Malformations of cortical development and epilepsy: evaluation of 101 cases (Part II)

Serdal Güngör[1], Dilek Yalnızoğlu[2], Güzide Turanlı[2], Işıl Saatçi[3]
Emel Erdoğan-Bakar[2], Meral Topçu[2]

[1]Department of Pediatrics, İnönü University Faculty of Medicine, Malatya, and Departments of [2]Pediatrics, and [3]Radiology, Hacettepe University Faculty of Medicine, Ankara, Turkey

SUMMARY: Güngör S, Yalnızoğlu D, Turanlı G, Saatçi I, Erdoğan-Bakar E, Topçu M. Malformations of cortical development and epilepsy: evaluation of 101 cases (Part II). Turk J Pediatr 2007; 49: 131-140.

Malformations of cortical development (MCD) form a spectrum of lesions produced by insult to the developing neocortex. Clinical presentation and electrophysiologic findings of MCD are variable and depend on the affected cortical area. We evaluated epilepsy, EEG, and response to antiepileptic treatment in patients with MCD with respect to the neuroimaging findings. We studied 101 patients, ranging between 1 month and 19 years of age. Fifty-four patients were diagnosed with polymicrogyria (PMG), 23 patients with lissencephaly, 12 patients with schizencephaly, and 12 patients with heterotopia. With regards to epilepsy and seizure type, 72/101 (71.3%) patients had epilepsy, and 62/101 (61.4%) patients presented with seizures. Overall, 32.7% of patients had generalized seizures, and 25.7% had complex partial seizures. Mean age at the onset of seizures was 2.7±3.4 years. The onset of epilepsy tended to be younger in patients with lissencephaly and older in patients with heterotopias. Of the cases, 79.2% had abnormal EEG (56.3% with epileptiform abnormality, 22.9% with non-epileptiform abnormality). EEG was abnormal in 44.9% (13/29) of the cases without epilepsy. EEG showed bilateral synchronous and diffuse epileptiform discharges in 90% of patients with lissencephaly. Patients with schizencephaly had mostly focal epileptiform discharges. Heterotopia cases had a high rate of EEG abnormalities (72.7%). Patients with PMG had epileptiform abnormality in 59.5% of the cases. Patients with heterotopias and PMG achieved better seizure control in comparison with the other groups. In conclusion, epilepsy is the most common problem in MCD. Epilepsy and EEG findings of patients with MCD are variable and seem to be correlated with the extent of cortical involvement.

***Key words:** malformations of cortical development, lissencephaly, heterotopia, polymicrogyria, schizencephaly, epilepsy, MRI, EEG.*

Clinical findings in malformations of cortical development (MCD) are variable, and depending on the function of the affected area, have a wide spectrum between developmental delay, epilepsy and focal neurological abnormalities[1-9]. In lissencephaly, migration of all cortical neurons has been severely affected and the brain is abnormally smooth; gyri may be flat and few (pachygyria) or absent (agyria); the gray-white interface is smooth[10]. Polymicrogyria (PMG) is characterized by an excessive number of small and prominent convolutions spaced out by shallow and enlarged sulci, giving the cortical surface a lumpy aspect[11]. Neuronal heterotopias are the mildest clinical form of the migration disorders. They are due to the cessation of neurons during radial migration from the periventricular germinal layer resulting in ectopic localization of neurons in other than the place they have to occupy[12]. Schizencephaly

**This data was presented at the AES, 2004.*

(cleft brain) consists of a unilateral or bilateral full-thickness cleft of the cerebral hemispheres with communication between the ventricle and extraaxial subarachnoid spaces[11].

Clinical and electrophysiological findings are usually non-specific. Epileptic seizures generally start in early life with partial or generalized attacks according to the spread of the lesion. On the other hand, seizures may not be present in all patients, and response to anti-epileptic drug (AED) treatment may be reliable[4,13]. Electroencephalography (EEG) is helpful for the diagnosis of MCD, but findings are not specific[4,13]. In 75% of patients, it is useful for the diagnosis of epilepsy due to cortical dysplasia[13]. Magnetic resonance imaging (MRI) is a major tool for the diagnosis of cortical dysplasia and helps to identify 50-70% of the malformations. Volumetric MRI can be used for the best evaluation of cortical dysplasia[4]. In patients who underwent epilepsy surgery, abnormal MRI findings were correlated with clinical and EEG findings in 84% of the cases[14]. We studied seizure types, electrophysiological characteristics and responses to the treatment in patients with MCD and correlated these findings with neuroradiological data.

Material and Methods

We studied 101 cases (51 male, 50 female) diagnosed as MCD with cranial MRI at Hacettepe University Faculty of Medicine (HUFM), İhsan Doğramacı Children's Hospital, Pediatric Neurology Unit between 2002 and 2004. HUFM is a tertiary referral center.

