

Clinical, Neuroradiological and Electroencephalographic Findings of Epileptic Patients with Malformation of Cortical Development



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Epilepsi ve Kortikal Gelişimsel Malformasyonu Olan Hastaların Klinik, Nöroradyolojik ve Elektroensefalografik Bulguları

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Summary

Objectives: We aimed to review the clinical, neuroradiological and electroencephalographic (EEG) findings of patients with epilepsy and malformation of cortical development (MCD).

Methods: A retrospective analysis of the medical records of epilepsy outpatients was done. Patients with epilepsy, MCD, and ≥ 18 years of age were included and classified according to the Barkovich classification (BC).

Results: The files of 2027 patients were assessed, and 17 out of 1395 epilepsy patients who were followed-up were found to have MCD. The mean age was 26.5 years. Ten patients were male and 7 were female. The mean time of seizure onset was 13 years. In terms of seizure type, 11 patients had focal, 10 had generalized tonic-clonic, 1 had absence, 1 had tonic-atonic, and 1 had myoclonic. MRI showed 7 patients with cortical dysplasia, 4 with heterotopia, 2 with periventricular nodular heterotopia, 2 with schizencephaly, 2 with lissencephaly, 1 with agyria, 1 with pachygyria, 1 with macrogyria, 1 with polymicrogyria, and 1 with tuberous sclerosis. EEG revealed focal epileptiform discharges in 5 patients, high-frequency activity in 2, generalized epileptiform discharge in 1, diffuse disorganized background activity in 1, and focal disorganized background activity in 1. EEG was normal in 7 patients. Four of them were on monotherapy and 13 on polytherapy.

Conclusion: The MCDs classified in group 1 and 2 according to BC are more frequent. Treatment-resistant or good responsive cases can be seen and seizures can begin at any age. We concluded that the prevalence of MCD is 1.21%. The spectrum of epilepsy seen is extensive and the most common type of MCD is focal cortical dysplasia.

Keywords: Epilepsy; malformation of cortical development; polytherapy.

Özet

Amaç: Epilepsi ve kortikal gelişimsel malformasyonu (KGM) olan hastaların klinik, nöroradyolojik ve elektroensefalografik (EEG) bulgularını gözden geçirmektir.

Gereç ve Yöntem: Epilepsi polikliniği tıbbi kayıtları geriye dönük olarak incelendi. Epilepsi, KGM ve yaşı ≥ 18 olan hastalar dahil edildi ve hastalar Barkovich sınıflamasına (BC) göre gruplandırıldı.

Bulgular: İki bin yirmi yedi hasta dosyası incelendi. Takibe devam eden ve epilepsi tanısı konan 1395 olgunun 17'sinde KGM saptandı. Hastaların yaş ortalaması 26.5 yıl idi. Hastaların 10'u erkek, yedisi kadındı. Nöbet başlangıç yaşları ortalaması 13 yıl idi. Olguların 11'inde fokal, 10'unda jeneralize tonik klonik (JTKN), birinde absans, birinde tonik-atonik, birinde miyoklonik nöbet saptandı. MRG'de yedi hastada kortikal displazi, dört hastada heterotopi, iki hastada periventriküler noduler heterotopi, iki hastada şizensefali, iki hastada lizensefali, bir hastada Tuberöler skleroz, bir hastada agiri, bir hastada pakigiri, bir hastada makrogiri, bir hastada polimikrogiri vardı. EEG'leri değerlendirildiğinde beşinde fokal epileptiform deşarj, ikisinde hızlı ritim, bir hastada jeneralize epileptiform deşarj, bir hastada fokal organizasyon bozukluğu, bir hastada yaygın organizasyon bozukluğu, görülmüştür. Yedi hastanın EEG'leri normaldi. Hastaların üçü monoterapi, 14'ü politerapi altında idi.

