Seizure 21 (2012) 377–384

Contents lists available at SciVerse ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

Malformations of cortical development and epilepsy in adult patients

C.E. Papayannis [a,b,*], D. Consalvo [a,b], M.A. Kauffman [a,b], G. Seifer [a,b], S. Oddo [a,b], L. D'Alessio [a,b], P. Saidon [a,b], S. Kochen [a,b]

[a] Epilepsy Section, Neurology Department, Ramos Mejía Hospital, Buenos Aires, Argentina
[b] Lab. de Epilepsia, Inst. de Biología Celular y Neurociencias (IBCN), CONICET – Facultad de Medicina, Universidad de Buenos Aires, Buenos Aires, Argentina

ARTICLE INFO

Article history:
Received 2 October 2011
Received in revised form 15 March 2012
Accepted 16 March 2012

Keywords:
Epilepsy
Malformations of cortical development
Classification

ABSTRACT

Objective: To describe clinical features of epilepsy secondary to Malformation of Cortical Development (MCD) in a series of adult patients.
Materials and methods: We searched our database for all cases with confirmed epilepsy and MCD and included in the study only those with complete data. Mean age, sex, age at seizure onset (ASO), seizure types, abnormal neurological exam (ANE), mental retardation, family history, gestational or perinatal insults (G-PI), interictal EEG and response to treatment were analyzed. Cases were classified into the 3 main groups (G) according to the Barkovich classification (BC) and then compared: (G1) "malformations due to abnormal cell proliferation", (G2) "malformations due to abnormal migration" and (G3) "malformations due to abnormal cortical organization".
Results: We identified 152 (5.06%) patients with MCD from a total of 3000 with epilepsy. In total, 138 patients with complete medical data were included in this study. The mean age of patients was 36.2 years, 52.2% were female, the mean ASO was 12.3 years, 5.1% of cases had a positive family history and 21% had G-PI. An ANE was observed in 21% and mental retardation in 31.9%. Most of the patients (84.8%) had refractory epilepsy. The distribution of cases according to the BC was: 51.4% in G1, 28.9% in G2 and 19.6% in G3. Comparing the 3 groups, we found that an ANE was statistically more frequent in G3 and was present in 70.4% of cases.
Conclusion: Our series of adult patients with epilepsy and MCD suggests that MCD are identified as commonly in a developing country as in previous "first world" series. Neurological deficits were more common in the subgroup of patients with polymicrogyria and schizencephaly (BC Group 3).

1. Introduction

Malformations of cortical development (MCD) are responsible for a wide spectrum of clinical manifestations that include epilepsy, mental retardation and neurological deficits.[1,2] MCD are considered the second most common cause of medically refractory partial epilepsy in adults after hippocampal sclerosis.[3] Diagnosis of MCD has notably been improved in the past 2 decades as a result of advances in modern imaging, especially magnetic resonance imaging (MRI), and genetics.[4] Epilepsies that were considered cryptogenic in the past are now recognized as secondary to MCD.

The anatomical and histological subtypes of MCD depend on the severity of the insult or the genetic anomaly affecting the normal development of the brain and the moment that the failure occurred.[5,6] A variety of etiologies have been related to MCD, including genetic defects and intrauterine insults (infections, traumatisms, strokes or drug exposure). Some insults could also have happened in postnatal life.[6,7]

In 1996, Barkovich et al.[8] proposed a classification of MCD based on the first point at which the developmental process is disturbed. The Barkovich classification (BC) categorizes patients into 3 main groups: Group 1 includes "malformations due to abnormal cell proliferation", Group 2 includes "malformations due to abnormal migration" and Group 3 includes "malformations due to abnormal cortical organization". The BC was updated in 2001 and 2005, due to the constant advances in knowledge.[9,10]

In this article, we describe a series of adult patients with epilepsy associated with MCD who were assessed at an epilepsy center in the city of Buenos Aires. All patients included in this study were classified into 1 of the 3 main groups defined in BC and comparisons were made of the clinical findings in the different groups.

The main purpose of this study was to investigate the clinical features of MCD in our population and compare our results with those of previous reports on the subject, taking into account that our center is located in a developing country and that there are not many reports of this pathology in this region.

