Dicle Tıp Dergisi /
Dicle Medical Journal

2014; 41 (3): 457-462
doi: 10.5798/diclemedj.0921.2014.03.0454

ORIGINAL ARTICLE / ÖZGÜN ARAŞTIRMA

Malformations of cortical development and epilepsy: Clinical, EEG and neuroimaging findings in children

Kortikal gelişim bozukluğu ve epilepsi: Çocuklarda klinik, EEG ve nörogörüntüleme bulguları

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ABSTRACT

Objective: of this study was to evaluate the relationship between clinical and treatment features of malformations of cortical development (MCD) in children

Methods: We performed a comprehensive analysis of EEG features, treatment, clinical and neuroimaging findings in 40 consecutive patients.

Results: We are reporting a series of 40 cases with cortical malformation and epilepsy. The ages of our patients at the time of evaluation varied between 4 month and 17 years with a mean of 5.4 years. 57.5% were male and 12.2% of the cases had a family history of epilepsy or other neurological disease, and 15% had gestational or a perinatal insult. Delayed motor and mental milestones were observed in 70%. All type of seizures were reported, but generalized seizures was the most common (18/40, 45%). Patients were on either a single antiepiletic drug (13/40, 32.5 %) or multiple drugs (27/40, 67.5%). Complete seizure control was achieved in 19/40 patients (45.5%), partial control in 7/40 (17.5%) patients, and no control in 14/40 (35%). Lissencephaly, schizencephaly and polymicrogyria were seen as the most common neuroimaging findings in our study. Epilepsy was controlled in most patients with schizencepahly and polymicrogyria. In contrast, seizures were not controlled in patients with lissencephaly and hemimegalencephaly.

Conclusion: Malformations of cortical development are responsible for a wide spectrum of clinical manifestations that include develomental delay, mental retardation and medically refractory epilepsy.

Key words: Epilepsy, malformations of cortical development, MRI, EEG

ÖZET

Amaç: Bu çalışmada kortikal gelişim bozukluğu olan çocuklarda klinik özellikler ve tedavi bulguları arasındaki ilişkinin değerlendirilmesi amaçlanmıştır.

Yöntemler: Kortikal gelişim bozukluğuna sahip 40 hastanın EEG bulguları, tedavi, klinik ve nörogörüntüleme bulguları detaylı bir şekilde değerlendirilmiştir.

Bulgular: Olguların değerlendirilme anındaki yaşları 4-17 yaş aralığında ve ortalama yaşları 5,4 yıldı. %57,5'i erkek, %12,2'sinde epilepsi ve diğer nörolojik hastalık açısından pozitif aile öyküsü, %15'inde ise gebelik ya da doğum sonrası döneme ait travma öyküsü vardı. Olguların %70'inde nöromotor gelişim basamaklarında gerilik tespit edildi. Her tür nöbet tipi görülmesine karşın en sık gözlenen nöbet tipi jeneralize nöbetlerdi (%45). Olguların %32,5'i tek antiepileptik ilaç alırken, %67,5'i çoklu antiepileptik ilaç kullanmaktaydı. Tam nöbet kontrolü olguların %45,5'inde sağlanırken, %17,5'inde kısmi kontrol sağlanmıştı. Olguların %35'inde ise nöbet kontrolü sağlanamamıştı. Serimizde lizensefali, şizensefali ve polimikrogiri en sık görülen kortikal gelişim bozukluklarıydı. Şizensefali ve polimikrogirisi olan olgularda epilepsi kontrolü sağlanırken lizensefali ve hemimegalensefalili olgularda nöbet kontrolü sağlanamamıştı.

Sonuç: Kortikal gelişim bozukluğu gelişme geriliği, zeka geriliği ve medikal tedaviye dirençli epilepsi gibi geniş bir klinik yelpazeden sorumludur.

