

# Neurodevelopmental Findings and Epilepsy in Malformations of Cortical Development

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## What is already known on this topic?

- Cortical developmental malformations occur due to failure of proper development in any of the components of the new classification, including neural / glial proliferation, migration, and cortical organization processes. These malformations could either present with easily controlled epilepsy or intractable epilepsy starting at the first days of life, which causes severe neurocognitive deficiency.

## What this study adds on this topic?

- Little knowledge is available in the literature about the specific phenotypic findings of malformation subtypes. This could be due to clinical differences in presentations of pediatric and adult populations, inappropriate study population selection (primarily chosen from patients with epilepsy), and determination of subgroups according to opportunities in the countries studied. There are limited studies in the literature evaluating microcephaly together with other subgroups. We believe that our study will be useful in understanding the clinical, electrophysiological and neurodevelopmental characteristics of the cases and the differences between the groups, because of the current classification basis and inclusion of subgroups such as microcephaly differ from those in the literature.

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## ABSTRACT

**Aim:** The purpose of this study is to classify the malformations of cortical development in children according to the embryological formation, localization, and neurodevelopmental findings. Seizure/epilepsy and electrophysiological findings have also been compared.

**Material and Methods:** Seventy-five children (age: 1 month–16.5 years; 56% male) followed with the diagnosis of malformation of cortical development, in Marmara University Pendik Research and Educational Hospital Department of Pediatric Neurology, were included in the study. Their epilepsy characteristics, electroencephalogram (EEG) findings, and prognosis were reported. Neurodevelopmental characteristics were evaluated by the Bayley Scales of Infant and Toddler Development (Bayley-III) for the ages of 0–42 months ( $n = 30$ ); the Denver Developmental Screening Test-II (DDST-II) for ages 42 months–6 years ( $n = 11$ ); and the Wechsler Intelligence Scales for Children (WISC-R), used for children 6 years and older ( $n = 34$ ).

**Results:** The patients were classified as 44% premigrational (14.6% microcephaly, 24% tuberous sclerosis, 2.7% focal cortical dysplasia, 1.3% hemimegalencephaly, and 1.3% diffuse cortical dysgenesis); 17.3% migrational (14.6% lissencephaly, 2.7% heterotopia); and 38.6% postmigrational (14.6% schizencephaly, 24% polymicrogyria) developmentally. According to involved area, the classification was 34.7% hemispheric/multilobar, 33.3% diffuse, and 32% focal. Seventy-five percent of the patients had a history of epilepsy, and 92% were resistant to treatment. The seizures started before the age of 12 months in diffuse malformations, and epileptic encephalopathy was more common in microcephaly with a rate of 80% and lissencephaly with a rate of 54.5% in the first EEGs. Ninety-five percent of patients had at least one level of neurodevelopmental delay detected by DDST/Bayley-III; this was more common in patients with accompanying epilepsy ( $P < .05$ ). As seen more commonly in patients with diffuse pathologies and intractable frequent seizures, mental retardation was detected by WISC-R in 64.5% of patients ( $P < .05$ ).

**Conclusion:** In cases with cortical developmental malformation, epilepsy/EEG features and neurodevelopmental prognosis can be predicted depending on the developmental process and type and extent of involvement. Patients should be followed up closely with EEG.

**Keywords:** Malformations of cortical development, epilepsy, Bayley-III, WISC-R, DDST-II, Barkovich 2012 classification

## INTRODUCTION

Cortical developmental malformations (CDM), are among the most important underlying reasons for mental retardation, epilepsy, and sensory and motor abnormalities in childhood. These malformations are subclassified as problems in developmental proliferation, migration, and organization and are based on clinical, histopathological, radiological, and genetic findings.<sup>1-4</sup>

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Electroencephalogram (EEG) is useful for diagnosis. However, findings vary according to subtypes and location. Magnetic Resonance Imaging (MRI) is the most valuable diagnostic tool for CDM.<sup>5</sup>

In this study, the developmental stage of malformation, localization, lateralization, and seizure/epilepsy relation to neurodevelopmental functions of children and adolescents with CDM has been evaluated retrospectively among the subgroups identified in the current classification,<sup>4</sup> with the aim of elucidating the neurocognitive prognosis with relevant MRI findings and epilepsy/EEG characteristics.

## METHODS

This study was performed on patients followed with CDM diagnosis between April 2013 and December 2016 at Marmara University Pendik Research and Educational Hospital Pediatric Neurology Clinic retrospectively. Patients with insufficient MRI quality and central nervous system (CNS) congenital malformations other than CDM have been excluded from the study. The study was approved by the Marmara University Faculty of Medicine Clinical Research Ethics Committee (09.2015.177).