Neuroradiological examinations were evaluated by two pediatric neurologists and two neuroradiologists in our hospital. MRI scans were accepted as satisfactory when they had at least two sequences (T1- and T2-weighted). The MRI scans obtained in our center were performed on 0.5T Philips Intera, 1.5T Siemens Symphony and 3T Siemens Allegra systems and contained narrow slice width, coronal and T1-T2 weighted volumetric evaluations and inversion recovery (IR) sequences. MRI scans were evaluated for the severity of malformation, location, size, spread of lobar involvement and other accompanying central nervous system malformations in sagittal, axial and coronal sequences. Cases were grouped as agyria-pachygyria complex, PMG, schizencephaly and heterotopia.

Detailed medical and family histories were obtained in addition to neurological examinations and neurophysiological tests. Systemic and neurological examinations were performed by at least two pediatricians, one of whom was a pediatric neurologist. All cases were carefully evaluated for the presence of seizure. Seizure type and epilepsy syndromes were classified according to ILAE (International League Against Epilepsy) 1989 classification[15]. Seizure type was determined according to the history from the parents and witnessed seizures during the examinations. Routine EEG evaluations were performed with electrodes placed according to international 10-20 system. EEG records were evaluated by two different child neurologists who were blinded to the diagnosis.

Kruskal-Wallis and Mann-Whitney U test together with Bonferroni correction, one-way analysis of variance (ANOVA), Tukey HSD and chi-square tests were performed with SPSS 11.0 program for the statistical analysis.

Results

One hundred and one cases with the diagnosis of MCD were included in this study. Demographic and clinical properties and EEG and MRI findings were evaluated.

1) Demographic Features: There were 51 males and 50 females (M/F:1.0) and no significant difference was present between the sexes ($p>0.05$). The ages of the cases at the time of evaluation varied between 1 month and 19 years (mean 6.1±4.4 years), and there was statistical significance between patients with lissencephaly and patients with heterotopia ($p<0.001$). The mean age at time of diagnosis was 4.3±4.0 years. The mean age at diagnosis was the youngest in patients with lissencephaly and highest in patients with heterotopia (Table I).

2) MRI Findings: Fifty-four cases were diagnosed as PMG, 23 cases as agyria-pachygyria (lissencephaly), 12 cases as heterotopia and 12 cases as schizencephaly (Fig. 1).

– Localization of cortical malformations: Malformations detected were bilateral in 60.4% (61/101) and unilateral in 39.6% (40/101) of the cases ($p<0.001$). Bilateral diffuse involvement was more common in patients with lissencephaly (78.2%), whereas unilateral involvement was more common in patients with schizencephaly (78%).

Table I. Demographic Features of Patients

Group	n	%	Sex M/F	Age (year)	Age of the diagnosis (year)	Age of onset of seizures (min-max)
PMG	54	53.5	28/26	6.3±4.2 1 month-17 years	4.8±3.9 10 months-14 years	2.7±3.3 year 1 day-10.8 years
Lissencephaly	23	22.8	12/11	3.6±3.5 2 months-12 years	2.0±2.5 2 months-10 years	1.2±1.4 year 2 months-5 years
Heterotopia	12	11.9	7/5	9.4±5.2 1.1-19 years	6.9±5.0 1.1±19 years	6.1±5.1 year 6 months-18 years
Schizencephaly	12	11.9	4/8	6.9±3.8 1.3-14 years	2.8±2.8 1 month-9 years	1.9±1.9 year 4 months-6.9 years
Total	101	100	51/50	6.1±4.4 1 month-19 years	4.3±4.0 1 month-19 years	2.7±3.4 year 1 day-18 years

PMG: Polymicrogyria. M: Male. F: Female.

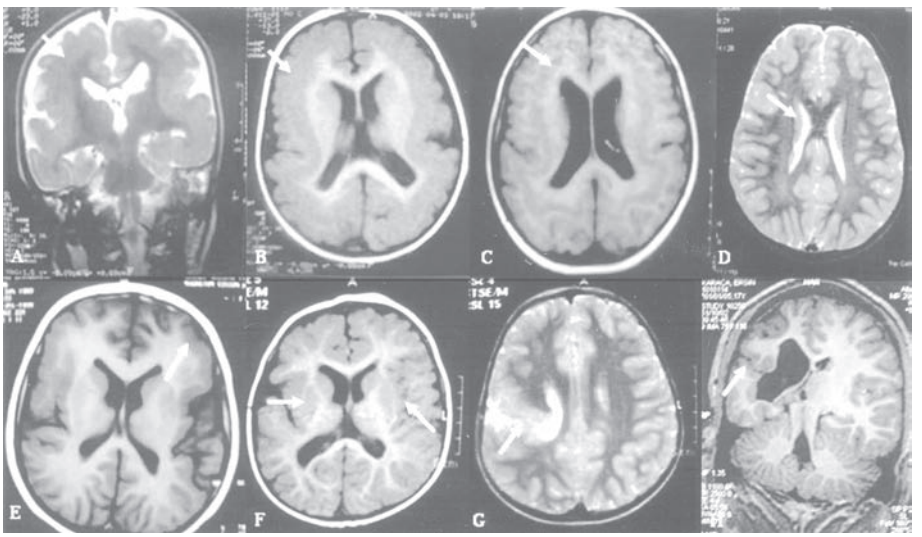

Fig 1. Coronal T2- (A) and transverse T1-weighted (B) magnetic resonance images showing diffuse lissencephaly; transverse T1-weighted image showing double cortex (C); transverse T2-weighted image showing periventricular nodular heterotopia (D); transverse T1-weighted image showing bilateral frontal polymicrogyria (E); transverse T1-weighted image showing bilateral perisylvian polymicrogyria (F); and transverse T2- (G) and coronal T1- (H) weighted images showing unilateral closed lip schizencephaly.

