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THE CLINICAL SPECTRUM OF MALFORMATIONS OF CORTICAL DEVELOPMENT

Maria Augusta Montenegro[1], Fernando Cendes[2], Iscia Lopes-Cendes[2], Carlos A.M. Guerreiro[3], Li M. Li[2], Marilisa M. Guerreiro[2]*

ABSTRACT - *Background:* Malformations of cortical development (MCD) usually manifest in childhood with epilepsy, developmental delay and focal neurological abnormalities. *Objective:* To evaluate the presentation and severity of epilepsy in the different types of MCD. *Method:* We evaluated the first 100 consecutive patients with a neuroimaging diagnosis of MCD. They were identified among all the high resolution magnetic resonance imaging exams performed at our service between 1997 and 2001. The causes of referral were diverse, according to the routine of the neurology outpatient clinic. After magnetic resonance imaging diagnosis of the subtype of MCD a detailed clinical assessment was performed. *Results:* There were 55 females and 45 males, with ages ranging from five months to 71 years old (mean=15.2 years). Seventy-seven patients presented with epilepsy. Sixty-one had partial epileptic syndromes, 13 secondary generalized syndromes, and in three, the type of epileptic syndrome could not be established. Epilepsy was less frequent in patients with the MCD subtypes of polymicrogyria and schizencephaly ($p<0.001$). Patients with schizencephaly and polymicrogyria had their seizures more easily controlled by antiepileptic drugs ($p<0.001$). *Conclusion:* That the frequency of epilepsy is lower and seizures are more easily controlled in the setting of polymicrogyria and schizencephaly. Patients with MCD frequently present with secondary generalized epilepsy early in childhood.

KEY WORDS: malformations of cortical development, EEG, epilepsy, childhood.

Espectro clínico das malformações do desenvolvimento cortical

RESUMO - *Introdução:* As malformações do desenvolvimento cortical (MDC) geralmente se manifestam na infância, na forma de crises epilépticas, retardo do desenvolvimento neuropsicomotor ou anormalidades focais. *Objetivo:* Avaliar a apresentação clínica e a gravidade da epilepsia nos diferentes tipos de MDC. *Método:* Cem pacientes com diagnóstico de MDC estabelecido por neuroimagem foram avaliados. Os pacientes foram identificados através de exames de ressonância magnética de alta resolução realizados entre 1997 e 2001. As causas para investigação por imagem foram diversas, conforme as indicações de rotina dos ambulatórios de neurologia. Após a determinação do subtipo de MDC, uma avaliação clínica detalhada foi realizada. *Resultados:* Entre os 100 pacientes, 55 eram do sexo feminino e 45 do masculino, com idade variando entre 5 meses e 71 anos (média=15,2 anos). Setenta e sete pacientes apresentaram epilepsia. Sessenta e um tinham síndrome epiléptica parcial, 13 síndrome epiléptica secundariamente generalizada e em três, o tipo de crise não pode ser definido. Epilepsia foi menos freqüente em pacientes com polimicrogiria e esquizencefalia ($p<0.001$). As crises epilépticas foram controladas mais facilmente por drogas antiepilépticas em pacientes com polimicrogiria e esquizencefalia ($p<0.001$). *Conclusão:* A freqüência de epilepsia é menor e as crises são mais facilmente controladas em pacientes com polimicrogiria e esquizencefalia. Pacientes com MDC freqüentemente apresentam síndrome epiléptica secundariamente generalizada.

PALAVRAS-CHAVE: malformações do desenvolvimento cortical, EEG, epilepsia, infância.

Malformations of cortical development (MCD) can be defined as derangements in the development of the neocortex associated with a range of morphologic features and with multiple putative etiologic factors, including genetic and environmental influences[1]. The different types of MCD are the result of abnormalities that occurred at different stages of cortical development[2]. The first dysplastic lesions described were anatomopathological findings, and only severely disabled patients could be identified[3]. With the improvement in neuroimaging techniques, smaller lesions have been described[4,5]. This led to the iden-

Departments of Neurology and *Medical Genetics State University of Campinas, (UNICAMP), Campinas SP, Brazil: [1]Professora Doutora; [2]Professor Associado; [3]Professor Titular.

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Dra. Marilisa M. Guerreiro - Department of Neurology / FCM / UNICAMP - P.O. Box 6111 - 13083-970 Campinas SP - Brasil. E-mail: mmg@unicamp.br

tification of patients presenting with less severe symptoms than previously described.