Two independent neuroradiologists evaluated sagittal, axial, and coronal sections of T1-T2 and "inversion recovery (IR)" sequences of cranial MRI images taken in our center or referred from different centers to our clinic. The 3T Siemens Verio system was used for MRI images taken in our center. Revised Barkovich cortical malformations classification 2012 was used for classification.<sup>4</sup>

The patients were classified as premigrational (tuberous sclerosis, microcephaly, focal cortical dysplasia, hemimegalencephaly, and diffuse cortical dysgenesis), migrational (lissencephaly, heterotopia) and postmigrational (schizencephaly, polymicrogyria) developmentally; as microcephaly, tuberous sclerosis, lissencephaly, polymicrogyria, schizencephaly in CDM subgroups (except focal cortical dysplasia, hemimegalencephaly, diffuse cortical dysgenesis, heterotopia depending on the number of cases); and focal, hemispheric/multilobar and diffuse according to involved area.

A follow-up chart including history, MRI findings, seizure-EEG characteristics and developmental test results was filled for each patient. Seizure types were evaluated clinically and classified according to ILAE (International League Against Epilepsy) 2010 classification. Patients on antiepileptics were classified into 2 groups, monotherapy (one antiepileptic drug) and polytherapy (two or more antiepileptics).

EEG readings were recorded with a 32-channel EEG recorder (Nihon Koden), including minimum 20-minute sleep period with 10-20 electrodes placed, and were read by pediatric neurology consultants of the clinic in a standard manner. In the evaluations, background activity anomaly (sleep-wakefulness), bioelectrical disruption, maturation, presence of epileptic activity (focal, multifocal, generalized), epileptic potential frequency (rare, frequent), and presence of epileptic encephalopathy (electrical status epilepticus in slow sleep-hypsarhythmia, others) were examined. Spike wave activity more than once

per minute was evaluated as frequent epileptic potential. EEG results were grouped as normal epileptic disorder (focal/regional-multifocal/ bilateral/generalized), abnormal non-epileptic disorder (slowing of background activities, focal or generalized slowing down, sleep cycle disruption), epileptic, and non-epileptic disorder.<sup>6</sup>

The patients were classified functionally into 3 groups: confined to bed, only sitting, and ambulatory, from the age of 24 months (Each case was followed at least for 24 months). Neurodevelopmental and cognitive tests were performed by a child development specialist and psychologist working in our clinic. The tests done were Bayley Scales of Infant and Toddler Development (Bayley-III) for 1-42 months, Denver Developmental Screening Test-II (DDST-II) for 42 months-6 years, and Wechsler Intelligence Scale for Children-Revised (WISC-R) for children older than 6 years. Bayley-III, developed by Nancy Bayley and revised in 1993 (Bayley-II) and 2006 (Bayley-III) is a gold standard test to evaluate and detect any delays in cognitive, language, and motor functions in 0-42 month-old-children.<sup>7-11</sup> The standard scoring system developed for American children can be used for Turkish children as well.<sup>12,13</sup> Additionally, Janssen et al.,<sup>14</sup> in their study using Bayley-II in Germany, stated that using American norms in test scoring is appropriate because it covers a very large sample group of 1700 children. DDST-II, which is widely used globally to evaluate the development of children under 6 years, has been validated and standardized in our country by Hacettepe University Pediatric Neurology Department and revised in 1996 and 2009 been used widely in our country since then.<sup>15,16</sup> WISC-R is used to assess verbal and performance abilities of 6 to 16-year-old children, was first developed in 1949<sup>17</sup>, revised in 1974,<sup>18</sup> and was translated and adapted to the Turkish version<sup>19</sup> and accepted by Turkish Psychology Society in 1995.

Patients were evaluated by Bayley-III and DDST-II according to chronological or corrected age. In Bayley-III, the patient passed tests were scored as "1" and the tests that they could not pass were scored as "0" and total row scores for each section were converted into standardized, scaled, and compound scores. Patients with scaled score over 8 and compound score over 90 were classified as normal, and the patients with lower scores were classified as delayed for their section. In DDST-II, patients under 90% of the curve (on the left side) were classified as having developmental delay. Bayley-III/DDST-II results were grouped as delay in 1 section or 2 or more sections or not able to take the test in personal, social, gross motor, fine motor, and language sections. WISC-R results were scored according to DSM-V (Diagnostic and Statistical Manual of Mental Disorders) criteria. Patients were classified as mild-medium-severe mental retardation for 35-69 points; borderline-low level-normal intelligence or too low level to be evaluated by WISC-R.