Malformations were mostly diffuse (37.5%). Focal malformations were most common in perisylvian (19.8%), frontal (18.7%) and parietal regions (17.7%); occipital lobe (6.2%) was the least common site. Perisylvian (29.6%), bilateral diffuse (27.7%) and frontal (11.1%) regions were more common sites in patients with PMG. Periventricular nodular heterotopia (PVNH) or subependymal heterotopia (SEH) constituted 41.6% (5/12) of the cases; focal subcortical heterotopia (SCH) was seen in 33.3% (4/12), and subcortical band heterotopia (SBH) in 3/12 of the cases.

Accompanying malformations: In 34.6% (35/101) of our cases, additional malformations were present. Hypoplasia/dysplasia of corpus callosum (20.8%) was the most common. Other malformations were arachnoid cysts (4.9%), cerebellar hypoplasia/dysplasia (3.9%), brain stem hypoplasia (3.9%), nonspecific white matter alterations (3.9%), cerebellar vermis hypoplasia/agenesis and Dandy-Walker malformations. There were no significant differences between the four groups according to the frequencies of these malformations ($p>0.05$). Malformations of the corpus

callosum were most common in patients with lissencephaly (39.1%) and patients with PMG (16.6%). PMG was accompanying in patients with schizencephaly and in half of the patients with heterotopia.

3) Epilepsy: Among our patients, 61.4% were admitted because of epileptic seizures. Eight of 12 patients each (66.7%) with heterotopia and with schizencephaly, 35/54 (64.9%) of patients with PMG and 11/23 (47.8%) of patients with lissencephaly were first admitted because of seizures. In 11.3% (7/62) of these cases, initial seizure was febrile convulsion.

Seizure type: Epileptic seizures were present in 71.3% (72/101) of our cases. Generalized seizures were present in 32.7%, complex partial in 25.7% and secondary generalized in 11% of the cases. Seizure frequencies showed no significant difference between different groups of patients with MCD ($p>0.05$). At least one seizure history was present in 83% of patients with schizencephaly, in 75.9% of patients with PMG, in 66.7% of patients with heterotopia and in 56.5% of patients with lissencephaly. In PMG, the most common seizure types were generalized (40.7%) and complex partial (29.6%). Generalized (21.7%) and secondary generalized (13%) were seen in lissencephaly and partial seizures (49.9%) in heterotopias. Generalized seizures were more common in diffuse cortical malformations. In 67.2% of bilateral malformations, generalized seizures (34.4%) and complex partial seizures (19.6%) were most often present, and in 75% of unilateral malformations, complex partial (35%), generalized (30%) and secondary generalized (15%) seizures were present ($p>0.05$).

Age at onset of seizures: The mean age at onset of seizures were 2.7±3.4 years (1 day-18 years), with the youngest age in patients with lissencephaly and oldest age in patients with heterotopia. There was significant difference in the ages of groups at onset of seizures ($p<0.05$). Seizures started in the first year of life in 48.6% of the cases in general, in 62.5% of lissencephaly, in 53.7% of PMG, in 40% of schizencephaly and in 12.5% of heterotopia cases (Table I).

Treatment for epilepsy: Among 72 cases with seizures, 48% of patients were on polytherapy and 51.4% on monotherapy. Polytherapy was most common in lissencephaly (69.3%) and heterotopia (50%) cases. Complete seizure control was achieved in 30.6% of cases, while seizures continued in 69.5% of the cases with varying frequencies. Of patients with heterotopia, 37.5%, and of cases with PMG, 34.1%, were seizure-free under AED treatment. Corpus callosotomy was performed in a patient with diffuse PMG for seizure control and during one-year follow up seizure frequency decreased by more than 80%.

4) EEG Findings: EEG recordings were obtained in 96 of 101 cases; 79% of them had abnormalities (epileptiform abnormality 56.3%, non-epileptiform abnormality 22.9%). In 20.8% of the cases, normal EEG findings were found. In 44.9% of 29 cases without clinical seizures, 20.7% had epileptiform and 24.2% had non-epileptiform abnormalities in EEG. EEG features in patients with MCD are shown in Table II. Epileptiform abnormalities were either generalized or localized to the area of cortical malformation. Epileptiform abnormalities were observed most commonly in patients with heterotopia and in patients with PMG. Epileptiform activity was in the form of spike-wave and sharp-wave related with the localization of the lesion. There was no significant difference in presence of epileptiform/nonepileptiform findings of cases with unilateral (40/101) and bilateral (61/101) malformations ($p>0.05$). Focal slowing of baseline activity was present in diffuse malformations such as lissencephaly, diffuse PMG and diffuse band heterotopia.