* Corresponding author at: Diaz Velez 3769 8°A, Buenos Aires 1200, Argentina. Tel.: +54 11 49824276; fax: +54 11 49326101.
E-mail address: cpapayonis@intramed.net (C.E. Papayannis).

1059-1311/$ – see front matter © 2012 British Epilepsy Association. Published by Elsevier Ltd. All rights reserved.
doi:10.1016/j.seizure.2012.03.009

2. Materials and methods

We retrospectively reviewed the clinical records of adult patients (≥18 years of age) that visited the Epilepsy Centre of the Ramos Mejía Hospital in the city of Buenos Aires and whose first evaluations were between 1985 and 2007. From our standardized clinical database, we included all cases with confirmed diagnosis of epilepsy and whose MRI had identified MCD. A standardized 1.5 T MRI study that included T1- and T2-weighted, inversion recovery and fluid-attenuated inversion recovery acquisitions was used. Patients who were first observed in the era before MRI had their diagnosis of MCD later during their follow up, when MRI became available. We only included cases in which the opinion of two different neurologists (one of them specialized in imaging techniques) agreed on the diagnosis. Cases that were lost to follow up or that had missing clinical, epidemiological or interictal EEG data were excluded from the study.

It is important to explain the referral pattern of our center to understand the composition of this patient population. The center in this study belongs to a public hospital, which means that, even though any patient with suspected epilepsy could ask for an appointment, most of the patients lack health insurance and have low income. In addition, this center is considered a referral center and receives complex cases transferred from others health centers all over the country. Only adult patients are treated in this center because patients under 18 years old are generally assessed by pediatric neurologists in other specialized pediatric hospitals.

We analyzed the following variables: sex, age at last follow up, age at seizure onset, seizure types, epilepsy syndromes, presence of an abnormal neurological exam, mental retardation, family history of epilepsy or neurological disease (first degree relatives) and the existence of prenatal (intrauterine) or perinatal insults. A patient was considered mentally retarded when his IQ was below 80 according to the WAIS test (borderline deficiency or a lower degree). Seizures were classified as focal or generalized according to the last report of the International League Against Epilepsy (ILAE) Commission on Classification and Terminology, 2005–2009[11] and epilepsy syndromes, based in semiology, and were divided into temporal, frontal, parietal or occipital lobe epilepsy.[12]

Interictal EEG recordings were also evaluated and classified as normal, abnormal with epileptic discharges or abnormal without epileptiform discharges. Epileptiform discharges were divided into focal-regional or multifocal-bilateral discharges. Video EEG recordings were performed in some of the refractory epileptic patients to establish the epileptogenic zone and whether they were candidates for surgery.

To classify whether patients were responsive to treatment, we used the latest definition proposed by the ILAE. According to this definition, patients were considered to have drug resistant epilepsy when at least two adequate and tolerated antiepileptic drug (AED) schedules failed to achieve sustained seizure freedom.[13] Each AED was used at the highest tolerated dose and AED levels, available for the classic drugs, were measured for different purposes (to establish adherence, toxicity, etc.).

In accordance with ILAE Treatment Guidelines,[14] carbamazepine is most often selected in our center as the first choice for adults with partial onset seizures. Monotherapy is always seen as the best alternative whenever possible, and newer drugs are usually used as add-on therapies.

A detailed assessment of MRI features allowed us to determine the MCD subtype according to BC scheme,[10] which can be summarized by 3 main groups:

Group 1: "malformations due to abnormal cell proliferation"
Group 2: "malformations due to abnormal migration"
Group 3: "malformations due to abnormal cortical organization"

In the BC, focal cortical dysplasias (FCDs) are included in Group 1 only when balloon cells are present, and other FCDs are incorporated into Group 3. In this study, cases with FCD were all classified as belonging to Group 1, assuming that most of our cases with FCD correspond to subtype IIb, according to the new ILAE classification[15] and Palmini et al.'s classification,[16] as they are easier to detect by MRI.

We classified patients as having *dual pathology* when the MCD was associated with hippocampal sclerosis (HS).

After classifying patients in these 3 groups, we made a comparison of their clinical presentation.

All evaluated data were recorded in a database (Microsoft Excel v. 2003) and then exported to SPSS version 11.5 software (IBM, USA) for statistical analysis. One-way Anova tests were used to calculate the *p*-values for continuous quantitative variables, and Fisher exact tests were used to calculate the *p*-values for qualitative variables. A *p*-value lower than 0.05 was considered statistically significant.