## Statistical Analysis

Data were analyzed using the SPSS program, Version 15. Statistical normality was assessed with the Shapiro-Wilk test and histogram graphics. All data were described as mean  $\pm$  standard deviation, median (interquartile range), or frequencies. Pearson chi-square and Fischer's exact tests were used as appropriate. The accepted level of significance for the probability of error of the first order was .05.

## RESULTS

### General Findings

Table 1 shows the subgroup distribution of 75 patients (56% male) included in the study, according the Barkovich 2012 classification.

Of the total participants, 24 patients (32%) had focal, 26 patients (34.7%) hemispheric/multilobar, and 25 patients (33.3%) diffuse involvement. Presentation age was between 0.1 and 140 months (mean 14.7 ± 27.9, median 27.9 months). Follow-up time was mean 65.4 ± 57.8, median 57.8 months.

### Seizure-EEG Findings

Fifty-six patients (74.7%) had seizure history. The seizure was the presenting symptom in 37 patients (49.3%). Seizure onset age was between 0.1 and 156 months (mean 21.4±35.9, median 5.5 months). In microcephaly, tuberous sclerosis (TS), lissencephaly, and polymicrogyria (PMG), the age of seizure onset was below 12 months in at least 70%; while in 75% of schizencephaly it was over 12 months. Seizures started earlier than 12 months in diffuse pathologies compared to focal lesions ( $P = .023$ ) (Table 2). Mean seizure age was 19.5 months in focal lesions and 4.5 months in diffuse lesions ( $P = .045$ ).

Twenty-nine patients out of 56 (51.8%) with seizure history had daily seizures. During follow-up, change in seizure type or new seizure type developed in 30 patients (53.6%). The most frequently seen seizure types at presentation were focal (21/56, 37.5%), epileptic spasm (18/56, 32.1%), and generalized (17/56, 30.4%), respectively. During follow-up, the most commonly seen seizures were dyscognitive/behavioral arrest type seizures (25/56–44.6%), epileptic spasms (23/56–41.1%), and generalized tonic–clonic (17/56, 30.4%) seizures (Table 3). Generalized tonic–clonic seizures were less frequent in premigrational group ( $P = .038$ ). Epileptic spasm frequency was low in focal lesions ( $P = .022$ ).

Seventy-three patients had EEG recordings (57 had 2 EEG recordings, 16 had 1 EEG recording). Mean age for first EEG

was 45.3 ± 53.1 (median 17 months). The mean age for the second EEGs was 81.9 ± 58.7 (median 77 months). The mean time between EEG recordings was 44.0 ± 42.0 months (median 27 months). Analysis showed that 75.3% (55/73) of the first EEG results and 89.5% (51/57) of the second EEG results were pathologic. In the first EEG records, the rate of epileptic+non-epileptic disorder was highest in microcephaly with 80% (8/10) (Table 4).

Less than 50% seizure control was achieved in 28 patients (50%), 50–100% in 20 patients (35.7%), and 100% in 8 patients (14.3%). There was no significant difference between groups in seizure control (Table 5). Seventeen patients were given monotherapy (30.4%), 39 patients polytherapy (69.6%), 2 patients ketogenic diet (3.6%), and 4 patients (7.1%) underwent epilepsy surgery. The case with TS on ketogenic diet had a history of daily seizures, and the case with PMG at least once a week. Both cases were receiving polytherapy, and seizure control was between 50–100% after treatment for both. Two of the patients who underwent epilepsy surgery were diagnosed as TS, the other patients had focal cortical dysplasia (FCD) and hemimegalencephaly (HMG). All of the patients mentioned above had a history of daily seizures and were receiving polytherapy. After surgery, seizure control was below 50% in the case with FCD, 100% in the case with HMG, between 50–100% in one patient with TS, and 100% in the other.

### Neurodevelopmental Characteristics

Gross motor function evaluation revealed that being bedridden was 63.6% in lissencephaly, 54.5% in microcephaly, and 5.6% in TS. Ambulation frequency was low in diffuse pathologies ( $P < .001$ ) (Table 6).

In all, 95.1% of patients showed retardation in at least one part of DDST-II/Bayley-III, and 64.8% showed mental retardation in WISC-R. There was no statistically significant difference in

Types of Cortical Developmental Malformation	Number (n)	Percent (%)
Premigrational malformations (Type 1)	33	44.0
Tuberous sclerosis	18	24.0
Microcephaly	11	14.7
Focal cortical dysplasia	2	2.7
Hemimegalencephaly	1	1.3
Diffuse cortical dysgenesis	1	1.3
Migrational malformations (Type 2)	13	17.3
Lissencephaly	11	14.7
Heterotopia <sup>a</sup>	2	2.7
Postmigrational malformations (Type 3)	29	38.7
Polymicrogyria	18	24.0
Schizencephaly	11	14.7
Total	75	100.0

<sup>a</sup>Anterior predominate and diffuse periventricular nodular heterotopia.