Anahtar kelimeler: Epilepsi, kortikal gelişim bozukluğu, MRİ, EEG

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Geliş Tarihi / Received: 20.07.2014, Kabul Tarihi / Accepted: 07.08.2014

INTRODUCTION

Malformation of cortical development (MCD) represent among the major causes of epilepsy and neuropsychomotor development delay in children. This is one of the most common causes of refractory epilepsy in children and adults, but seizures usually do not have pathognomonic semiologic features [1-4]. Through widespread utilization of high resolution neuroradiological imaging techniques, previously referred to as cryptogenic or idiopathic epilepsy are now found to be secondary to malformation of cortical development [5,6].

In this study we aimed at describing the clinical characteristics, electrophysiologic features and seizure control with antiepileptic drugs associated with the different forms of malformations of cortical development.

METHODS

We retrospectively reviewed the clinical records of patients with a diagnosis of malformation of cortical development, who were followed up by a secondary care pediatric neurological center of the Selçuk University, Meram Medical School between January 2004 and January 2010. Records of patients aged 18 or older, who had a prior diagnosis of Tuberous Sclerosis or dysembryoblastic neuroectodermal tumors at the time of evaluation were excluded from the study. Each patient's retrospective chart was reviewed to collect clinical information: age, sex, antenatal, perinatal and postnatal events, consanguinity between parents, family history of seizures, developmental milestones, head circumference and neurological examination, age at seizure onset, type and frequency of seizures, the number of medications used, seizure control and characteristic features of electroencephalographic (EEG) abnormalities.

Brain magnetic resonance imaging was performed at 1.5 T to analyze T2-weighted, fluid-attenuated inversion recovery, T1-weighted with/without enhancement by gadolinium diffusionweighted imaging.

All scans were evaluated by both a neuroradiologist and a pediatric neurologist. Cases that were lost to follow up or that had missing clinical, epidemiological or interictal EEG data were excluded from the study.

Seizure, syndrome classifications and response to treatment were decided on according to the International League Against Epilepsy proposals. According to this definition, patients were considered to have drug resistant epilepsy when at least two adequate and tolerated antiepileptic drug schedules failed to achieve sustained seizure freedom. Each antiepileptic drug was used at the highest tolerated dose and levels, available for the classic drugs, were measured for different purposes (to establish adherence, toxicity, etc.). We defined complete control of seziure as the cessation of all seziures for at least 3 months.

The patient's data (both clinical and neuroradiological data) were analyzed using the SPSS Version 11.0 statistical package. Results of the study are expressed as mean with standard deviation and range, for continuous variables and as percentages for discrete variables. We used the chi-square test to analyze the occurrence of epilepsy and seizure control in the different types of malformation of cortical development. We used a significance level of 0.05.

RESULTS

Clinical and epidemiological data

A total of 64 patients with a diagnosis of epilepsy and malformation of cortical development, as shown by magnetic resonance imaging, were identified from approximately 1200 clinical records (frequency of 4.6%). This study included 40 of these 64 patients. The remaining 24 patients were excluded from the study due to incomplete data or loss to follow up. The ages of our patients at the time of evaluation varied between 4 month and 17 years with a mean of 5.4 years. 57.5% were male and 12.2 % of the cases had a family history of epilepsy or other neurological disease. Family history of consanguinity was present among 15% of the patients. A history of gestational or a perinatal insult (e.g., perinatal anoxia, preterm labor) was found in 15% of patients.

An abnormal neurological exam was found in 60% (n: 24) of patients. The main abnormal neurologic findings encountered were psychomotor retardation in 16 (40%) patients, followed by spasticity

in 15 (37.5%) patients (hemiparesis 5/40, 12.5%, quadriparesis 6/40, 15%, diplegia 4/40 10%), generalized hypotonia in [3] 7.5% patients. Macrocephaly was present in one patient and microcephaly in 8 patients. Delayed motor and mental milestones were noted in 28 (70%) patients.