3. Results

3.1. Clinical and epidemiological data: (see Table 1)

A total of 152 patients with a diagnosis of epilepsy and MCD, as shown by MRI, were identified from approximately 3000 clinical records (frequency of 5.06%). This study included 138 of these 152 patients. The remaining 14 patients were excluded from the study due to incomplete data or loss to follow up. The mean age at last follow up in the study population was 36.2 years (range 18–77), 52.2% were female and 5.1% of the cases had a family history of epilepsy or other neurological disease. An abnormal neurological exam was found in 21% of patients, and 31.9% of the patients presented with some degree of mental retardation (IQ less than 80). A gestational or a perinatal insult (e.g., perinatal anoxia, preterm labor) occurred in 15.2% of patients.

3.2. Types of seizures and epilepsy data: (see Table 1)

The mean age at seizure onset was 12.3 years (range 0–66), with 23% of cases starting their epilepsy in adulthood (≥18 years of age), and the mean duration of epilepsy was 23.9 years (range 3–60). A history of epileptic spasms or West syndrome was reported to be

Table 1
Clinical features.

	Mean	Range
Age at last follow up (y)	36.2	18–77
Age of seizure onset (y)	12.3	0–66
Duration of epilepsy (y)	23.9	3–60
	N = 138	%
Female gender	72	52.2
Family history	7	5.1
History of perinatal injury	21	15.2
History of spams/West syndrome	6	4.3
Neurological deficit	29	21.0
Mental retardation	44	31.9
Focal seizures	138	100
Secondary generalized seizures	102	73.9
Temporal lobe epilepsy	41	29.7
Frontal lobe epilepsy	39	28.3
Parietal lobe epilepsy	16	11.6
Occipital lobe epilepsy	9	6.5
Seizures corresponding to more than 1 lobe	27	19.6
Seizure not indicative of one lobe	6	4.3
EEG with epileptiform discharges	100	72.5
EEG with bilateral discharges	75	54.9
Drug resistant epilepsy	117	84.8

Table 2
Subtypes included in each group of MCD.

Group 1	Subtype	N	Group 2	Subtype	N	Group 3	Subtype	N
N = 71	FCD	34	N = 40	PNH	22	N = 27	SCHI	10
	FCD plus GNT[a]	10		Sub H	7		PMG	17
	Dual Pat[b]	10		Mix H	4		-BPP	6
	GNT	7		Dual Pat[c]	5		-BPOP	1
	TS	7		DC	2		-UP	10
	HME	1						
	FHME vs. FCD	2						

FCD: focal cortical dysplasia; FCD plus GNT: focal cortical dysplasia plus glioneuronal tumor; Dual Pat: dual pathology; GNT: glioneuronal tumor; TS: tuberous sclerosis; HME: hemimegalencephaly; FHME vs. FCD: focal hemimegalencephaly vs. focal cortical dysplasia; PNH: periventricular nodular heterotopia; Sub H: subcortical heterotopia; Mix H: mixed forms of heterotopia; DC: doble cortex or subcortical band heterotopia; SCHI: schizencephaly; PMG: polymicrogyria; BPP: bilateral perisylvian polymicrogyria; BPOP: bilateral parieto occipital polymicrogyria; UP: unilateral polymicrogyria.

[a] Co-existence of MRI features of both entities in the same area.

[b] Co-existence of MCD with hippocampal sclerosis: 1 patient had a lesion classified as FCD plus GNT and the other nine patients had FCD.

[c] In group 2, dual pathology consisted of PNH plus hippocampal sclerosis.

the first epileptic manifestation in early infancy in 6 patients, all of them belonging to Group 1 of BC scheme (3 with diagnosis of FCD and 3 with tuberous sclerosis).

All patients developed focal seizures, and 73.9% of cases experienced focal evolving to bilateral seizures (or secondary generalized tonic–clonic seizures) at least once during evolution. Semiology of these focal seizures can be divided into the following epileptic syndromes: temporal lobe epilepsy in 41 patients, frontal epilepsy in 39 patients, parietal epilepsy in 16 patients, occipital lobe epilepsy in 9 patients, seizures corresponding to more than one lobe in 27 patients and semiology not indicative of a particular lobe in 6 patients.