	Seizure Onset Time (Month) <sup>a</sup>	
	<12 Months n (%)	Cases 12 Months and Older n (%)
Cases with seizures	39 (69.7)	17(30.3)
Developmental main groups		
Type 1 (n = 27)	22 (81.4)	5 (18.6)
Type 2 (n = 11)	7 (63.7)	4 (36.3)
Type 3 (n = 18)	10 (55.6)	8 (44.4)
CDM subgroups (n = 51)		
Microcephaly (n = 8)	6 (75.0)	2 (25.0)
TS (n = 15)	13 (86.6)	2 (13.4)
Lissencephaly (n = 10)	7(70.0)	3 (30.0)
Schizencephaly (n = 8)	2 (25.0)	6 (75.0)
PMG (n = 10)	8 (80.0)	2 (20.0)
Lesion involvement <sup>b</sup> (n = 56)		
Focal (n = 16)	7 (43.8)	9 (56.2)
Hemispheric/Multilobar (n = 20)	15 (75.0)	5 (25.0)
Diffuse (n = 20)	17 (85.0)	3 (15.0)

TS, tuberous sclerosis; PMG, polymicrogyria.  
<sup>a</sup>Line percent; <sup>b</sup>Fisher's exact test;  $P < .05$ .

**Table 3.** Distribution of Seizure Types of the Cases

	Focal			Evolving to Bilateral Convulsive Seizure n (%)	Generalized						
	Focal Motor n (%)	Dyscognitive/Behavioral Arrest n (%)			Absence n (%)	Myoclonic n (%)	Clonic n (%)	Tonic n (%)	Tonic-Clonic n (%)	Atonic n (%)	Epileptic Spasm
<b>Cases with seizures</b>	10 (17.9)	25 (44.6)		5 (8.9)	1 (1.8)	2 (3.6)	1 (1.8)	10 (17.9)	17 (30.4)	2 (3.6)	23 (41.1)
<b>Developmental main groups</b>											
Type 1 (n = 27)	3 (11.1)	16 (59.3)		3 (11.1)	1 (3.7)	1 (3.7)	1 (3.7)	3 (11.1)	4 (14.8)	1 (3.7)	14 (51.9)
Type 2 (n = 11)	2 (18.2)	3 (27.3)		1 (9.1)	0 (0.0)	1 (9.1)	0 (0.0)	4 (36.4)	4 (36.4)	0	4 (36.4)
Type 3 (n = 18)	5 (27.8)	6 (33.3)		1 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)	3 (16.7)	9 (50.0)	1 (5.6)	5 (27.8)
<b>CDM subgroups (n = 51)</b>											
Microcephaly (n = 8)	0 (0.0)	2 (25.0)		1 (12.5)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (62.5)
TS (n = 15)	2 (13.3)	10 (66.7)		0 (0.0)	1 (6.7)	0 (0.0)	1 (6.7)	2 (13.3)	3 (20.0)	1 (6.7)	9 (60.0)
Lissencephaly (n = 10)	2 (20.0)	2 (20.0)		0 (0.0)	0 (0.0)	1 (10)	0 (0.0)	4 (40.0)	4 (40.0)	0 (0.0)	4 (40.0)
Schizencephaly (n = 8)	4 (50)	1 (12.5)		0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	4 (50.0)	0 (0.0)	2 (25.0)
PMG (n = 10)	1 (10.0)	5 (50.0)		1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (20.0)	5 (50.0)	1 (10.0)	3 (30.0)
<b>Lesion involvement<sup>a</sup>(n = 56)</b>											
Focal (n = 16)	4 (25.0)	9 (56.3)		2 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	2 (12.5)	6 (37.5)	1 (6.3)	2 (12.5)
Hemispheric/Multilobar (n = 20)	5 (25.0)	11 (55.0)		1 (5.0)	1 (5.0)	0 (0.0)	1 (5.0)	3 (15.0)	5 (25.0)	1 (5.0)	10 (50.0)
Diffuse (n = 20)	1 (5.0)	5 (25.0)		2 (10.0)	0 (0.0)	2 (10.0)	0 (0.0)	5 (25.0)	6 (30.0)	0 (0.0)	11 (55.0)

TS, tuberous sclerosis; PMG, polymicrogyria

<sup>a</sup>Percentage of cases (line percentage) has been evaluated (total is more than 100%), 1 patient has more than one seizure type, <sup>b</sup>Fisher's exact test; P < .05.