Discussion

Clinical and electrophysiological findings in malformations of the cerebral cortex are usually nonspecific. Severe malformations can be recognized with developmental delay and early onset recurrent seizures, while mild ones can be detected after diagnostic approaches for the seizures beginning at any age[4,13,16]. Epilepsy accompanying cortical malformations is generally severe but incidence is variable depending on the type of the malformation. Generalized seizures can be observed in diffuse malformations, while partial or secondarily generalized seizures are present in focal malformations[11,14].

There are no specific EEG findings of cortical developmental malformations, but EEG is helpful for their diagnosis. Two different EEG

Table II. EEG Features in Patients with Malformations of Cortical Development

	Slowing of background activity			EEG abnormality			Epileptiform abnormality		
	Focal	Diffuse	Asymmetric vertex/voltage suppression	NE	E	N	Generalized	Focal	Secondary generalized
PMG n=53	9	13	3	13 24.5%	31 58.5%	9 17%	14/31	12/31	5/31
Lissencephaly n=21	1	10	–	5 23.8%	11 52.4%	5 23.8%	8/11	3/11	–
Heterotopia n=11	1	3	–	1 9.1%	7 63.6%	3 27.3%	5/7	2/7	
Schizencephaly n=11	4	–	1	3 27.3%	5 45.4%	3 27.3%	2/5	3/5	
Total n=96	15	26	4	22 22.9%	54 56.3%	20 20.8%	29/53	20/53	5/53

PMG: Polymicrogyria. NE: Nonepileptiform. E: Epileptiform. N: Normal.

patterns have been described. The first pattern is composed of baseline activity with abnormally elevated amplitudes, beta activity with 15-25 Hz abnormal speed and continuing bursts. This interesting pattern is commonly observed in diffuse cortical dysplasia cases. The second pattern has focal interictal spike-waves or sharp-waves, decrease in baseline activity amplitude, asymmetric sleep spindle and unilateral electro-decremental pattern. Repetitive epileptiform discharges and continuous epileptiform activity are the sensitive and specific signs of localized cortical dysplasia[4,13].

Lissencephaly: Localization and spread of the malformations are variable. In our patients with lissencephaly, malformations were usually bilaterally diffuse with frontoparietal localization. In the literature[9,17,18,19], pachygyria is reported to be generally located in frontal and temporal regions while agyria has posterior location. Barkovich et al.[20] had stated that the frontal lobe is most severely affected and the parietal lobe to a lesser extent in lissencephaly cases. Corpus callosum malformations accompanied lissencephaly in 39.1% of our cases. The frequency of the presence of corpus callosum malformations in patients with lissencephaly was reported as 17%[19] and 22%[20] in the literature. The higher percentage in our series can be related with the genotypic features of the cases, but no genetic analysis was performed. Epileptic seizures were present in 56.5% of our patients with lissencephaly; among them generalized seizures and secondary generalized seizures were the most common types. Epileptic seizures at the time of diagnosis in our lissencephaly cases were less than in other malformations. This can be related with the early diagnosis of lissencephaly in the first months of life with presentations other than seizures like microcephaly. On the other hand, corpus callosum agenesis/dysplasia, which generally accompany diffuse malformations, are supposed to have an inhibitor effect on the spread of discharges in these cases[21,22]. Seizures have been reported in 76% and 90% of lissencephaly cases, and infantile spasm develops in 35% of these cases[11,16,19].

Seizures can start in patients with lissencephaly during the neonatal period or in the first 6 to 12 months of life[6,7,11,23-25]. The earliest onset of seizures in our series was in the lissencephaly group, with the mean age at onset of 1.2 years, and seizures were observed within the first year of life in 61.5% of the cases. There are some studies reporting the onset of seizures in 70-80% of cases within the first 6 months[16,11,19], while others report it as 24-25.6 months[17,26]. The age at onset varies completely according to the location and spread of the lesion, and seizures start earlier in diffuse compared with localized malformations.

EEG abnormalities are usually bilateral in patients with lissencephaly and may not be present until the 4th to 6th months of age[4,7,13,24]. In almost 90% of our cases, generalized epileptiform discharges and mostly bilateral diffuse spike-waves or sharp-waves were present. Kurul et al.[17] reported abnormal EEG findings (49% diffuse, 40% localized epileptiform disorder) in 89% of the cases. The absence of clinical seizure history in 4 of the 11 lissencephaly cases with abnormal EEG findings demonstrates the necessity of an EEG recording to define the subtle seizures that are not identifiable. Typical interictal EEG pattern in lissencephaly cases includes the following: 1) Rapid activity with definitely elevated amplitudes, 2) Rapid activity with teta frequency (this activity matures with age), 3) Bursts of sharp and slow wave complexes with elevated amplitudes, 4) Spike and slow wave complexes interrupted with diffuse voltage suppression periods, and 5) Irregular teta and delta activity. Some of the patterns in lissencephaly are age-dependent[4,6,7,11,27,28].

Seizure control rate was low in our cases, and recurrent seizures were present in 69.2%. It has been reported that patients with lissencephaly have bad response to antiepileptic therapy in the long-term[6]. Kurul et al.[17] reported that the ratio of good response to treatment was 75% and of resistant seizures was 25% and that bilateral diffuse malformations had worse treatment results when compared to localized malformations. Montenegro et al.[26] reported the seizure control rate in the agyria-pachygyria group as 5% with AEDs. Poor responses to AED treatment in these cases are related with accompanying diffuse malformations.