3.3. EEG recordings

Interictal EEG recordings were normal in 27.5% of cases and showed epileptiform discharges in 72.5% of cases. Of these abnormal EEGs, 54.9% showed bilateral or multifocal discharges, and 45.1% had focal or regional epileptiform activity.

Video EEG monitoring was performed in 29 patients due to the presence of refractory epilepsy and was used to confirm the focal onset of seizures, define the epileptogenic zone and to evaluate therapeutic options. Most of these patients belonged to Group 1. This study was not performed in cases that were considered bad candidates for resective surgery; for example, patients with bilateral or non-resectable malformations.

3.4. Response to treatment and epilepsy surgery

According to the definition proposed by the ILAE,[12] 84.8% of patients had drug resistant epilepsy because they failed to achieve sustained seizure freedom with at least two adequate and tolerated AED schedules.

Of the patients that achieved complete seizure control, 42.85% (9 out of 21) were on monotherapy. With regard to refractory patients, all of them were on polytherapy, 38.45% (45 out of 117) having tried 5 or more AEDs in different combinations.

Surgery was performed in only 9 patients. All of the operated patients belonged to Group 1. The preoperative MRI in these patients allowed the following diagnoses: 4 patients had FCD type IIB, 3 patients had dual pathology (FCD type IIb + HS), 1 patient had a glioneuronal tumor (GNT) and 1 patient had tuberous sclerosis (TS). In 8 of these patients, 5.7% of the total population included in this study, surgery was performed with the objective of ameliorating epilepsy. The patient with the diagnosis of TS was operated on with the goal of resecting a giant cell tumor. The 8 patients that underwent epilepsy surgery have now had at least two years of follow up after surgery (mean 6.8 years). The mean age at surgery was 33.44 years (range: 19–62). Lesions were located in the temporal lobe in 5 cases and in the frontal lobe in 3 cases. Chronic stereo-electroencephalography was used in 3 patients to determine with more precision the epileptogenic zone. 5 of these 8 operated cases (62.5%) were free of all types of seizures (Engel 1A) on their last follow up visit. Histopathological findings confirmed what MRI in all of the operated patients suspected: 4 patients with FCD type IIb, 3 patients with dual pathology (FCD type IIb + HS), 1 Dysembryoplastic Neuroepithelial Tumor (DNET) and 1 giant cell tumor.

3.5. Comparison of the different subtypes of MCD

The distribution of cases according to BC was as follows: 71 patients (51.4%) belonged to Group 1 (malformations due to abnormal cell proliferation); 40 patients (28.9%) belonged to Group 2 (malformations due to abnormal migration) and 27 patients (19.6%) belonged to Group 3 (malformations due to abnormal cortical organization). The different subtypes included in each group are shown in Table 2.

Cases in Group 1 were diagnosed as having FCD (see Fig. 1), dual pathology, GNT, FCD plus GNT, TS, hemimegalencephaly or focal hemimegalencephaly vs. FCD.

Group 2 included patients with periventricular nodular heterotopia (PNH) (see Fig. 2), subcortical heterotopia, mixed forms of heterotopia, dual pathology and double cortex.

Group 3 included cases with polymicrogyria (PMG) and schizencephaly.

The following definitions provide clarification on some of these diagnoses:

- *Focal cortical dysplasia*: conventional MRI criteria that are suggestive of FCD include gyration anomalies, focal thickening of the cortex, blurring of the gray-white matter junction and abnormal cortical and subcortical signal intensity.[17,18] We included all FCDs in Group 1 with the assumption that most of our FCD correspond to subtype IIb, according to the new ILAE classification[14] and Palmini et al. classification,[16] as this subtype could be easier to detect by MRI. For example, the "transmantle sign", (a white matter signal alteration that goes from crown of a gyrus or bottom of a sulcus toward the ventricle) first described by Barkovich in 1997, is almost exclusively found in FCD Type IIb.[15] Transmantle characteristics were found in 16 of 34 of our FCD patients. However, a certain diagnosis is possible only with histopathological data, which were available in only a few of the patients of our series.
- *Dual pathology*: according to Blümcke et al.[15] this term refers only to patients with hippocampal sclerosis who have a second principal lesion affecting the brain (which may be located outside