Sonuç: BC'ye göre grup 1 ve 2'ye giren KGM'lere daha sık rastlanmaktadır. Tedaviye dirençli veya iyi cevap veren olgular görülebilir ve nöbetler her yaşta başlayabilir. Prevalans %1.21 bulundu. Görülen epilepsi spektrumu geniştir ve en sık karşılaşılan KGM tipi fokal kortikal displazidir.

Anahtar sözcükler: Epilepsi; kortikal gelişimsel malformasyon; politerapi.

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Introduction

In the developing brain tissue, an interruption in the neuronal or glial proliferation, migration, and organization constitute malformations of cortical development (MCD). MCD is being recognized as an important underlying cause of developmental delay, epilepsy, and other neurological disorders in human beings. The incidence of cerebral cortical developmental abnormalities is not known exactly but the frequency of MCD is thought to be 1/100 000.^[1]

Development of the central nervous system, between the 2nd month and the perinatal period of pregnancy, requires the completion of many complex cellular processes. Any failure of this mechanism results in the development of some malformations. The most recent developmental event is myelination, which lasts until adulthood.^[2] The exact cause of MCD is unknown but consideration of genetic and environmental factors is important. Many people being affected in the same family has led to the idea that genetic factors may be involved in the etiology of MCD.

In recent years, genetic defects (LIS1, DCX, RELN, ARX, 14-3-3E, EMX2, POMT1, etc.) have been reported in some patients.^[3-5] Environmental factors such as placental ischemia, intrauterine CMV infection, ionizing radiation, CO poisoning, and early gestational bleeding seriously affect neuronal migration.^[6-8] Apart from prenatal events, there is information that neonatal periventricular hemorrhage and early postnatal traumas also cause dysplastic lesions.^[9,10]

Materials and Methods

Design

We conducted a retrospective analysis of the medical records of patients from the epilepsy outpatient clinic who were followed-up between July 1995 and January 2015.

Sample

Patients who had epilepsy and radiological diagnosis of MCD on their MRI and who were ≥ 18 years of age were included in the study. Patients whose diagnosis was in doubt were excluded. MRI scans had been done with a 1.5 T scanner which included standard 3-D (sagittal, axial and coronal) images. MRI studies included conventional T1/T2-weighted studies, inversion recovery, and fluid-attenuated inversion recovery acquisitions.

Analysis

Current patient age, seizure onset age, type of epilepsy, use of anticonvulsant drugs, EEG and MRI findings, family history, and other pathologies were assessed.

Patients were classified into 3 main groups according to the Barkovich classification (BC): "Malformations due to abnormal cell proliferation" (G1), "Malformations due to abnormal migration" (G2), and "Malformations due to abnormal cortical organization" (G3).^[11,12]

Method of evaluation

Mean values of age and time of seizure onset were calculated. The type of MCD and associated age of seizure onset, seizure frequency, and used drugs were presented. The results were compared with past literature.

Results

The files of 2027 patients were assessed, and 17 out of 1395 epilepsy patients who were followed-up were found to have MCD. The mean age was 26.5 years (range: 18–54 years). Ten patients were male and 7 were female. The mean time of seizure onset was 13 years (range: 3 months–22 years).

Detailed information about the patients is shown in Table 1. In terms of seizure type, 11 patients had focal, 10 had generalized tonic-clonic, 1 had absence, 1 had tonic-atonic, and 1 had myoclonic. Syndromic classification revealed 12 patients with symptomatic focal epilepsy, 3 with symptomatic generalized epilepsy, 1 with Dyke-Davidoff syndrome, and 1 with juvenile myoclonic epilepsy (JME) phenotype.

MRI showed that 7 patients had cortical dysplasia, 5 had heterotopia, 2 had periventricular nodular heterotopia (Fig. 1), 2 had schizencephaly, 2 had lissencephaly, 1 had agyria, 1 had pachygyria, 1 had macrogyria, 1 had polymicrogyria (Fig. 2), and 1 had tuberous sclerosis. There were also some patients who had more than one MCD subtype.

