure semiology, neurological examination and EEG. Based on this, patients were advised neuroimaging. 76 patients were diagnosed as having developmental CNS malformations by neuroimaging. Of these, CT scan could diagnose brain malformations in 33 patients and 27 patients underwent MRI only; 16 cases underwent both CT scan and MRI. The same neuroradiologist reviewed all the scans. Video EEG was performed in cases with doubtful seizure semiology, to identify the seizure type and concomitant EEG abnormality. In each patient, an attempt was made to correlate the epileptic seizures with the location, extent and type of CNS malformation and EEG features.

Results

Seventy six cases were identified to have epileptogenic brain malformations based on neuroimaging. These malformations included dysgenetic corpus callosum (DCC) (n = 19), lissencephaly(n = 9), focal cortical dysplasia (FCD) (n = 9), pachygyria (n = 6), polymicrogyria (n = 3), heterotopia(n = 4), schizencephaly(n = 2), holoprosencephaly(n = 4), hemimegalencephaly(n = 1), and phakomatoses like tuberous sclerosis (TS)(n = 15), Sturge Weber syndrome (SWS)(n = 3) and linear cutaneous nevus syndrome (LCNS) (n = 1). There was a male preponderance (60.5%) in our study, mainly in pachygyria and heterotopias (100%). Patients with Aicardi syndrome were females (3/3). CT scan could mainly diagnose phakomatoses and holoprosencephaly (4/4) and hemimegalencephaly (1/1). Sixteen patients with neuronal migrational abnormalities, previously not diagnosed by CT scan were recognized by a subsequent MRI scan.

Forty six out of 76 (60.5%) cases had their first seizure in infancy, and included 13 neonates. Patients with holoprosencephaly (4/4) and hemimegalencephaly (1/1) presented in neonatal period; generalized disorders like lissencephaly and DCC in infancy whereas focal disorders like polymicrogyria, heterotopia and phakomatoses like SWS had a later age of seizure onset.

The seizures, as per the classification by the International League Against Epilepsy(2), were partial in 27/76 (35.6%) and generalized in 31/76 (40.7%) cases. 15/76 (19.7%) presented with infantile spasms, of which 7 had TS, 5 had lissencephaly and 3 had DCC. Two patients had unclassifiable seizures. Multiple seizure types were seen in 38.2% cases.

Six patients were born of a consanguineous marriage, including 2 siblings with lissencephaly and six had a family history of epilepsy.

At presentation, 15/76 (19.7%) patients had normal neurodevelopmental assessment, 49/76 (64.5%) patients had global delay in milestones, 5 had motor delay, 2 had isolated speech delay and 4 patients (5.3%) showed neuro-regression. 22/76 (28.9%) patients exhibited microcephaly, whereas macrocephaly was seen with hemimegalencephaly (1/1). Dysmorphic features (n = 10) were clue to syndromes like Miller-Dieker, Aicardi, Sotos and Pierre-Robin and 4 patients had

holoprosencephalic facies. Neuro-cutaneous markers like ash-leaf macules, adenoma sebaceum, shagreen patch, café-au-lait spots, and nevus were seen in 17 patients. Focal neurological deficit and tone abnormalities were observed in 13 and 29 children respectively.

Eighty per cent of DCC and 55.5% cases with lissencephaly had other associated CNS abnormalities, which included colpocephaly, Dandy-Walker variants, cysts, heterotopia, FCD, polymicrogyria and pachygyria. All patients with holoprosencephaly and hemi-megalencephaly had associated pachygyria.

As shown in *Table I*, 64/76 (84.2%) patients had abnormal EEG, whereas 12 /76 (15.8%) had a normal EEG. EEG of 17.1% cases showed modified hypsarrhythmia, presented clinically with infantile spasms and constituted the West syndrome. 11/19 (58%) patients with DCC showed asymmetry between the two hemispheres on EEG (*Fig. 1*). Two cases with alobar holoprosencephaly exhibited a unique type of EEG abnormality showing frequent, asynchronous sharp waves, spike, and spike-wave and polyspike-wave complexes over both frontal regions, with decreasing gradient of potentials over the frontal to occipital leads. They also showed high amplitude rhythmic delta activity in the centro-temporal region with almost isoelectric record posteriorly. High amplitude fast rhythms of *a*- and *b*-activity was identified in patients with lissencephaly (*Fig. 2*). Both patients with schizencephaly showed asymmetry between the 2 hemispheres with epileptiform discharges in the hemisphere with the cleft and absence of secondary generalization.