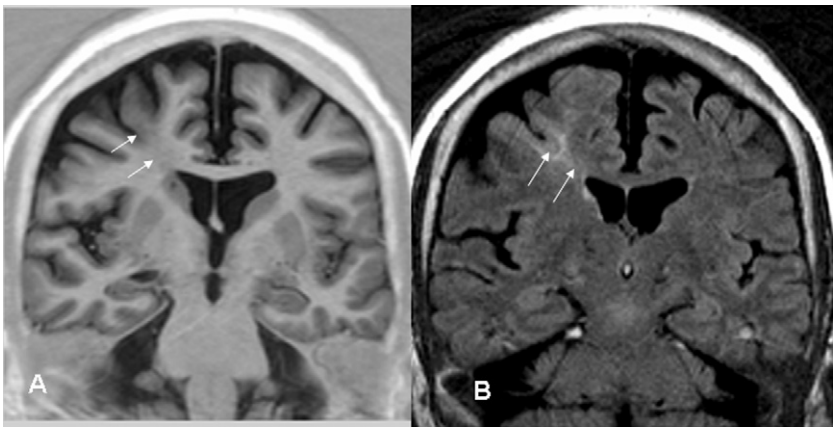

Fig. 1. (A) Inversion recovery (IR) and (B) fluid attenuation inversion recovery (FLAIR) MRI sequence showing a transmantle focal cortical dysplasia in the superior and middle frontal gyrus at the right side.

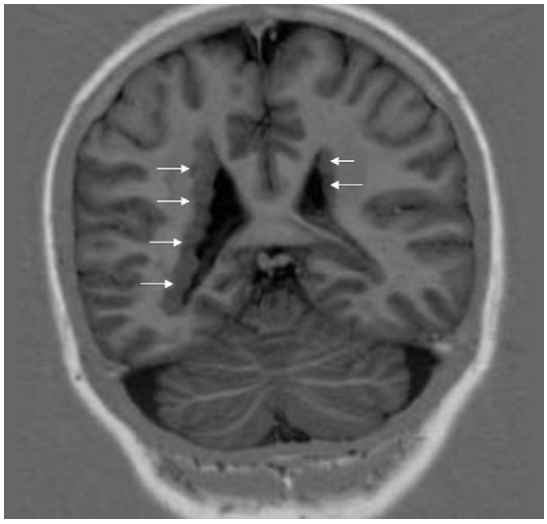

Fig. 2. IR sequence of a patient with periventricular nodular heterotopia.

the ipsilateral temporal lobe). In Group 1, the second lesion is a FCD or a GNT. It should be distinguished from FCD Type IIIa with histopathologically confirmed architectural abnormalities in the temporal lobe associated with hippocampal sclerosis. This last type of FCD was not included in this study. In Group 2, patients with dual pathology had HS and PNH.

- *Glioneuronal tumor*: These tumors are associated with disordered cortex, so they are included in Group 1 of the BC in the neoplastic subcategory (1C2). The tumor subtypes included are gangliolioma, gangliocytoma and dysembryoplastic neuroepithelial tumor.
- *Focal cortical dysplasia plus glioneuronal tumor*: We classified in this category those cases with mixed characteristics observed in the MRI (features of FCD together with GNT findings in the same area), although we did not have histological confirmation. In the ILAE classification of FCD, these cases would correspond to type IIIb: cortical lamination abnormalities adjacent to a glioneuronal tumor.[15]
- *Focal hemimegalencephaly vs. focal cortical dysplasia*: The dividing line between an FCD and hemimegalencephaly (HME) is not always obvious; therefore, it can sometimes be difficult to distinguish these two entities by means of an MRI alone. These two malformations are often considered as part of a spectrum, in which HME would be a severe form of cortical dysplasia.

The localization and extent of the lesions in each group are given in Table 3. Multi-lobar involvement was higher in Group 2

Table 3
Localization and extent of lesions in each group.