EEG revealed focal epileptiform discharges in 5, high-frequency activity in 2, generalized epileptiform discharge in 1, focal disorganized background activity in 1 and diffuse disorganized background activity in 1. The EEG was normal in 7 patients.

Table 1. Detailed information about the patients

Patient	Patient malformation	Age of seizure onset	Frequency of seizure	Type of seizure	Drugs	EEG findings
1	Heterotopia (G2A)	13 years	3-4 times in a week	FS\GTCS	Valproic acid	FED
2	Cortical dysplasia (G1)	19 years	No seizure for 13 years	FS	Carbamazepine	Normal
3	Lissencephaly (G2B) Agyria, pachygyria	10 months	Once in 2 months	FS\GTCS\tonic- atonic S.	Carbamazepine Topiramate Pregabalin	HFA
4	Lissencephaly (G2B) Macrogyria	20 years	Once in a month	GTCS	Valproic acid Levetiracetam	HFA
5	Cortical dysplasia (G1)	16 years	1-2 times in a year	GTCS\myoclonic S	Valproic acid Levetiracetam	Normal
6	Cortical dysplasia (G1)	3 years	3-4 times in a year	FS\GTCS	Levetiracetam	Normal
7	Periventricular nodular Heterotopia (G2A)	21 years	2 times in a week	FS	Carbamazepine Topiramate	Normal
8	Heterotopia (G2A), Schizencephaly (G3A)	3 years	3-4 times in a day	FS\GTCS	Valproic acid Levetiracetam Topiramate	FED
9	Cortical dysplasia (G1)	20 years	Once in 2 months	FS	Carbamazepine Levetiracetam	Normal
10	Polymicrogyria (G3A)	1 years	2-3 times in a week	FS	Valproic acid Levetiracetam Carbamazepine	FED
11	Heterotopia (G2A)	14 years	Once in a week	GTCS	Carbamazepine Lamotrigine	GED
	Heterotopia (G2A), Schizencephaly (G3A)	18 years	Once in a week	GTCS	Levetiracetam Lamotrigine	GDBA
	Tuberous sclerosis (G1) Heterotopia (G2A)	22 years	Once in a month	FS	Valproic acid Levetiracetam	FDBA
	Periventricular nodular Heterotopia (G2A)	3 months	5-6 times in a month	FS	Topiramate Vigabatrin	FED
	Cortical dysplasia (G1)	13 years	Once in a month	FS	Carbamazepine	Normal
	Cortical dysplasia (G1)	20 years	2-3 times in a day	FS	Valproic acid Levetiracetam Carbamazepine	FED
	Cortical dysplasia (G1)	17 years	3-4 times in a year	GTCS\absence S.	Valproic acid	Normal

MCD subtype according to BC scheme, Group 1(G1): "Malformations due to abnormal cell proliferation"; Group 2 (G2): "Malformations due to abnormal migration", and Group 3 (G3): "Malformations due to abnormal cortical organization" G2A: Group 2A; G2B: Group 2B; G3A: Group 3A; G3C: Group 3C; S: Seizure; FS: Focal seizure; GTCS: Generalized tonic clonic seizure; FED: Focal epileptiform discharges; GED: Generalized epileptiform discharges; HFA: High frequency activity; FDBA: Focal disorganized background activity; DDBA: Diffuse disorganized background activity.

Mental retardation was present in 5 patients and autism was seen in 2.

Family history of epilepsy was present in 8 patients, consanguinity in 5, head trauma in 2, and history of difficulty during delivery in 1.

Four patients were on monotherapy but 13 of them were on polytherapy.