Discussion

Our study illustrates the spectrum of CNS malformations in 76 pediatric epileptic patients, diagnosed by neuroimaging, with relevant clinical features and EEG findings. Unfortunately, there are not many comparable studies below 12-yr age group encompassing the entire spectrum of brain malformations. Kapoor, *et al.*(3), reported developmental lesions only in the 0-3 year age group, these included atrophy, dilated ventricles, aqueductal stenosis and porencephaly, besides other structural lesions. Raymond, *et al.*(4) studied the spectrum of cortical anomalies in the adult population. Many of our references are therefore, limited to individual studies on subcategories of these malformations.

CT scan can easily identify phakomatoses due to its calcified lesions and gross anomalies like holoprosencephaly and hemimegalen-cephaly. However, neuronal migrational anomalies are better identified by MRI due to its multiplanar imaging and higher anatomic resolution (5).

Abnormalities of gyration and DCC were amongst the commonest anomalies in our study, similar to the one on adult population by Raymond, *et al.*(4). However, they had large number of heterotopias (28%) as compared to 5.3% in our study, suggesting that patients with heterotopias may present in adulthood. TS formed 19.7% of our cases in comparison with 5% in the same adult study.

60.5% of our patients presented in infancy, including 43.4% in the 1 month-1 year age group, which is in concordance with the Indian study by Kapoor, *et al.*(3). All 4 patients with heterotopia (3 with peri-ventricular and 1 with subcortical heterotopia) were male, which is in contrast to previous studies(4,6,7), where a female preponderance was definitely noted in periventricular heterotopias suggesting an X-linked dominant inheritance. However, no such sex

TABLE I–*EEG Features of Developmental Malformations.*

Category (No. of patients)	Generalised neuronal hyper-excitability	Focal epileptic form discharges	Secondary generali-sation	Burst suppre-ssion	Asym-metry	Hypsar-rhythmia	Low to absent brain activity	Normal
DCC (19)	1	7	2	1	11	3	-	1
Lissencephaly (9)	3	3	-	-	2	3	-	-
Pachygyria (6)	-	4	-	-	-	-	-	2
Polymicrogyria (3)	1	2	-	-	-	-	-	-
Heterotopia (4)	-	3	-	-	1	-	-	-
FCD (9)	-	1	3	1	1	1	-	3
Schizencephaly (2)	-	1	-	-	2	-	-	-
TS(15)	2	-	2	-	-	6	-	5
SWS (3)	-	1	-	-	1	-	-	1
LCNS (1)	-	-	-	-	1	-	-	-
Holoprosencephaly (4)	2	-	-	-	-	-	2	-
Hemimegalencephaly (1)	-	-	-	1	-	-	-	-

* Some patients had more than one EEG abnormality.

preponderance is noted for subcortical heterotopias. Probably, the male preponderance in our study reflects the referral pattern in our country.

The seizure semiology in our series varied widely and did not always appear to predict either the location or morphology of the cortical malformation, which is in agreement with other authors(8,9). The same CNS malformation was associated with both partial and generalized seizures. However, focality of the malformation was an important factor in the causation of partial seizures in cases of FCD, pachygyria, SWS and LCNS. 19.7% seizures were described as infantile spasms, an age-related seizure pattern, and are more common in a pediatric study. 8/15 patients with TS had infantile spasms, which is the commonest seizure type described in TS(10).

64.5% of our patients had global delay compared to 10% in the adult study by Raymond, *et al.*(4), reflecting that earlier onset of seizures denote severity of malformation. All cases of lissencephaly showed global developmental delay, which is comparable to the study by Barkovich, *et al.*(11). 5.3% patients had neuroregression, which could be attributed to recurrent, refractory seizures. Microcephaly is a well-documented finding in congenital CNS malformations. Macrocephaly was observed in our patient with hemimegalencephaly, consistent with Kalifa, *et al.*(12).