	MCD subtypes[a]	Multilobar involvement	Frontal lobe involvement	Temporal lobe involvement	Parietal lobe involvement	Occipital lobe involvement
Group 1	FCD ($n=34$)	4	24	12	3	1
($n=71$)	Dual Pat ($n=10$)	4	0	10	3	1
	DCF plus GNT ($n=10$)	2	1	7	1	3
	GNT ($n=7$)	1	1	6	0	1
	TS ($n=7$)	7	7	5	4	5
	HM ($n=1$)	1	1	1	1	1
	FHM vs. D ($n=2$)	1	1	1	0	1
Group 2	PNH ($n=22$)	NA	NA	NA	NA	NA
($n=40$)	Sub H ($n=8$)	5	2	7	5	3
	Mix H ($n=4$)	3	1	4	2	2
	Dual Pat ($n=4$)	NA	NA	NA	NA	NA
	DC ($n=2$)	2	2	2	2	2
Group 3	SCHI ($n=10$)	4	5	5	5	0
($n=27$)	PMG ($n=17$)	6				
	-BPP ($n=6$)	1	6	6	0	0
	-BPOP ($n=1$)	6	0	0	1	1
	-UP ($n=10$)		7	5	5	4

NA: not applicable. *Note*: The sum of the boxes can be more than the total as cases can have more than 1 lobe involvement.
[a] MCD subtypes: abbreviations are the same that those given in Table 2.

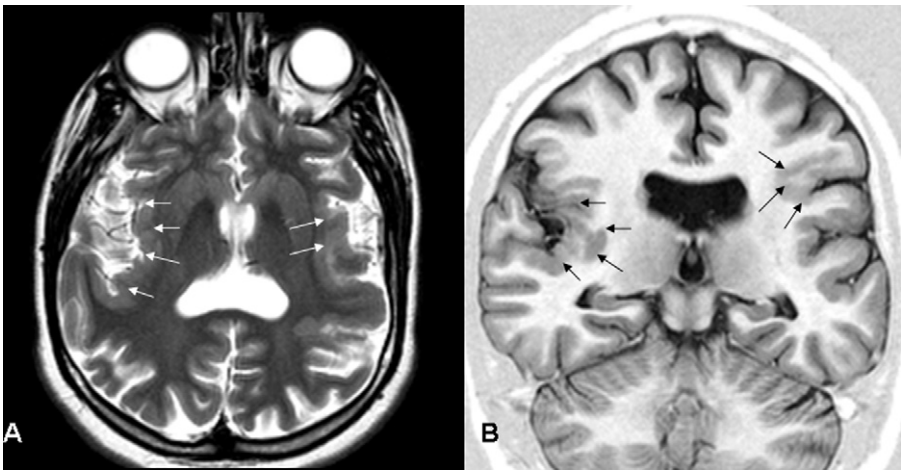

Fig. 3. (A) axial T2-weighted image and (B) coronal IR sequence showing a case with bilateral perisylvian polymicrogyria.

and Group 3 compared to Group 1: 71% of cases in Group 2 (10 out of 14, excluding PNH in which this concept cannot be applied), 63% in Group 3 (17 out of 27) and 28% of in Group 1 (20 out of 71).

Epileptic syndromes in the different groups (see Table 4):

- In Group 1, excluding the patients with TS which usually have multifocal lesions, ($n = 64$), epileptic syndromes according to semiology were as follows: frontal lobe epilepsy was present in 23 patients, temporal lobe epilepsy was present in 23 patients, parietal lobe epilepsy was present in 7 patients, occipital lobe epilepsy was present in 3 patients and seizures corresponding to more than 1 lobe were present in 6 patients. Semiology was not indicative for a particular lobe in 2 patients. In the case of TS patients ($n = 7$): 4 had semiology of frontal lobe epilepsy and 3 had more than 1 seizure type.
- In Group 2 ($n = 40$), seizure semiology had the following distribution: 14 patients had seizures with onsets corresponding to more than 1 lobe, 12 patients had semiology of temporal lobe epilepsy, 5 patients had occipital lobe epilepsy, 3 patients had frontal lobe epilepsy, 4 patients had parietal lobe epilepsy and seizures not indicative for a particular lobe were found in 2 patients.
- In Group 3 ($n = 27$), seizure semiology had the following distribution: frontal lobe epilepsy was present in 9 patients, temporal lobe epilepsy was present in 6 patients, parietal lobe epilepsy was present in 5 patients, occipital lobe epilepsy was present in 1 patient, 4 patients had seizures corresponding to more than 1 lobe and 2 patients had non-localized semiology.

Comparing epidemiological, clinical and electroencephalographic data between the 3 groups (see Table 4), just one variable reached statistical significance: the existence of a neurological deficit. This variable was higher in Group 3 ($p = 0.0001$) and was present in 70.4% of the cases included in this group.