Discussion

Reviewing clinical, neuroradiological and electroencephalographic (EEG) findings of patients with epilepsy and MCD was the aim of this study. Although the true prevalence of MCD in patients with epilepsy is not known, our study revealed a prevalence of 1.21%. It was found to be 3% in the prospective study of Everitt et al.^[13] In the study by Papayannis et al.,^[14] where all patients had MRI scans with a

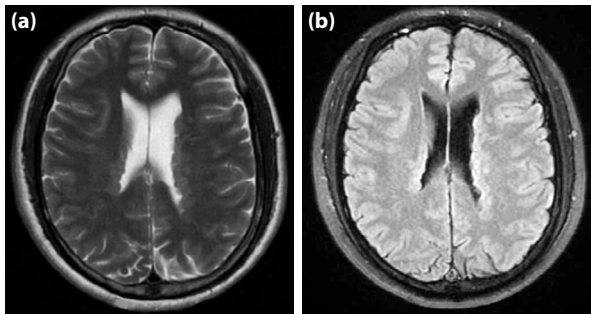


Fig. 1. (a, b) Periventricular nodular heterotopia areas are seen in the neighborhood of both lateral ventricles (this patient showed normal EEG with focal seizures).

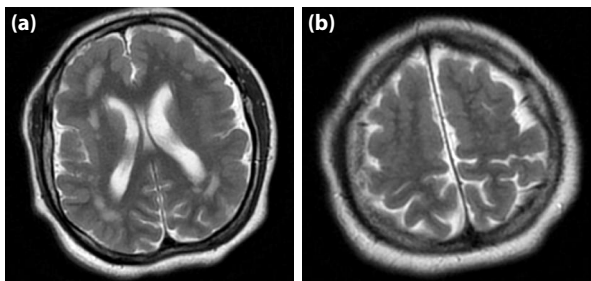


Fig. 2. (a, b) At the level of bilateral frontoparietal lobes, cortical irregularity, irregularity in cortical gray-white matter region, and small irregular gyrus occurrences were evaluated as polymicrogyria. T2A and FLAIR series was seen in the subcortical white matter of frontoparietal regions as multiple, focal, small, longitudinal and ovoid hyperintensities without sharp borders (this patient showed focal epileptiform discharges on EEG and had focal seizures).

3.0 T or 1.5 T, there were 152 (5.06%) cases with MCD from a total of 3000 patients with epilepsy. The prevalence of MCD could differ between different countries due to the social conditions of study populations, use of low-high resolution magnetic resonance imaging techniques, and ages of the study populations.

Many different classification systems for MCD and focal cortical dysplasia (FCD) have been introduced to date. Taylor et al.^[15] first described FCD in patients with drug-resistant epilepsy who underwent surgical resection in 1971. Mischel et al.^[16] proposed a neuropathologic grading system including balloon cells, heterotopia, polymicrogyria, neurons in the molecular layer, and cortical disorganization in 1995. Barkovich et al. described a classification system for MCD according to MRI analysis in 1996 and 2005. In many epilepsy centers, the Barkovich classification is widely used. One of the leading classification systems used for focal cor-

tical dysplasia is the Palmini classification of FCD (based on histopathologic findings) published in 2004, recently replaced by a newer classification, the Blümcke^[17] classification of focal cortical dysplasia in 2011. This system reviews the clinical, imaging, genetic, and especially histopathologic understanding of FCDs. The classification supported by ILAE and written by Task Force commissions was not used in our study because it required histopathologic data and included only FCD.