Polymicrogyria: In our patients with PMG, malformations were most common at the perisylvian region, followed by diffuse involvement and frontal region. Perisylvian and frontal regions are the most commonly affected sites in PMGs[29]. Occipital regions were the least affected sites, in accordance with the literature[30,31]. Palmini[32] reported 47% of the cases with focal neuronal migration disorders as unilateral and most commonly (27%) with frontal location. In 35.2% of our cases, accompanying malformations were present, with corpus callosum malformations the most common. Corpus callosum thinning has been reported in 31% of patients with bilateral frontal PMG[33].

Generalized and complex partial seizures were the most common seizure types in 75.9% of our cases with seizures. Atypical absence, tonic, atonic and generalized tonic clonic seizures are seen in 50-85% of the patients with PMG[6]; generalized type seizures in 94% of the patients with bilateral frontoparietal PMG[34,35]; partial motor seizures in 77.7% of the patients with unilateral PMG[36]; and focal seizures in 86% of the patients with perisylvian PMG[29]. There are remarkable differences between these ratios with respect to the localization and spread of the lesions.

The mean age at the onset of seizures was 2.8 years. Seizures were defined in the first year in 53.7%. The age at onset of seizures has been reported as 1-6 years in patients with unilateral PMG[31,36]; 4-12 years in patients with bilateral perisylvian PMG[16]; and 20 months-15 years in patients with bilateral parietooccipital PMG[37].

Seizure control was achieved in 34.1% of the cases, and seizures continued in 65.9% despite treatment. Resistant seizures were reported in 60% of patients with bilateral perisylvian syndrome[4,16] and in 78% of patients with bilateral parietooccipital PMG[37]. Seizure outcome in our series is similar to the literature data, as our cases usually had diffuse and perisylvian malformations. Montenegro et al.[26] reported seizure control rate as 53% in their PMG group.

EEG abnormalities were determined in 58.5% of our patients with PMG. EEG was normal in the presence of seizures in 17% of the cases. Generalized epileptiform abnormality was present in 50% and focal epileptic disorders in 40% of the cases. EEG abnormalities were correlated with the spread and localization of the lesion. Epileptiform discharges were localized to the area of malformation. Non-epileptiform abnormalities like irregularity of baseline activity and asymmetry were present in 24.5% of the cases. In the literature, bilateral synchronized and asynchronized spike and sharp wave and polyspike have been reported in bilateral frontoparietal PMG[6,33]; diffuse epileptiform abnormalities together with normal baseline activity in bilateral parietooccipital PMG[37]; and electrical status epilepticus during sleep (ESES) in some children with unilateral and bilateral perisylvian PMG[38]. We defined ESES in two cases: one with unilateral right perisylvian PMG and one with bilateral frontal

PMG. It has been reported that all of the 36 cases with unilateral PMG had unilateral spike and secondary bilateral synchronization during sleep[36]. Sleep EEG was performed in only 26 of our PMG cases. If it had been performed in all cases, this number might have increased.

Heterotopia: Heterotopias are named according to the localization. All of our SBH cases located just below the cortex as a symmetrical band of gray matter were bilateral and diffuse. In the literature, SBHs are reported most commonly in frontoparietal regions[9,25]. Our PVNH (SEH) and SCH cases were not located in a specific site. Occipital regions are reported as the least common localizations[6]. Heterotopias are most commonly accompanied by other cerebral malformations. Arachnoid cysts were present in 16.6% of our cases. In the literature, corpus callosum agenesis and cerebellar malformations were reported in 25% of PVNH cases[24,38]; corpus callosum agenesis and hypogenesis in 70% of SCH cases[6,39]; and corpus callosum agenesis, hydrocephalus, mega cisterna magna and cerebellar hypoplasia in SBH cases[40]. In 50% of our heterotopia cases, PMG accompanied heterotopia in the neighboring cerebral cortex.

Epileptic seizures were present in 66.7% of our cases and partial seizures, especially complex partial type seizures, were more common (49.9%). Complete seizure control was obtained with AED treatment in 37.5% of the cases, in approximately one year. Epilepsy, mostly treatment-resistant partial seizure type starting at any age, was recorded in 80-90% of PVNH cases[12,25,41-43]. In a series including 42 SBH cases, 95% had epilepsy; of these, 51% had generalized and 49% had partial type epilepsy, and 65% of them were drug-resistant[11]. On the other hand, 88% of SCH cases had seizures and 88% of them were drug-resistant[16]. Treatment of seizures with AED in our heterotopia cases demonstrated better results when compared with other malformations.