**Table 4.** Distribution of EEG Features

	First EEG (n = 73)					Second EEG (n = 57)					
	Number of Cases with First EEG	Focal/Regional Epileptic Disorder n (%)	Multifocal/Bilateral-Generalized Epileptic Disorder n (%)	Abnormal Non-epileptic Disorder n (%)	Epileptic+Non-epileptic Disorder n (%)	Toni Number of Cases with Second EEG c n (%)	Normal n (%)	Focal/Regional Epileptic Disorder n (%)	Multifocal/Bilateral-Generalized Epileptic Disorder n (%)	Abnormal Non-epileptic Disorder n (%)	Epileptic+Non-epileptic Disorder n (%)
Cases with EEG	73	18 (24.7)	15 (20.5)	7 (9.3)	4 (5.5)	29 (39.7)	6 (10.5)	18 (31.6)	5 (8.8)	6 (10.5)	22 (38.6)
Developmental main groups											
Type 1	32	6 (18.8)	5 (15.6)	6 (18.8)	0 (0.0)	15 (46.9)	4 (14.8)	8 (29.6)	3 (11.1)	2 (7.4)	10 (37.0)
Type 2	13	2 (15.4)	3 (23.1)	0 (0.0)	2 (15.4)	6 (46.2)	0 (0.0)	2 (20.0)	1 (10.0)	1 (10.0)	6 (60.0)
Type 3	28	10 (35.7)	7 (25.0)	1 (3.6)	2 (7.1)	8 (28.6)	2 (10.0)	8 (40.0)	1 (5.0)	3 (15.0)	6 (30.0)
CDM subgroups (n = 51)											
Microcephaly	10	2 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	8 (80.0)	0 (0.0)	1 (12.5)	1 (12.5)	2 (25.0)	4 (50.0)
TS	18	3 (16.7)	5 (27.8)	5 (27.8)	0 (0.0)	5 (27.8)	4 (25.0)	7 (43.8)	1 (6.3)	0 (0.0)	4 (25.0)
Lissencephaly	11	1 (9.1)	2 (18.2)	0 (0.0)	2 (18.2)	6 (54.5)	0 (0.0)	1 (11.1)	1 (11.1)	1 (11.1)	6 (66.7)
Schizencephaly	11	5 (45.5)	2 (18.2)	0 (0.0)	1 (9.1)	3 (27.3)	1 (14.3)	2 (28.6)	0 (0.0)	2 (28.6)	2 (28.6)
PMG	17	5 (29.4)	5 (29.4)	1 (5.9)	1 (5.9)	5 (29.4)	1 (7.7)	6 (46.2)	1 (7.7)	1 (7.7)	4 (30.8)
Lesion involvement <sup>b</sup> (n = 56)											
Focal	23	7 (30.4)	5 (21.7)	3 (13.0)	2 (8.7)	6 (26.1)	1 (7.1)	6 (42.9)	2 (14.3)	2 (14.3)	3 (21.4)
Hemispheric/Multilobar	26	6 (23.1)	6 (23.1)	4 (15.4)	0 (0.0)	10 (38.5)	4 (17.4)	8 (34.8)	3 (13.0)	1 (4.3)	7 (30.4)
Diffuse	24	5 (20.8)	4 (16.7)	0 (0.0)	2 (8.3)	13 (54.2)	1 (5.0)	4 (20.0)	0 (0.0)	3 (15.0)	12 (60.0)

TS, tuberosus sclerosis; PMG, polymicrogyria.

<sup>a</sup>Fisher's exact test.

**Table 5.** Distribution of Seizure Control

	Seizure Control		
	<50% n (%)	50-100 n (%)	100% n (%)
Developmental main groups <sup>a</sup> (n = 56)			
Type 1 (n = 27)	11 (40.7)	11 (40.7)	5 (18.5) <sup>b</sup>
Type 2 (n = 11)	8 (72.7)	2 (18.2)	1 (9.1) <sup>c</sup>
Type 3 (n = 18)	9 (50.0)	7 (38.9)	2 (11.1)
CDM subgroups(n = 51)			
Microcephaly (n = 8)	4 (50.0)	4 (50.0)	0 (0.0)
TS (n = 15)	6 (40.0)	6 (40.0)	3 (20.0)
Lissencephaly (n = 10)	8 (80.0)	2 (20.0)	0 (0.0)
Schizencephaly (n = 8)	3 (37.5)	5 (62.5)	0 (0.0)
PMG (n = 10)	6 (60.0)	2 (20.0)	2 (20.0)
Lesion involvement <sup>a</sup> (n = 56)			
Focal (n = 16)	7 (43.8)	6 (37.5)	3 (18.8)
Hemispheric/Multilobar(n = 20)	9 (45.0)	8 (40.0)	3 (15.0)
Diffuse (n = 20)	12 (60.0)	6 (30.0)	2 (10.0)