Barkovich et al.^[11,12] presented an updated version of the developmental and genetic classification of MCD in 2012. A detailed assessment of MRI features allowed us to classify participants based on MCD subtype into 3 groups as they are easier to detect by MRI. In our study, the histopathologic data of patients after surgery were not available because the patients that we thought suitable for surgery were directed to the relevant centers. The distribution of our patients according to BC was as follows: 8 patients (47.1%) were in group 1, 9 patients (53%) in group 2, and 3 patients (17.6%) in group 3. Group 1 was diagnosed as having FCD and tuberous sclerosis. Group 2 included patients with periventricular nodular heterotopia (PNH), subcortical heterotopia, mixed forms of heterotopia, and lissencephaly. Group 3 included cases with polymicrogyria (PMG) and schizencephaly. In their study, Papayannis et al.^[14] found the distribution of cases according to the BC was: 51.4% in group 1, 28.9% in group 2 and 19.6% in group 3. Liu et al.^[18] revealed that 29% of their patients were classified in group 1, 41% in group 2, and 24% in group 3. Gestational and perinatal insults in different countries vary. Also, the number and age of population included in the studies affect the distribution of MCD subtypes. These factors may explain the differences in results between studies. Although the BC allows us to group patients according to MRI findings, certain diagnoses are possible only with histopathologic data.

MCD is often accompanied by epileptic seizures and can be recognized by brain MRI. They can lead to severe epileptic encephalopathies and drug-resistant focal or generalized epilepsy. In the present study, a majority of the seizures were focal. Eleven out of 17 patients in our study had focal seizures.

The spectrum of seizures in patients with MCD is quite variable. Although MCD is the underlying cause of most of the severe and treatment-resistant epilepsy cases in children

and adults, it is possible that patients with MCD do not show resistant epilepsy.^[19] In our study, 11 patients had a seizure frequency of once a month or more. Only 1 patient who had cortical dysplasia had been seizure-free for 13 years with carbamazepine treatment.

The most common type of MCD in this study population was FCD (41.2%). A recent study observed relatively late epilepsy onset in 150 epilepsy patients with MCD in western China and reported that the most common type of MCD was FCD (29%) as well.^[18] According to this study, patients with simple MCD (patients had a deformity of a single characteristic MCD in the absence of other malformations) had lower seizure frequency. The multiple MCD group (patients had MCD associated with additional cerebral malformations) experienced seizures more often. These results were similar to our study. We also observed that patients with multiple malformations had more frequent and antiepileptic drug-resistant seizures. These patients mostly had daily or weekly seizures.

The clinical presentation time of patients with epilepsy could begin at any age but it mostly begins in the first or second decade of life, usually after the age of 2–3 years.^[20] In our study, 5 out of 17 patients had their first seizure at 3 years or younger. The explanation of why 12 out of 17 patients had a seizure onset after 3 years of age could be that most patients with an earlier seizure onset are followed-up by a pediatric neurologist and only some of them survive till adulthood. The mean time of seizure onset was 13 years in our study, which was similar to the study by Papayannis et al. (12.3 years of age).

The patient with the highest seizure onset time in our study, which was at 22 years, had heterotopia and literature also supports us in terms of the clinical age onset of epilepsy in this pathology. Heterotopias are known to have high epileptic potential and can remain silent until adulthood.^[21,22] On the other hand, our patient with the earliest seizure onset time, which was at 3 months, had heterotopia.

As a consequence of the association of MCD with drug-resistant epilepsy, polytherapy is necessary for many patients.^[23] Thirteen of our patients received polytherapy. On the contrary, MCD can sometimes cause late-onset and good drug-responsive seizures. Three of our patients with cortical dysplasia and 1 with heterotopia took monotherapy.

Interestingly, a case of a patient with JME phenotype and MRI-detected FCD has been recorded by Oguni, where he mentioned about difficulties to differentiate idiopathic generalized epilepsies from symptomatic epilepsies and gave an example of a boy 4-year-old who had epilepsy with myoclonic-astatic seizures. His brain MRI showed right FCD and he had clinical and EEG patterns similar to myoclonic-astatic seizures.^[24] On the other hand, Carney et al.^[25] showed 2 patients with absence epilepsy and PNH in their study and investigated whether PNH is associated with absence seizures using EEG-functional MRI. This study demonstrated that the periventricular nodules can show connectivity to the absence network and may be involved in seizure generation. If we could have performed EEG-fMRI to our patient who was diagnosed with JME phenotype and FCD, we would have seen whether FCD was connectivity to the JME network or not.