Heterotopia cases usually present with epileptic seizures that start at any age, related with the localization of the malformation. The mean age at onset of seizures was 6.1 years in our heterotopia cases with milder clinical findings. These seizures were the first recognized sign by the families. Epileptic seizures were recognized within the first year in only 12.5% of the cases and seizure frequency in the first five years was 50%. Seizures had started anywhere between 5-19 years in the remaining 50%. Epileptic seizures are seen most commonly in the second decade of life in PVNH and in the first or second decade of life in SCH[6,25,44], but can also be seen at any time between one month and adulthood[16]. d'Orsi et al.[40] reported the age at onset of seizures in the PVNH plus group accompanied by other malformations as 4.25 years and in the simple PVNH group as 19.2 years. Epileptiform activity is believed to originate from the heterotopic neuron in SBH and early onset is not common[16], but usually starts during childhood[6].

EEG abnormalities were shown in 72.7% of our heterotopia cases. Of these EEG abnormalities, 63.6% were in the form of generalized epileptic discharges. The remainder of the cases had normal EEG findings besides the presence of clinical seizures. EEG findings are variable in heterotopia cases. Multifocal and generalized epileptiform discharges and generalized slow-waves are observed in SBH[6,45]. Similarly, diffuse slowing in baseline activity and generalized epileptiform discharges were present in our SBH cases. EEG findings are heterogeneous in PVNH and focal EEG abnormalities are usually present related with the localization of periventricular nodule[40]. Battaglia et al.[41] reported that epilepsy in PVNH patients is generated by abnormal anatomic circuitries including the heterotopic nodules and adjacent archicortical and neocortical areas. Focal or generalized epileptiform abnormalities related with the localization were present in 5 of our PVNH cases.

Schizencephaly: Malformations in our cases, which were mostly unilateral (78%) and closed type, were located in the parietal region. Schizencephalic cleft is more commonly located close to pre- and post-central gyrus and to a lesser extent around temporal and occipital regions[46]. Denis[21] had reported that unilateral schizencephaly was more commonly located at frontal and parietal lobes. Perisylvian region is also one of the more common sites[11,16]. In a series of 15 unilateral schizencephaly cases, 11 had frontoparietal localization[36].

Accompanying malformations were present in 66.7% of our schizencephaly cases, as corpus callosum malformation (25%) and arachnoid

cyst (16.6%). Different frequencies are reported in the literature for the accompanying cerebral malformations[21,22,47]. All of our cases had PMG neighboring the cleft. Barkovich[1] stated that PMG accompanied all schizencephaly cases, but not all PMGs were accompanied with schizencephaly. In a different series, polymicrogyric cortices were common around the clefts[48].

Epileptic seizures are related with the type and spread of the malformation. Ten of our cases had unilateral and most commonly closed type schizencephaly; 83% of them had generalized partial and secondary generalized seizures. Patients with unilateral schizencephaly are characterized with focal seizures and one-third of these cases are drug-resistant[21,22,49]. Different frequencies have been reported in the literature for seizures, ranging from 37% to 81%[16,21,22,36]. These differences are perhaps related with the localization and spread of the malformation.

The mean age at onset of seizures was found to be 2 years in our cases, which were mostly unilateral closed type schizencephaly. Seizures had started within the first year in 40% and within the first three years in 90% of the cases. The age at onset of seizures is late childhood and adolescence in unilateral schizencephaly cases, while it is early childhood in bilateral and open type cases[21,22,49,50]. It is 2.5 years of age in unilateral schizencephaly cases, and seizures are generally in the form of focal motor seizures[36]. Our cases were mostly unilateral and age of onset was parallel to this. In the literature, seizures are reported to start in 80% of the cases in the first three years[51]. Denis et al.[21] reported the age of onset of epilepsy as 4 years and the type of seizures most commonly as generalized and to a lesser extent complex partial. Seizures are recurrent and drug-resistant if malformations are bilateral[11,16]. We achieved total control of seizures in 20% of our cases. Seizure control has been reported as 62% in bilateral open type and as 33% in bilateral closed type[22]. Our low success rate with AED treatment supports this data.

Epileptic disorders were present in EEG in 45.4% of our cases. These were generally focal type and to a lesser extent generalized type epileptic disorders correlated with the lesions. In our study, baseline irregularity was present in 27.3% and normal EEG pattern in 27.3% of the cases. In the literature, EEG abnormalities are reported in all of the unilateral schizencephaly cases with seizures, and in 60% of them, the EEG findings were on the same side as the cleft[21]. Besides the correlation of spike-slow wave and sharp-slow wave discharges with the lesion localization[21], it is also reported that there is no specific EEG pattern[16].

Conclusion

Lissencephaly cases are usually in the form of bilateral diffuse malformations and accompanying corpus callosum malformations are common. Antiepileptic-resistant generalized seizures are present, starting in the first year of life. Non-specific generalized epileptic discharges are observed in their EEG. Perisylvian and frontal localization is more common except in diffuse PMG cases. Other central nervous system malformations can accompany in one-third of the cases. According to the spread of the malformation, generalized or focal epileptic disorders are present. Treatment response is better in focal malformations. EEG is normal or non-epileptiform in nearly half of the cases despite the presence of seizure. Clinical findings are milder in heterotopia cases and they are diagnosed at any age but especially after seizures in the later childhood period. Partial seizures are usually common. They result in epileptic abnormalities in EEG at a higher ratio. Generalized epileptic abnormalities are common, and best response to antiepileptics is obtained in these cases. Unilateral and closed type and parietal localization are more common in schizencephaly cases. Age at diagnosis is generally slightly related with the associated seizure. Non-specific focal epileptic disorders related with the localization of the lesion are common in unilateral closed type schizencephaly. Treatment response is poor in these seizures.