TS, tuberous sclerosis; PMG, polymicrogyria.  
<sup>a</sup>P > .05 <sup>b</sup>1 case is hemimegalencephaly, 1 case is focal cortical dysplasia, <sup>c</sup>1 case is heterotopia.

DDST-II/Bayley-III results between the groups. However, there was a significantly high number of patients for whom WISC-R could not be applied in the diffuse pathologies group (85.7%) (P = .018) (Table 7).

Out of 56 patients with seizure history, DDST-II/Bayley-III was administered to 28 patients and WISC-R was administered to 28 patients. Patients with normal/retardation in only one level (3 patients) had seizures less frequent than once a month, however retardation in more than one level or patients unable to take any test 64% (16/25) had seizures daily, 4% (1/25) had weekly seizures (P < .05). In the study, 66.7% (6/9) of patients with borderline-low normal-normal intelligence group in WISC-R had seizure frequency less than once a month, whereas 62.5% of the group with mental retardation (mild-moderate-severe) and 63.6% (7/11) of the group unable to take WISC-R had daily seizures (P < .05).

Polytherapy was the treatment modality in 100% of the group (11/11) unable to take any test, 62.5% (5/8) of the

mild-moderate-severe mental retardation group, and 22.2% (2/9) of borderline-low normal-normal group in cases above 6 years of age evaluated by WISC-R (P = .01). When treatment response was compared with WISC-R results, 54.5% of patients were unable to take any test, and 75% of the patients with mild-moderate-severe mental retardation had less than 50% seizure control, but seizure control was above 50% in all patients with borderline-low normal-normal intelligence level (P = .04).

**DISCUSSION**

Cortical developmental malformations of the cerebral cortex are among the important causes of mental retardation, epilepsy, and sensory-motor deficit in childhood. They are formed as a response of the brain to genetic and environmental factors in the fetal or perinatal period. While severe forms are incompatible with life, there is clinical heterogeneity in individual survivors.<sup>1-3</sup>

**Table 6.** Gross Motor and Functional Evaluation of the Cases

	Gross Motor and Functional Evaluation <sup>a</sup>		
	Confined to Bed n (%)	Only Sitting n (%)	Ambulatory n (%)
All Cases	21 (28.0)	12 (16.0)	42 (56.0)
Developmental main groups (n = 69)			
Microcephaly (n = 11)	6 (54.5)	2 (18.2)	3 (27.3)
TS (n = 18)	1 (5.6)	1 (5.6)	16 (88.9)
Lissencephaly (n = 11)	7 (63.6)	1 (9.1)	3 (27.3)
Schizencephaly (n = 11)	3 (27.3)	1 (9.1)	7 (63.6)
PMG (n = 18)	3 (16.7)	5 (27.8)	10 (55.6)
Lesion involvement (n = 75) <sup>b</sup>			
Focal (n = 24)	3 (12.5)	6 (25.0)	15 (62.5)
Hemispheric/ Multilobar (n = 26)	3 (11.5)	1 (3.8)	22 (84.6)
Diffuse (n = 25)	15 (60.0)	5 (20.0)	5 (20.0)

TS, tuberous sclerosis; PMG, polymicrogyria.  
<sup>a</sup>Line percent; <sup>b</sup>Fisher's exact test; P < .001.

**Table 7.** Distribution of WISC-R Results of the Cases

	WISC-R <sup>a</sup>		
	Mild-Medium-Severe Mental Retardation n (%)	Borderline-Low Level-Normal n (%)	Level Too Low to Be Evaluated n (%)
Lesion involvement <sup>b</sup> (n = 41)			
Focal (n = 14)	6 (42.9)	5 (35.7)	3 (21.4)
Hemispheric/Multilobar (n = 13)	6 (46.2)	5 (38.5)	2 (15.4)
Diffuse (n = 7)	0 (0.0)	1 (14.3)	6 (85.7)

<sup>a</sup>Line percent; <sup>b</sup>Fisher's exact test; *P* < .05.