Although MCD usually manifest in childhood with epilepsy, developmental delay and focal neurologic signs, some patients may have normal or near-normal cognitive function and no seizures[6]. Moreover, the identification of familial cases of MCD[7,8] and the understanding of its molecular basis[9-13] has proven that the clinical spectrum of MCD is much wider than previously suspected.

The objective of this study is to describe the frequency of epilepsy, seizure control with antiepileptic drugs, and type of epileptic syndrome associated with the different forms of MCD.

METHOD

We evaluated the first 100 consecutive patients with a neuroimaging diagnosis of MCD. They were identified among all high resolution magnetic resonance imaging (MRI) exams performed at our service between 1997 and 2001. The causes of referral were diverse, according to the routine of the neurology outpatient clinic, with the main reasons for performing an MRI being epilepsy, developmental delay and focal neurologic signs. After MRI diagnosis of the subtype of MCD a detailed clinical assessment was performed.

Signed informed consent was obtained from all patients according to the declaration of Helsinki, and the protocol was approved by the ethical committee of our institution.

All patients were seen and examined by at least one of us. Clinical information was collected on follow-up visits, and by review of clinical notes. Investigation included neuroimaging evaluation, neurological examination, serial electroencephalograms (EEG) and long term video-EEG monitoring when appropriate. When several EEGs were performed in the same patient, we included the information of all reports.

We used a semi-structured questionnaire to assess the occurrence of epilepsy, seizure control and age at first seizure. We also reviewed the clinical files of all patients. Seizures and epileptic syndromes were classified according to the ILAE classification[14]. Being seizure-free for at least one year was considered seizure control.

For analysis of the data, patients were divided into groups according to the type of MCD based on MRI findings: focal cortical dysplasia, hemimegalencephaly, unilateral periventricular heterotopia, bilateral periventricular nodular heterotopia, lissencephaly (agyria-pachygyria), subcortical laminar heterotopia, polymicrogyria, and schizencephaly.

We used the chi-square test to analyze the occurrence of epilepsy and seizure control in the different types of MCD. In addition, we assessed the type of epileptic syndrome associated with the different types of MCD. We used a significance level of 0.05.

MRI – The diagnosis of MCD was established according to MRI findings. The same MRI machine was used throughout this study. The MRI was performed in a 2T scanner (Elscint Prestige, Haifa, Israel) using our epilepsy protocol: *(a) sagittal* T1 spin-echo, 6 mm thick (TR=430, TE=12) for optimal orientation of the subsequent images; *(b) coronal* T1 inversion recovery, 3 mm thick (flip angle=200°; TR=2800-3000, TE=14, inversion time TI=840, matrix=130X256, field of view (FOV)=16X18 cm; *(c) coronal* T2-weighted fast spin echo, 3-4 mm thick, (flip angle=120°; TR=4800, TE=129, matrix=252X320, FOV=18X18cm), *(d) axial* images parallel to the long axis of the hippocampus; T1 gradient echo, 3 mm thick (flip angle=70°, TR=200, TE=5, matrix=180X232, FOV=22X22 cm); *(e) axial* T2 fast spin echo, 4 mm thick, (flip angle - 120°, TR=6800, TE=129, matrix 252X328, FOV=21X23cm); *(f) volumetric* (3D) T1 gradient echo, acquired in the sagittal plane for multiplanar reconstruction, 1 - 1.5 mm thick (TA=35°, TR=22, TE=9, matrix=256X220, FOV=23X25 cm). We performed multiplanar reconstruction and curvilinear reformatting in all 3D MRI.

EEG – Electroencephalographic recordings were performed routinely, using the International 10–20 system for electrode placement. The EEG findings were classified as normal or abnormal. Only epileptiform abnormalities were considered, and these could be focal or generalized.

We evaluated the epileptiform abnormalities according to the patient's age. The epileptiform abnormalities were classified into four types: a) random high-voltage slow waves and spikes which vary both in location and duration, or hypsarrhythmia[15], b) slow, <2.5Hz, spike-and-wave complexes (Lennox-Gastaut syndrome), c) focal, and d) generalized. Non-epileptiform abnormalities or EEGs within normal limits were not included in this analysis. According to the patient's age, the type of EEG abnormality was plotted in a box plot bar chart.

RESULTS

There were 55 females and 45 males, with ages ranging from five months to 71 years old (mean=15.2 years). Twenty-eight patients had focal cortical dysplasia, 28 polymicrogyria, 16 schizencephaly, nine lissencephaly (agyria-pachygyria), five subcortical laminar heterotopia, five unilateral heterotopia, five bilateral periventricular nodular heterotopia, and four hemimegalencephaly (Fig 1).