There are drug-resistant epileptic seizures in MCD cases that are not only related with the type of malformation but also with the spread of the malformation and accompanying malformation. There are no specific EEG findings or drug treatments for MCD types. Further studies are needed to evaluate the phenotypic properties, epileptogenesis and treatment modalities of these malformations.

Acknowledgements

This study is supported by Hacettepe University Scientific Research Unit (Project no: 01G010) Dr. Dilek Yalnızoğlu is supported by NIMH ICORTHA Fogarty International Center Mental Health and Developmental Disabilities Research Training Program (D43TW05807) at Children's Hospital Boston.

REFERENCES

1. Barkovich AJ, Kuzniecky RI, Jackson GD, Guerrini R, Dobyns WB. Classification system for malformations of cortical development. Neurology 2001; 57: 2168-2178.
2. Pilz D, Stoodley N, Golden JA. Neuronal migration, cerebral cortical development, and cerebral cortical anomalies. J Neuropathol Exp Neurol 2002; 61: 1-11.
3. Couillard-Despres S, Winkler J, Uyanik G, Aigner L. Molecular mechanisms of neuronal migration disorders, Quo vadis? Curr Mol Med 2001; 1: 677-688.
4. Whiting S, Duchowny M. Clinical spectrum of cortical dysplasia in childhood: Diagnosis and treatment issues. J Child Neurol 1999; 14: 759-771.
5. Blaser SI, Jay V. Disorders of cortical formation. Radiologic-pathologic correlation. Neurosurg Clin N Am 2002; 37: 41-62.
6. Kuzniecky RI, Barkowich AJ. Malformations of cortical development and epilepsy. Brain Dev 2001; 23: 2-11.
7. Volpe JJ. Neuronal proliferation, migration, organization and myelination. In: Neurology of the Newborn (3rd ed). Philadelphia: W.B. Saunders Company; 1995: 43-92.
8. Golden JA. Cell migration and cerebral cortical development. Neuropathol Appl Neurobiol 2001; 27: 22-28.
9. Barkowich AJ, Gressens P, Evrard P. Formation, maturation and disorders of brain neocortex. AJNR 1992; 3: 423-446.
10. Sisodiya SM. Malformations of cortical development: burdens and insights from important causes of human epilepsy. Lancet Neurol 2004; 3: 29-38.
11. Guerrini R. Genetic malformations of the cerebral cortex and epilepsy. Epilepsia 2005; 46 (Suppl): 32-37.
12. Leventer RJ, Dobyns WB. Periventricular gray matter heterotopias: a heterogeneous group of malformations of cortical development. In: Barth PG (ed). Disorders of Neuronal Migration. London: Mac Keith Press; 2003: 72-82.
13. Koehn MA, Duchowny M. Preoperative clinical evaluation and noninvasive electroencephalogram in cortical dysplasia. Neurosurg Clin N Am 2002; 37: 35-39.
14. Kuzniecky RI, Garcia J, Faught E. Cortical dysplasia in temporal lobe epilepsy: magnetic resonance imaging correlations. Ann Neurol 1991; 29: 293-298.
15. Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. Epilepsia 1989; 30: 289-399.
16. Guerrini R, Carrozzo R. Epilepsy and genetic malformations of the cerebral cortex. Am J Med Genet 2001; 106: 160-173.
17. Kurul S, Çakmakçı H, Dirik E. Agyria-pachygyria complex: MR findings and correlation with clinical features. Pediatr Neurol 2004; 30: 16-23.
18. Barkovich AJ, Chuang SH, Norman D. MR of neuronal migration anomalies. AJNR 1987; 8: 1009-1017.
19. Dobyns WB, Elias ER, Newlin AC, Pagon RA, Ledbetter DH. Causal heterogeneity in isolated lissencephaly. Neurology 1992; 42: 1375-1388.
20. Barkovich AJ, Koch TK, Carrol CL. The spectrum of lissencephaly: report of ten patients analyzed by magnetic resonance imaging. Ann Neurol 1991; 30: 139-146.
21. Denis D, Chateil JF, Brun M, et al. Schizencephaly: clinical and imaging features in 30 infantile cases. Brain Dev 2000; 22: 475-483.
22. Packard AM, Miller VS, Delgado MR. Schizencephaly: correlations of clinical and radiologic features. Neurology 1997; 48: 1427-1434.
23. Dobyns WB, Leventer RJ. Lissencephaly; the clinical and molecular genetic basis of diffuse malformations of neuronal migration. In: Barth PG (ed). Disorders of Neuronal Migration. London: Mac Keith Press; 2003: 24-57.
24. Liang JS, Lee WT, Young C, Peng SS, Shen YZ. Agyria-pachygyria: clinical, neuroimaging, and neurophysiologic correlations. Pediatr Neurol 2002; 27: 171-176.
25. Kuzniecky RI. MRI in cerebral developmental malformations and epilepsy. Magn Reson Imaging 1995; 13: 1137-1145.
26. Montenegro MA, Gerreiro MM, Lopes-Cendes I, Guerreiro CA, Cendes F. Interrelationship of genetics and prenatal injury in the genesis of malformations of cortical development. Arch Neurol 2002; 59: 1147-1153.
27. Carabollo RH, Cersosimo RO, Espeche A, Fejerman N. Bilateral posterior agyria-pachygyria and epilepsy. Brain Dev 2003; 23: 122-126.
28. Sanghvi JP, Rajadhyaksha SB, Ursekar M. Spectrum of congenital CNS malformations in pediatric epilepsy. Indian Pediatr 2004; 41: 831-838.
29. Jansen AC, Leonard G, Bastos AC, et al. Cognitive functioning in bilateral perisylvian polymicrogyria (BPP): clinical and radiological correlations. Epilepsy Behav 2005; 6: 393-404.
30. Guerreiro MM, Hage SR, Guimaraes CA, et al. Developmental language disorder associated with polymicrogyria. Neurology 2002; 59: 245-250.
31. Caraballo R, Cersosimo R, Fejerman N. A particular type of epilepsy in children with congenital hemiparesis associated with unilateral polymicrogyria. Epilepsia 1999; 40: 865-871.
32. Palmini A, Andermann F, Olivier A, et al. Focal neuronal migration disorders and intractable partial epilepsy: a study of 30 patients. Ann Neurol 1991; 30: 741-749.
33. Guerrini R, Barkovich JA, Sztriha L, Dobyns WB. Bilateral frontal polymicrogyria. A newly recognized brain malformation syndrome. Neurology 2000; 54: 909-913.
34. Chang BS, Piao X, Bodell A, et al. Bilateral frontoparietal polymicrogyria: clinical and radiological features in 10 families with linkage to chromosome 16. Ann Neurol 2003; 53: 596-606.