With the improvements in molecular biology, genetic and imaging techniques, the number of patients diagnosed with CDM has increased. Revised classification in 2012 is based on neural and glial proliferation, neuronal migration, and cortical organization processes.<sup>4</sup> It has been emphasized that this classification could only be an intermediate system to help form a new classification based on specific gene mutations and protein functions involved.<sup>4,20,21</sup> Guerrini and Dobyns (2014) made a separate classification proposal based on the molecular pathway, showing that megalencephaly with normal cortical tissue, PMG-associated megalencephaly, and dysplastic megalencephaly (classical hemimegalencephaly) are due to the same gene mutations in the PI3K-AKT pathway, and some subgroups were examined under the heading, as in the example.<sup>22</sup>

#### Evaluation of the Demographic and Clinical Features of the Cases

In our study of 75 patients with CDM, 44% were premigrational, 17.3% migrational, and 38.6% postmigrational. In the literature, CDM subgroups and cortical lesion involvement differ according to chosen case groups and frequencies in studies. Migrational malformation rate in our study is lower than in the literature.<sup>5,23-32</sup>

Fifty-six percent of the patients were male, which is consistent with pediatric literature from our country.<sup>5,29,33,34</sup> In studies including pediatric populations, gender difference has not been noted. However, in adult studies, due to high mortality of X-linked inheritance in males, female predominance is reported.<sup>22,23,25,32,35</sup>

It is known that CDM show symptoms earlier among all CNS developmental malformations.<sup>5,26,36-38</sup> Age at presentation in our study was 0.1-140 months (mean 14.7±27.9, median 27.9 months).

#### Evaluation of Seizure and EEG Features of the Cases

A relation has been shown between CDM and epilepsy after clinical, experimental, neuropathological studies and EEG-radiological evaluations. Seizures result from abnormal location of normal cortical neurons or directly from abnormal neurons.<sup>26,39</sup> Although CDM are among the common reasons of severe intractable epilepsy, the real prevalence of epilepsy is still unknown.<sup>5,26,29,32,35,39,40</sup> It is also known that there are cases without epilepsy as well.<sup>5</sup> In our study, epilepsy was present in 74.7% of the population and 49.3% had seizure history at presentation. This rate is given as 40% to 61.4% in the literature.<sup>5,28-30,35</sup>

In our study, mean age of seizure onset was 21.4±35.9 months (median 5.5 months), and in 70% of the patients with epilepsy,

seizures started within the first year of life. Seizure onset age in CDM has been reported as 9.6-32.4 months in pediatric studies.<sup>5,30,32,41</sup> Differing from the literature, we included the microcephaly group in our study. Similar to our study, Yvette de Wit et al.<sup>41</sup> included the same group. They found the median age of seizure onset in microcephalic patients in the CDM study as 2.4 months, which was lower than other groups. According to Barkovich, classification microcephaly group has a broad spectrum of clinical presentation, from small head circumference and mild developmental delay alone to severe motor findings and neonatal epilepsy.<sup>4</sup> For this reason, more comprehensive studies are needed with greater number of patients from each group to compare clinical presentations of microcephalies. Median age of seizure onset was higher in focal lesions compared to hemispheric/multilobar or diffuse pathologies. It is known that clinical and seizure prognosis of unilateral schizencephalies is better compared to lissencephaly and other diffuse involvement types of polymicrogyrias, and seizures generally start after 2-3 years of life with very rare presence at neonatal period in focal cortical dysplasias.<sup>29,42</sup>

More than half of the patients in our study had daily seizures; similarly, in more than half of the patients, seizure type had changed or new seizures had developed during follow-up. Although the difference in seizure types has not been reported in major groups of CDM in the literature, generalized tonic-clonic seizures were less frequent in the premigrational group (*P* = .038).<sup>23,24</sup> Epileptic spasm frequency during follow-up was lower in focal pathologies compared to hemispheric/multilobar and diffuse pathologies. In the literature, epileptic spasms are more commonly reported in TS with hemispheric/multilobar involvement and diffuse malformations like lissencephaly due to early presentation age of seizures, as found similarly in our study.<sup>4,29,43</sup>

In our study population, 30.4% of the patients were on monotherapy, and 69.6% were on polytherapy. Polytherapy frequency was higher in intractable patients with less than 50% seizure control. In CDM, it can be predicted that resistance to monotherapy would most probably end with resistance to polytherapy as well. Intractable epilepsy frequency was 92% in our study; in the literature, 40% of children with intractable epilepsy have been diagnosed with CDM.<sup>36</sup>