EEG is an important tool in the study of childhood epilepsy and can provide a clue to the diagnosis of some developmental CNS malformations. Burst suppression pattern and hypsarrhythmias are age-related EEG patterns that present in infancy and may get modified later on. 58% patients with DCC showed

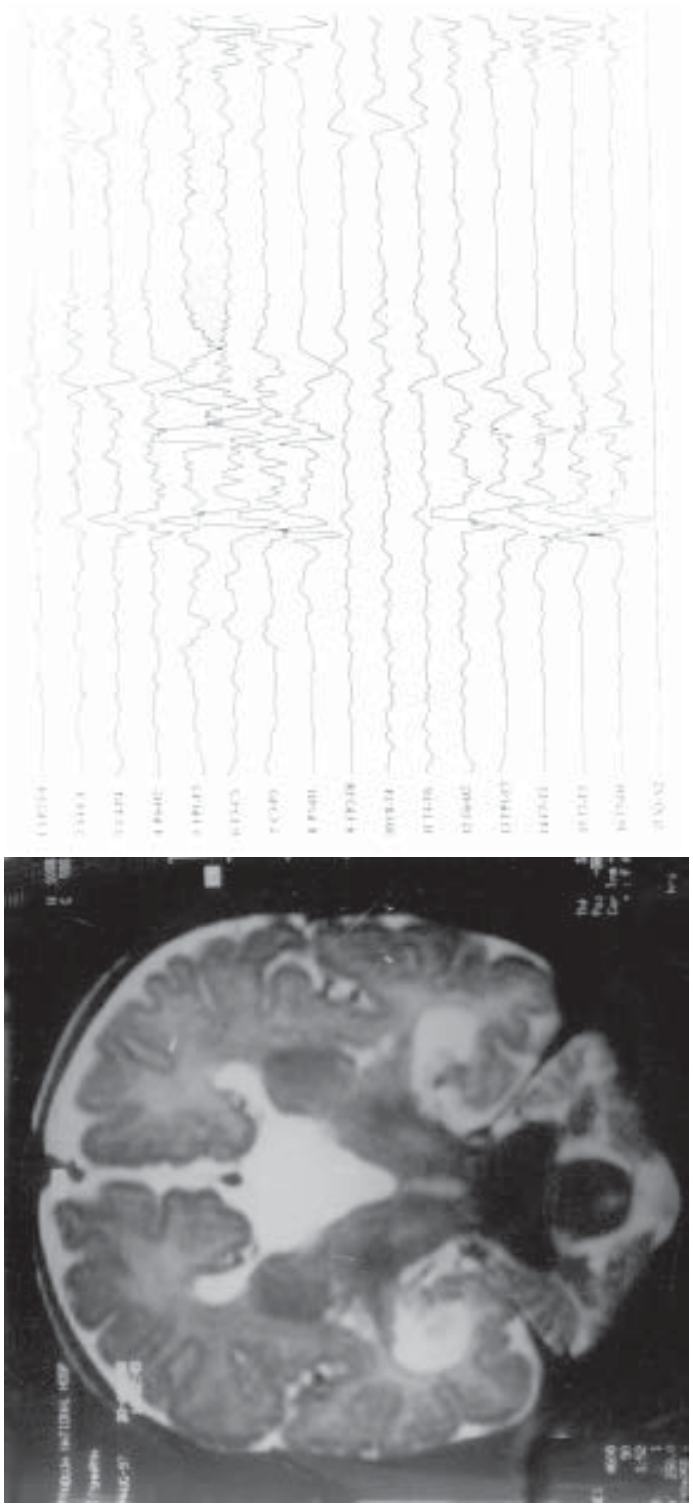

Fig. 1. Agenesis of corpus callosum. T2W coronal MR image revealing a typical "Viking-helmet" deformity of the lateral ventricle and the dilated and elevated 3rd ventricle. Simultaneous EEG Tracing shows asymmetry between the 2 hemispheres.