Scalp EEG in patients with MCD can either be normal or it can show focal or generalized epileptiform discharges, background slowing, or localized high-frequency activity. The most frequent EEG findings in our patients were focal epileptiform discharges and high-frequency activity. Localized high-frequency activity is reported to be associated with some MCDs like cortical dysplasia and lissencephaly.^[22,26] The EEG in 2 of our patients showed high-frequency activity. One of these patients had lissencephaly with agyria and pachygyria complex, and the other one had lissencephaly with macrogyria on MRI.

It is usually difficult to control seizures in patients with MCD. Wide-spectrum antiepileptic drugs such as valproic acid and their combinations are used for drug therapy-resistant cases. Eight patients in our study were taking antiepileptic drugs including valproic acid and its combinations. Most of our patients were under polytherapy. Selected patients can be offered surgical intervention. Patients with some forms of MCD such as polymicrogyria are not good surgical candidates because their condition can be multifocal or bilateral.^[17] A recent study by Pasca et al.^[27] that included 45 patients showed that a ketogenic diet might be effective in reducing seizure frequency in patients with drug-resistant epilepsy and MCD after surgery is deemed not viable. Abnormal neural migration and abnormal post-migrational development had the best response with seizure frequency reduction of >50 % and >64.7%, respectively. Also, a patient with polymicrogyria and a patient with microlissencephaly

remained seizure-free after undertaking a ketogenic diet. In addition, seizure outcome following surgery is variable with seizure-free rates in 30%–90% of MCD series.^[28–30] A study by Radhakrishnan et al.^[31] in which 66.67% of patients were seizure-free after surgery for at least the preceding 2 years, showed that a majority of patients with drug-resistant epilepsy and MCD were seizure-free when operated upon early. Also, a shorter duration of epilepsy was the most important pre-operative variable and absence of spikes in postoperative EEG may also predict a long-term favorable seizure outcome. Based on this information, we thought that it should be emphasized that surgery is preferable in possible patients and the ketogenic diet can be used in patients who are not suitable for surgery.

In the study by Papayannis et al.,^[14] 5.1% of the cases had a family history of epilepsy or other neurological diseases. Interestingly, 8 patients (47.1%) in our study have a family history of epilepsy. The number of patients evaluated in the study should be higher to make an analysis of accompanying disorders and consanguinity in family history.

Limitations

This study was a retrospective evaluation and had its characteristic restrictions. The sample size of the study was very small. It is known that among patients with drug-resistant epilepsy, MCD can be detected in the histopathologic evaluation of some operated patients because the supporting clinical and technical evaluation in the brain MRI is negative, however, there are no negative brain MRI cases in our study. We also do not have the histopathologic data of some patients who were referred to centers of epilepsy surgery. Another limitation of this study is the developing technology. With 3T MRI, the MCD could be visible in epileptic patients as well as a normal 1.5 T MRI study.

Conclusion

In this retrospective hospital-based study, the prevalence of MCD in patients diagnosed with epilepsy was 1.21%. The rate we found was not close to the previous studies^[13,14] which may be a consequence of different study populations and study design. The clinical presentation time of epilepsy in patients with MCD varies considerably. Majority of the seizures were focal and most patients required polytherapy. The most common type of MCD in this study population is FCD and the most frequent EEG findings are focal epileptiform discharges and high-frequency activity.

Peer-review

Externally peer-reviewed.

Conflict of interest

The authors declare that they have no conflict of interest.

Authorship Contributions

Concept: K.T.; Design: K.T., D.B.; Supervision: T.B., H.T.; Materials: D.B., Y.Ç.; Data collection &/or processing: D.B., T.B.; Analysis and/or interpretation: T.B.; Literature search: D.B., K.T.; Writing: D.B., K.T.; Critical review: H.T.

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