Abnormality was seen in 75.3% of basal EEG recordings (69.5% with epileptic potentials) and 89.5% of the second EEG recordings (79% with epileptic potentials). This rate is between 54% to 93.5% in the literature.<sup>5,23,25,29,35</sup> For 41.1% of patients without seizure history, EEG findings were abnormal in our study, whereas it is reported as 45% to 67% in the literature.<sup>5,35</sup> According

to this information, we can conclude that EEG recording should be performed despite an absence of seizure history. Abnormal EEG frequency of basal EEG recordings was higher in the microcephaly group compared to other CDM subgroups. This could be interpreted as more severe EEG findings in the group with younger seizure onset age. EEG findings of TS have been reported as irregular slow waves with focal/multifocal spikes.<sup>44</sup> In our series, more than half of the basal and second EEG recordings of TS group were focal and multifocal epileptiform anomalies that were consistent with the literature.<sup>1,5,45-47</sup> The lissencephaly group had the most common epileptic and non-epileptic disorder of basal EEG after microcephaly, and in the second EEG recordings as well, and although there was no significant distribution between the subgroups, the most severe EEG findings were in cases of lissencephaly. The schizencephaly group had the highest rate of normal basal EEG findings. This could be interpreted as being due to the fact that more than 80% of schizencephaly cases in our study were focal, and seizure onset age was relatively late. EEG findings of PMG varied depending on lesion involvement, and they were mostly generalized sharp and slow waves, with multifocal discharges, and irregularities in background reported in the literature.<sup>46</sup> In our study, depending on the extension and location of the lesions, one-third of the population had focal epileptiform activity and one-third had epileptic/non-epileptic EEG anomalies.

#### Evaluation of the Neurodevelopmental Features of the Cases

Of the patients in our study, 44% were nonambulatory and nearly one-third were bedridden. Yimenicioglu et al.<sup>26</sup> reported the most severe gross motor function retardation in CDM among CNS malformations. Considering types including schizencephaly, which only present with partial seizure relatively late in adulthood,<sup>29</sup> we can conclude that generally CDM have severe motor retardation but there are variations according to subtypes and lesion involvement. In accordance with the literature, being bedridden was commonly seen in lissencephaly, which constitutes most of diffuse pathologies, followed by microcephaly; this rate was the lowest at 5% in TS patients, which constitute most of the multilobar pathologies.<sup>26</sup>

We found developmental delay at least at 1 level, at 95.1%, and at 2 or more levels, at 87.8%, using the DDST-II/Bayley-III in our study group of CDM. The developmental delay has been evaluated more by history and physical examination in CDM studies, and its occurrence has been reported as 10-55.6% in the adult group and 70-89% in the pediatric population.<sup>24-26,28,30,35</sup> The explanation for this difference could be that the most severe forms of CDM most probably do not survive to adult age. Sadek et al.<sup>35</sup> commented that in developing countries like Egypt, because of the limited availability of radiologic opportunities, mild cases are more likely to be missed, and explained the 10% difference in the study by Raymond et al.,<sup>25,35</sup> in England, with this theory. In our study, neurodevelopmental delay severity was correlated with seizure frequency, and 65% of the patients with the most severe retardation had daily seizures. It can be predicted that severe growth retardation may accompany the clinical findings in CDM with resistant epilepsy and frequent seizures.

We detected mental retardation at different levels by WISC-R in 65% of the patients. This ratio has been reported as 68-89% in the

pediatric population and 9-69% in adult studies.<sup>5,23-26,28</sup> Similar to the Bayley-III/DDST-II results, intelligence scores are lower in the pediatric group compared to adults. In our study, mental retardation severity/frequency were highly correlated with diffuse pathologies, high seizure frequency, polytherapy, and intractable epilepsy. Gungor et al.<sup>5</sup> reported results similar to our study and commented that this could be either a result of severity of the malformation or loss in cognitive functions due to frequent severe seizures. Although it is stated that findings related to mental development in CDM vary from normal intelligence or mild learning disabilities to severe mental retardation, it has been emphasized that diffuse pathologies have poor verbal and performance IQ prognosis compared to those with focal lesions, in terms of intelligence.<sup>5,48</sup> There was no patient with normal intelligence in the diffuse pathologies group in our study, and 85.7% of the patients who could not cooperate with the test had diffuse pathologies.

The retrospective nature, the small number of subgroups, and classification of seizure types according to ILAE 2010 terminology are the limitations of our study.

## CONCLUSION

The results of our study show that CDM occurs with a broad spectrum of clinical presentations according to embryology, involvement level, and distribution. Genetic-neuroradiological developments and determination of cellular pathways that play a role in the pathophysiology of CDM will be a guide to determine the phenotypic findings specific to the malformation type, classification strategy, and treatment methods.

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