Frequency of epilepsy – All patients with hemimegalencephaly, unilateral periventricular heterotopia, subcortical laminar heterotopia and lissencephaly (agyria-pachygyria) had epilepsy. Epilepsy also occurred in 27/28 (96.5%) of the patients with focal cortical dysplasia, in 4/5 (80%) with bilateral periventricular nodular heterotopia, in 10/16 (62.5%) with schizencephaly, and in 13/28 (46.5%) with polymicrogyria. Epilepsy was less frequent in patients with polymicrogyria and schizencephaly ($p<0.001$).

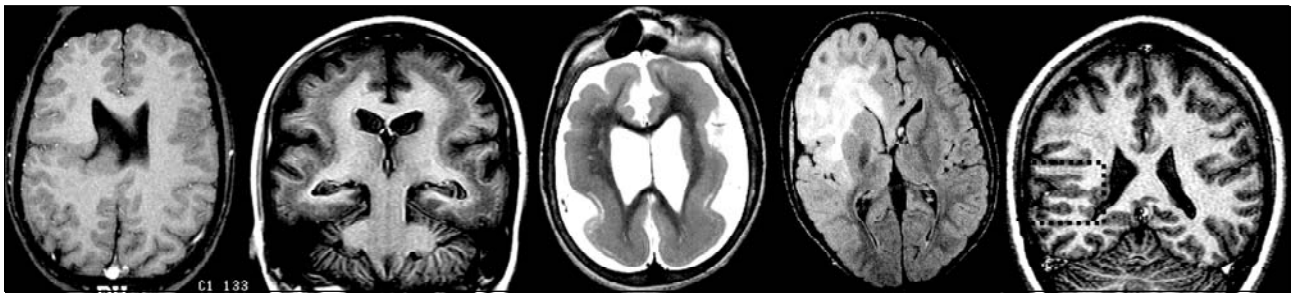

Fig 1. From left to right: right hemisphere schizencephaly, subcortical laminar heterotopia, agyria-pachygyria, hemimegalencephaly and unilateral heterotopia (box).

Seizure control with AED – None of the patients with subcortical laminar heterotopia and hemimegalencephaly had their seizures controlled with antiepileptic drugs (AED). Seizures were controlled in 1/28 (3%) of patients with focal cortical dysplasia, in 1/9 (11%) with lissencephaly (agyria-pachygyria), in 1/5 (20%) with unilateral heterotopia, in 1/5 (20%) with bilateral periventricular nodular heterotopia, in 5/13 (38.5%) with polymicrogyria and in 7/10 (70%) with schizencephaly. Patients with schizencephaly and polymicrogyria had their seizures more easily controlled by AED ($p<0.001$).

Type of epileptic syndrome – Seventy-seven patients presented with epilepsy. Sixty-one had partial epileptic syndromes, 13 secondary generalized syndromes, and in three patients the type of epileptic syndrome could not be established.

The type of epileptic syndrome may change as the brain matures and, during the first decade of life, 20 patients presented with secondary generalized epilepsy (West syndrome or Lennox-Gastaut syndrome): 6/9 had lissencephaly (agyria-pachygyria), 2/5 had subcortical laminar heterotopia, 3/4 had hemimegalencephaly, 2/19 had focal cortical dysplasia, 4/8 had schizencephaly, 1/4 had focal heterotopias and 2/8 had polymicrogyria.

EEG and neurological examination – Type of seizure, age at the first seizure, EEG characteristics, and the findings of neurological examination are shown in Tables 1 and 2. It is interesting to note that in 22% of the patients the EEG was normal and 38% had normal neurological examination.

Electroencephalographic evaluation was performed (1 to 5 recordings) in all but one patient with schizencephaly, one with periventricular nodular heterotopia and 10 patients with polymicrogyria. These patients without EEG evaluation did not have epilepsy.

Figure 2 shows the type of EEG abnormality according to the patient's age. A total of 134 abnormal EEG recordings were included in this analysis.