The demographic and clinical features of patients are listed in Table 1.

Table 1. Summary of the clinical data of the patients

No	Sex	Age (month)	Neurologic finding	Cognition	Seizures	EEG	NAED	Neuroimaging
1	M	26	Macrocephaly	Retarded	GS	Multifocal	3	Hemimegalencephaly
2	M	24	DP+ Microcephaly	Retarded	GS	Generalized	3	Lissencephaly
3	M	87	DP		GS	Focal	1	Schizencephaly
4	M	43			GS	Generalized	1	Polymicrogyria
5	M	52			Sec GS	Multifocal	2	Polymicrogyria
6	M	48			Sec GS	Multifocal	3	Heterotopia
7	M	49			CPS	Focal	3	FCD
8	F	65			CPS	Generalized	1	Schizencephaly
9	F	72		Retarded	GS	Multifocal	3	Polymicrogyria
10	M	44		Retarded	GS	Multifocal	3	Lissencephaly
11	F	22	QP+ Microcepahly	Retarded	GS	Generalized	3	Lissencepahly
12	M	40			GS	Multifocal	1	Polymicrogyria
13	F	107	HP		Sec GS	Focal	2	Schizencephaly
14	M	14	Hypotonia		IS	Hypsarrhytmia	3	Hemimegalencephaly
15	F	51			Sec GS	Multifocal	3	Polymicrogyria
16	M	75			Sec GS	Generalized	1	Schizencephaly
17	F	75			CPS	Focal	1	Polymicrogyria
18	M	125	QP +Microcephaly	Retarded	GS	Generalized	3	Lissencephaly
19	M	136	QP	Retarded	GS	Generalized	1	Lissencephaly
20	M	124	HP		CPS	Focal	1	FCD
21	M	129	QP +Microcephaly		CPS	Multifocal	2	Schizencephaly+Polymicrogyria
22	F	32			Sec GS	Multifocal	2	Schizencephaly
23	M	65	DP	Retarded	GS	Generalized	3	Heterotopia+Pachygyria
24	M	8	Hypotonia	Retarded	IS	Hypsarrhytmia	3	Lissencephaly
25	M	4	Hypotonia	Retarded	IS	Hypsarrhytmia	3	Lissencephaly
26	F	96			Sec GS	Focal	1	FCD
27	F	24	HP		CPS	Focal	1	Schizencephaly
28	M	93		Retarded	GS	Multifocal	2	Schizencephaly
29	F	169		Retarded	GS	Multifocal	3	Schizencephaly+Polymicrogyria
30	F	75		Retarded	GS	Generalized	2	Lissencephaly
31	M	144	DP		CPS	Generalized	3	Polymicrogyria
32	M	34		Retarded	GS	Multifocal	3	Lissencepahly
33	F	86	HP		Sec GS	Generalized	1	Schizencephaly
34	F	168	QP +Microcepahly		Sec GS	Generalized	3	Schizencephaly+Polymicrogyria
35	F	12			GS	Multifocal	3	Lissencephaly
36	M	12	Microcephaly+Hypotonia	Retarded	IS	Hypsarrhytmia	3	Lissencephaly
37	F	104			Sec GS	Multifocal	1	FCD
38	M	40			GS	Generalized	3	Heterotopia
39	F	65	QP +Microcepahly	Retarded	GS	Generalized	2	Lissencephaly
40	F	156	HP		CPS	Focal	1	Schizencephaly

GS: Generalized seizures, NAED: Number of antiepileptic drug, QP:Quadriparesic serebral palsy, HP: Hemiplegic cerebral palsy, DP: Diplegic cerebral palsy Sec GS: Seconder generalized seizure, CPS: Complex partial seziure FCD: Focal cortical dysplasia IS: Infantil spasm,

Types of seizures and epilepsy

The mean age at seizure onset was 1,4 years with a range from 4 days to 15 years. The most common type of seizure was generalized seizures, which was seen in 18 patients (45%), secondary generalized in 10 (25%), complex partial in 8 (20%), and infantile spasm in 4 (10%) patients respectively.