35. Sztriha L, Nork M. Bilateral symmetrical frontoparietal polymicrogyria. Eur J Paediatr Neurol 2002; 6: 229-232.

36. Caraballo RH, Cersosimo RO, Fejerman N. Unilateral closed-lip schizencephaly and epilepsy: a comparison with cases of unilateral polymicrogyria. Brain Dev 2004; 26: 151-157.

37. Guerrini R, Dubeau F, Dulac O, et al. Bilateral parasagittal parietooccipital polymicrogyria and epilepsy. Ann Neurol 1997; 41: 65-73.

38. Guerrini R, Genton P, Bureau M, et al. Multilobar polymicrogyria, intractable drop attack seizures, and sleep-related electrical status epilepticus. Neurology 1998; 51: 504-512.

39. Barkovich AJ. Anomalies of the corpus callosum and cortical malformations. In: Barth PG (ed). Disorders of Neuronal Migration. London: Mac Keith Press; 2003: 24-57.

40. d'Orsi G, Tinuper P, Bisulli F, et al. Clinical features and long term outcome of epilepsy in periventricular nodular heterotopia. Simple compared with plus forms. J Neurol Neurosurg Psychiatry 2004; 75: 873-878.

41. Battaglia G, Chiapparini L, Franceschetti S, et al. Periventricular nodular heterotopia: classification, epileptic history, and genesis of epileptic discharges. Epilepsia 2006; 47: 86-97.

42. Poussaint TY, Fox JW, Dobyns WB, et al. Periventricular nodular heterotopia in patients with filamin-1 gene mutations: neuroimaging findings. Pediatr Radiol 2003; 30: 748-755.

43. Huttenlocher PR, Taravath S, Mojtahedi S. Periventricular heterotopia and epilepsy. Neurology 1994; 44: 51-55.

44. Kuzniecky RI, Anderman F. Non-lissencephalic cortical dysplasias. In: Barth PG (ed). Disorders of Neuronal Migration. London: Mac Keith Press; 2003: 58-71.

45. Grant AC, Rho JM. Ictal EEG pattern in band heterotopia. Epilepsia 2002; 43: 403-407.

46. Barkovich AJ, Kjos BO. Schizencephaly: correlations of clinical findings with MR characteristics. AJNR 1992; 13: 85-94.

47. Curry CJ, Lammer EJ, Nelson V, Shaw GM. Schizencephaly: heterogeneous etiologies in a population of 4 million California births. Am J Med Genet A 2005; 137: 181-189.

48. Palmini A, Lüders HO. Classification issues in malformations caused by abnormalities of cortical development. Neurosurg Clin N Am 2002; 37: 1-16.

49. Battaglia G, Granata T. Schizencephaly. In: Barth PG (ed). Disorders of Neuronal Migration. London: Mac Keith Press; 2003: 127-134.

50. Kloss S, Pieper T, Pannek H, Holthausen H, Tuxhorn I. Epilepsy surgery children with focal cortical dysplasia (FCD): results of long–term seizure outcome. Neuropediatrics 2002; 33: 21-26.

51. Mizuguchi M, Takashima S, Kakita A, Yamada M, Ikeda K. Lissencephaly gene product. Localization in the central nervous system and loss of immunoreactivity in Miller-Dieker syndrome. Am J Pathol 1995; 147: 1142-1151.