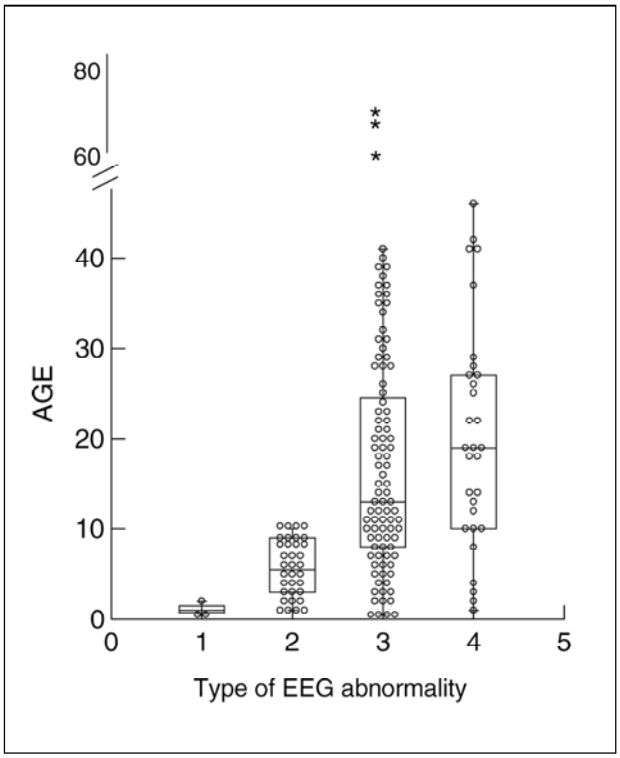

Fig 2. Distribution of the epileptiform abnormalities according to the patient's age. Type of EEG abnormality: 1, Hypsarrhythmia; 2, Slow spike-and-wave complexes, <2.5Hz; 3, Focal epileptiform abnormality; 4, Generalized epileptiform abnormality. Note that hypsarrhythmia occurs mostly in the first year of life, and slow spike-and-wave complexes predominate in the first decade.

EEG in patients without epilepsy – Twenty-three patients never had seizures. An EEG was performed in 12 patients without epilepsy (six with polymicrogyria and six with schizencephaly). The EEGs were normal in seven patients, and showed epileptiform abnormalities in five.

Table 1. Characteristics of epilepsy according to the different types of malformations of cortical development.

Type of MCD	Epilepsy	Seizures controlled with AED	Mean age of first seizure	Type of seizure*
Focal cortical dysplasia (n=28)	27/28 (96.5%)	1/27 (3%)	4.6 years	Partial - 100%
Hemimegalencephaly (n=4)	4/4 (100%)	None	2 months	Partial- 100% Generalized - 25%
Bilateral periventricular nodular heterotopia (n=5)	4/5 (80%)	1/4 (25%)	13.2 years	Partial - 75% Generalized – 25%
Unilateral periventricular heterotopia (n=5)	5/5 (100%)	1/5 (20%)	13.1 years	Partial - 100%
Subcortical laminar heterotopia (n=5)	5/5 (100%)	None	8.4 years	Partial - 75% Generalized - 25%
Agyria-pachygyria (n=9)	9/9 (100%)	1/9 (11%)	6 months	Partial - 33% Generalized - 55.5%
Polymicrogyria (n=28)	13/28 (46.5%)	5/13 (38.5%)	8.8 years	Partial - 54% Generalized - 15%
Schizencephaly (n=16)	10/16 (62.5%)	7/10 (70%)	4 years	Partial - 70% Generalized - 30%

AED, antiepileptic drugs. *Some patients presented with more than one type of seizure, neurological abnormality or EEG finding.

Table 2. Clinical characteristics and EEG findings, according to the different types of malformations of cortical development.

Type of MCD	Neurological examination*	EEG findings*
Focal cortical dysplasia (n=28)	Normal - 75% MR - 10% Hemianopsia - 7% MD - 3%	Focal - 21/28 (75%) Generalized - 7/28 (25%) Normal - 2/28 (7%) RED - 9 (32%)
Hemimegalencephaly (n=4)	MD - 100% MR - 100%	Focal - 4/4 (100%) RED -1/4 (25%)
Bilateral periventricular nodular heterotopia (n=5)	Normal - 80% MR - 20%	Focal - 1/4 (25%) Generalized - 1/4 (25%) Normal - 2/4 (50%)
Unilateral periventricular heterotopia (n=5)	Normal - 80% MR - 20%	Focal - 1/4 (25%) Generalized - 2/4 (50%) Normal - 2/4 (50%)
Subcortical laminar heterotopia (n=5)	Normal - 40% MR - 40% MD - 20%	Focal - 5/5 (100%) Generalized - 2/5 (40%)
Agyria-pachygyria (n=9)	MD - 55.5% MR - 55% Hypotonia - 33% VA - 22% Microcephaly- 11%	Focal - 5/9 (55%) Generalized - 7/9 (78%) Normal - 1/9 (11%)
Polymicrogyria (n=28)	PBP- 36% Speech delay - 28.5% MD - 28.5% Normal - 25% MR - 7% Hypotonia - 3% Microcephaly - 3%	Focal - 6/16 (37.5%) Generalized - 3/16 (19%) Normal - 10/16 (62.5%)
Schizencephaly (n=16)	MD - 50% MR - 50% VA - 20% PBP - 10% Microcephaly - 10%	Focal - 11/15 (73%) Generalized - 4/15 (27%) Normal - 5/15 (30%)

MD, motor deficit; MR, mental retardation; VA, visual abnormalities; RED, rhythmic epileptiform discharge. *Some patients presented with more than one type of seizure, neurological abnormality or EEG finding.