EEG findings

Multifocal epileptiform discharges and generalized epileptiform discharges were the most prevalent findings in the patients of our study. EEG findings showed multifocal epileptiform activity in 14 (35%) patients, generalized epileptiform discharges in 14 (35%) patients. In addition focal epileptiform discharges were observed in 8 (20 %) patients and hypsarrhytmia in 4 (10%) patients.

Treatment

Complete control of seizures was achieved in 19/40 patients (45.5%) and partial control in 7/40 patients (17.5%), while 14/40 patients (35%) exhibited poor or no response to both older and newer generation antiepileptic drugs. Seizures were apparently controlled with one antiepileptic drug in 13 (32.5%) patients, this included 8 patients with schizencepahly, 4 patient with polymicrogyria, and one patient with focal cortical dysplasia. Twenty-seven (67.5%) patients were on two or more antiepileptic drugs, of which 75 % received three antiepileptic drugs. None of our patients received non-pharmaceutical treatments such as surgery, ketogenic diet, or vagal nerve stimulation. None of the patients with lissencephaly, heterotopia and hemimegalencephaly had their seizures controlled with one or more antiepileptic drugs.

Epilepsy was controlled in most patients with schizencepahly and polymicrogyria. In contrast, seizures were not controlled in patients with lissencephaly and hemimegalencephaly.

Neuroimaging

Neuroimaging findings revealed multiple abnormalities in 4 (10%) cases. In patients with multiple abnormalities the commonest findings was a combination of schizencephaly and polimicrogyria in 3 patients, heterotopias and pachygyria in one patient. Lissencephaly (agyria-pachygyria) in 13 (32.5%) patients, schizencephaly in 9 (22.5%) patients, polymicrogyria in 7 (17.5%) patients, focal cortical dysplasia in 3 (7.5%) patients, heterotopias in 2 (5%) patients, hemimegalencephaly in 2 (5%) patients.

DISCUSSION

Malformations of cortical development are some of the most common causes of developmental delay and chronic epilepsy with onset during childhood. About 20-40% of children with drug-resistant epilepsy harbor a cortical malformation, and up to 50% of epilepsy surgery operations are carried out in children with an malformation of cortical development. Malformation of cortical development encompass many varied disorders with diverse clinical manifestations [7].

This study was conducted in a secondary care neurological center (Selçuk University, Meram Medical School Hospital) which cares for child neurology patients, especially those with epilepsy.

We found 64 patients with the diagnosis of malformation of cortical development and included 40 of these patients in the study. During a 6-year period, taking into account the patient population with epilepsy in our center, (nearly 1200) the frequency of presentation of malformation of cortical development was approximately 4.6%. Although the true incidence of malformation of cortical development is unknown, our findings are similar to the results of other patient series. In more heterogeneous case series, including patients with adult and children; malformation of cortical development prevalence ranges between 3% and 25% depending on the varying selection criteria and imaging techniques applied. Similar to our findings was the study reported by Brodtkorb et al. who reviewed 303 patients with epilepsy during a 3 year period [8]. They reported a frequency of malformation of cortical development in 4.3% of their cases. On the other hand, Lie et al. have reported 341 adult patients with refractory focal epilepsy malformation of cortical development in 12% of cases [9].

The rate of consanguinity in Turkey between parents ranges between 10 to 20%. Dobyns et al. [10] reported the consanguinity rate in lissence-

phalic children as 4.8%, while Kurul et al.[11] reported the consanguinity rate 27% in their study. In our study, the consanguinity rate was 15%. According to the previous studies, there exists a relationship between a high rate of consanguinity and the prevelance of autosomal recessive trait disorders [12]. Family history of epilepsy or other neurological disease in our cohort are similar to the observations of Raymond et al [13]. On the other hand, in the series of Montenegro et al.[14] family history of cortical dysplasia and mental retardation were present in 32% of the patients with agyria/pachygyria. These findings suggest that genetic factors were important in the etiology of malformation of cortical development.