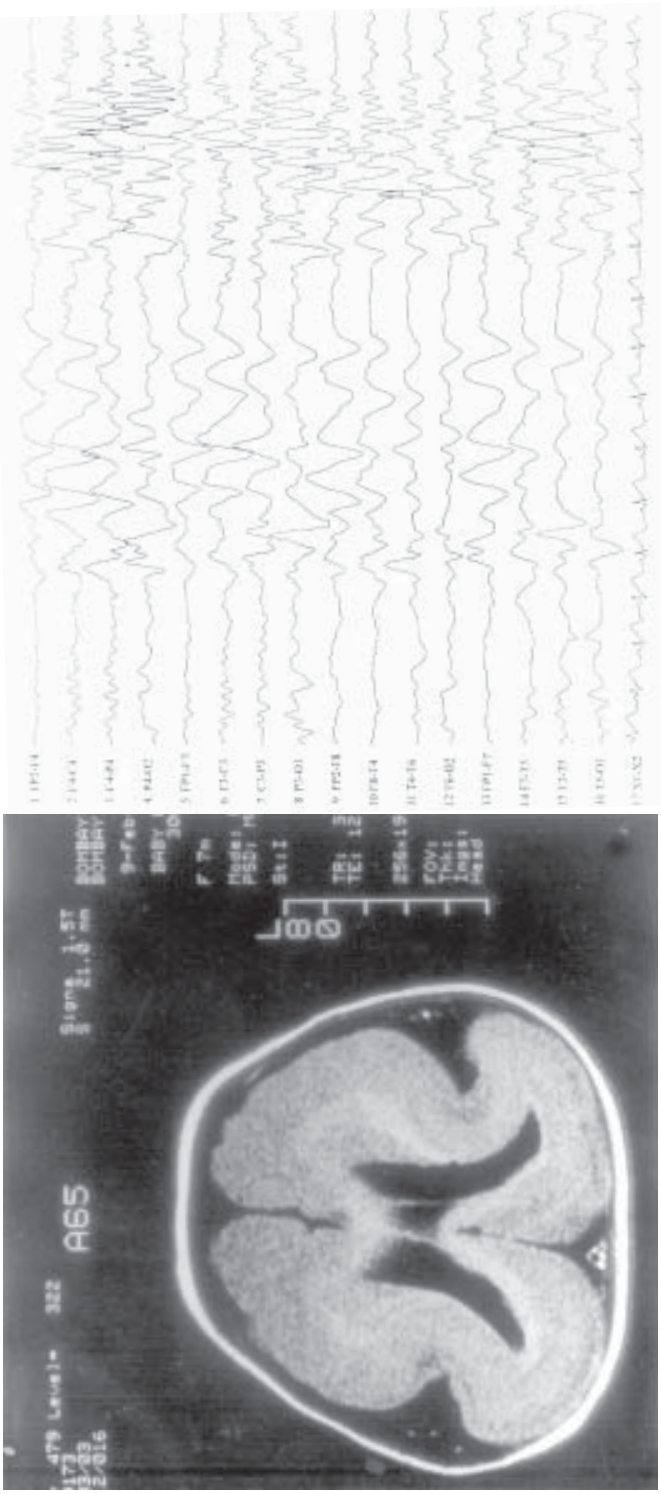

Fig. 2. Type I Lissencephaly. Axial MR image showing the classic "figure of 8" appearance and its EEG tracing showing high amplitude fast a and ß activity with a mixture of high amplitude q and d rhythm.

Key Messages

- Developmental CNS malformations must be suspected in a child who presents with seizures, neurodevelopmental delay and/or dysmorphic features and neuro-cutaneous markers.
- Although EEG can provide a clue to the diagnosis of these anomalies, neuroimaging is required for accurate anatomic diagnosis.

characteristic interhemispheric asynchrony similar to previous studies(13-15). The asynchronous EEG is later replaced by multifocal epileptiform abnormalities as seen in 15.8% of our patients. Isoelectric or almost flat EEG changes may be described in lesions like hydranencephaly, porencephaly, hematomas, hygromas, *etc*. However, a combination of inactivity posteriorly and bizarre activity anteriorly is seen exceptionally in alobar holoprosencephaly(14). High amplitude fast *a*- and *b*-rhythms alternating with *q* and *d*-rhythms are classical of lissencephaly(4). Granata, *et al*.(16) explained that the absence of generalization in EEG of patients with schizencephaly might be due to the cleft-induced anatomical rearrangements of cortico-cortical and cortico-subcortical pathways linking the 2 hemispheres thus preventing bilateral diffusion of the epileptiform discharges. However, absence of generalization per se can also be seen in other conditions like FCD, focal atrophy, *etc*.

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