DISCUSSION

The diagnosis of MCD is usually considered in severely disabled patients, especially in the setting of refractory epilepsy. However, some patients have normal, or near normal, cognitive function and no seizures[6]. Although many patients with MCD presenting in childhood often have more severe clinical manifestations[16], we found a normal neurological examination in 33% of our patients (Table 2). These patients were identified through a systematic investigation where an MRI was performed even when symptoms were mild.

Epilepsy is frequently seen in patients with MCD and a characteristic EEG pattern consisting of rhythmic epileptiform activity has been described[17]. It is important to note that although focal cortical dysplasia has intrinsic epileptogenicity[18], normal EEG findings should not preclude the diagnosis of MCD in patients with epilepsy. We found 22% of the patients with MCD had normal EEG findings, including 2/28 (7%) with focal cortical dysplasia. The type of epileptic syndrome associated with MCD can be variable, and the patient's age is one of the most important aspects in the determination of the epileptic syndrome. Epileptic syndromes in the first three months of life are characterized by burst-suppression, which reflects the dysfunction of thalamo-cortical connections. West syndrome is characterized by infantile spasms, hypsarrhythmia and developmental delay, and is seen mainly from the fourth to the seventh months of life. The age range of expression of hypsarrhythmia correlates with the differentiation of the intracortical synchronizing mechanism provided by intrinsically bursting neurons. In the second year of life there is sufficient degree of maturation to support sustained rhythmic discharges of spikes and waves. Lennox-Gastaut syndrome is the clinical expression of this age[19]. The electroencephalographic evaluation of our patients showed that the pattern of EEG abnormalities present in patients with MCD reflects clearly these three main stages of cerebral maturation (Fig 1). Hypsarrhythmia occurs in the first year of life. Generalized epileptiform activity characterized by slow spike-and-wave complexes are seen mainly in the first decade of life. Focal and generalized epileptiform activities are seen throughout life.

Electroencephalographic findings of patients with MCD are often stable over a period of time and some patients may develop slow waves or interictal spikes when followed serially for several years[1]. However, our data shows that, in childhood, the type of EEG finding depends mostly on the patient's age; that is, the type of epileptiform abnormality changes according to the degree of cerebral maturation (myelinization and synaptogenesis). It is interesting to note that, although most patients with epilepsy due to MCD show interictal spikes[20], we found epileptiform abnormalities in 42% (5/12) of the patients without epilepsy.

Malformation of cortical development is the most common cause of partial seizures in childhood[21]. However, it is noteworthy that 23% (9/39) of our children with a focal lesion presented with secondary generalized epilepsy. This finding is of utmost importance because, when faced with a child with refractory epilepsy, one has to consider the possibility of a focal lesion, even if he/she presents with a generalized epileptic syndrome. One of our patients with pathologically verified focal cortical dysplasia presented with West syndrome in the first months of life and became seizure free after AED treatment. Motor and cognitive developments were normal. His seizures restarted at age nine and at this time were partial, delineating the age dependent expression of the epileptic syndrome.

The frequency of epilepsy was lower ($p<0.001$) and seizures were more easily controlled ($p<0.001$) in patients with polymicrogyria and schizencephaly. These findings are in agreement with previous studies in which epilepsy was present in 57% to 87% of patients with polymicrogyria or schizencephaly[7,22-25]. It is also in keeping with our previous findings from a smaller series[26]. In these studies the epileptic spectrum was wide and most patients had a good seizure outcome. It should be noted that, because MCD are frequently associated with refractory epilepsy, most data about epilepsy and MCD come from epilepsy centers. In order to avoid this bias, we performed, whenever possible, an MRI evaluation of patients seen at our neurology clinic, enabling the identification of a higher number of patients with MCD who did not present with epilepsy. However, we believe that the frequency of epilepsy in patients with MCD is still underestimated, because almost asymptomatic patients with MCD cannot be identified as they do not seek medical help.

We conclude that in a group of patients with MDC, the frequency of epilepsy is lower and seizures are more easily controlled in patients with polymicrogyria and schizencephaly. Patients with MCD frequently present with secondary generalized epilepsy early in childhood.

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