In the present study, delayed motor and mental milestones were present in 70%. Mathev et al. reported that the history of delayed motor and mental milestones was 42.9% [15]. We consider the rates of delayed motor and mental milestones of malformation of cortical development that was detected in our study to be high. Mathew et al. found no history of any perinatal or prenatal insult, whereas in our series this was in 15% of the cases. Our findings suggest that gestational or a perinatal insult might be related to malformation of cortical development.

Malformations of cortical development have been reported as variable motor and mental manifestations which varied from hemiplegia to severe spastic quadriparesis and from normal intelligence to severe mental retardation. An abnormal neurological exam was found in 60% of our patients. In the series of Leventer et al. abnormal neurologic examination findings were present in 48% of the individuals [16].

The mean age of seizure onset in our study was at 1.4 years of age, and the age of onset was found to occur as early as in the infancy or as late as in adolescent age. Interestingly, we found a case of epilepsy that started at 15 years of age with the diagnosis of schizencephaly. Kovac et al has similarly reported a patient with late epilepsy onset at the age of 31 years [17]. The mechanisms leading to epileptogenesis in malformation of cortical development are yet not fully known.

In fact, although malformation of cortical development have been more frequently described in partial seizures, they could be a reason for all type of seizures or epileptic syndrome [18]. The majority of patients with diffuse cortical malformations such as lissencephaly have generalized seizures and seizure onset during the first year of life, whereas most of the focal malformations such as focal cortical dysplasia, have partial or secondarily generalized seizures that manifest during the first decade of life [19]. The most common type of seizure in our study was generalized seizures. In the study by Güngör et al. 32.7 % had generalized seziures and 36.7% had complex partial and secondary generalized seizures [20]. We thought these findings were due to diffuse cortical malformations more common in the current study than other studies.

The electroencephalographic findings associated with malformation of cortical development are also vary variable, in diffuse cortical dysplasia, it generally shows baseline activity with abnormally elevated amplitudes, beta activity with 15- 25 Hz abnormal speed and continuing bursts; in focal cortical dysplasia, the most frequent findings are repetetive epileptiform discharges and continuous epileptiform activity [21]. Multifocal and generalized epileptiform discharges were the most common EEG abnormality in our study, but there was no specific pattern consistent with the findings of other studies [15,16,19].

Prevalence and severity of epilepsy is variable in different malformations, however it is estimated that up to 40% children with drug resistant epilepsy have a cortical malformation [22]. Our results confirm this observation. In our study, 14 out of 40 patients had refractory or drug resistant epilepsy and all of them were on polytherapy. In the study by Mathew et al refractory epilepsy was observed in 79.4% of the patients [15].

Advances in high resolution magnetic resonance imaging techniques have great importance in detecting malformations of cortical development. Lissencephaly, schizencepahly and polymicrogyria were most prevelant findings in the patients of our study. It is also in keeping with previous findings in the literature. Polymicrogyria (61 out of 144 cases), lissencephaly (22 out of 144 cases) were the most commonly seen abnormality in the study of Pascual-Castroviejo et al., while polymicrogyria (54 out of 101), lissencephaly (23 out of 101) were

found to be the most common findings in the study of Güngör et al [23,20].

The study has several limitations. It was the retrospective, included a relatively small number of patients and the absence of an Epilepsy Surgery division at our center. Follow up information regarding epilepsy surgery and their patholgical findings for this reason were beyond reach.

In conclusion, malformations of cortical development are responsible for a wide spectrum of clinical manifestations including develomental delay, mental retardation and medically refractory epilepsy. To summarize our study, seizures were more easily controlled in patients with schizencephaly and polymicrogyria.

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