4. Discussion

In this article, we report a series of adult patients with symptomatic partial epilepsy secondary to MCD who were assisted in a specialized epilepsy center in the city of Buenos Aires. We found 152 patients with this diagnosis and included 138 of these patients in the study. Taking into account the active population of patients with epilepsy who attended our center in the specified period (near 3000 patients), the frequency of presentation of MCD was of approximately 5%. This is similar to what was reported in other patient series, although the true incidence of MCD is not known. In the diagnosis of focal epilepsy, MCD prevalence ranges between 3% and 25% depending on the varying selection criteria

Table 4
Comparison of epidemiological, clinical and electroencephalographic findings in the 3 groups.

	Group 1 ($n = 71$)	Group 2 ($n = 40$)	Group 3 ($n = 27$)
Age at last follow up (y)	36.8 (20.2–77.1)	37.1 (1.7–66.3)	36.2 (18.27–59.7)
Age at seizure onset (y)	11.9 (0.1–66)	12.9 (0.8–32)	12.5 (0.7–32)
Mean duration of epilepsy (y)	24.9 (6.74–60.1)	24.4 (3.0–52.23)	20.6 (7.42–47.7)
Female gender	32 (44%)	27 (66%)	13 (52%)
Family history	6 (8.4%)	1 (2.4%)	0
History of West Syndrome	6 (8.4%)	0	0
History of perinatal injury	8 (11.2%)	7 (17.5%)	6 (4.3%)
Mental retardation	23 (32.4%)	10 (25%)	11 (40.7%)
Neurological deficit	5 (7.0%)	5 (12.5%)	19 (70.4%)*
Secondary generalized seizures	53 (74.6%)	32 (80%)	15 (62.9%)
Temporal lobe epilepsy	23 (32.4%)	12 (30%)	6 (22.2%)
Frontal lobe epilepsy	27 (38.0%)	3 (7.5%)	9 (33.3%)
Parietal lobe epilepsy	7 (9.8%)	4 (10.0%)	5 (18.5%)
Occipital lobe epilepsy	3 (4.2%)	5 (12.5%)	1 (3.7%)
Seizures corresponding to more than 1 lobe	9 (12.7%)	14 (35%)	4 (14.8%)
Seizure not indicative of one lobe	2 (2.8%)	2 (5.0%)	2 (7.4%)
Epileptiform discharges in EEG	48 (67.6%)	31 (77.5%)	21 (77.8%)
EEG with bilateral discharges	33 (46.5%)	16 (40%)	6 (22.2%)
Refractory epilepsy	60 (84.5%)	35 (87.5%)	22 (81.4%)

* $p = 0.0001$.

and imaging techniques applied.[16] Li et al. applied MRI to 341 adult patients with refractory focal epilepsy and found MCD in 12% of cases.[19] MCD represented 8% of partial epilepsy cases in Semah et al.'s study.[20] An incidence of 3% was found in Everitt et al.'s prospective study.[21] Furthermore, the prevalence of MCD could be underestimated as a substantial proportion of patients, especially those with cortical dysplasia, have negative MRI studies and can be recognized only by a careful neuropathological study following surgery.[22] MCD rates near 25% have been reported in surgery studies, the majority of cases with FCD.[23,24] Due to the poor social conditions that may predispose a person to gestational and perinatal insults, it was hypothesized that the incidence of MCD could be higher in a developing country such as was studied in this report; however, this hypothesis is not confirmed by our study.

The mean age of seizure onset in our study was at 12.3 years of age, and the age of onset was found to occur as early as in the neonatal period or as late as in middle age. Interestingly, we found a case of epilepsy that started at 66 years of age with diagnosis of FCD. Fausser et al. has similarly reported a patient with late epilepsy onset at the age of 60.[25] The mechanisms leading to epileptogenesis in MCD are variable and are still under investigation. Similar to what is observed in other lesional epilepsies, the structural anomaly may precede epilepsy onset by many years. Moreover, epilepsy may never develop in a variable percentage of patients according to the type of MCD.

In the present series, cases were classified according to BC.[8–10] Seventy-one patients (51.4%) were diagnosed with malformations due to abnormal cell proliferation (Group 1), 40 patients (28.9%) had malformations due to abnormal migration (Group 2) and 27 patients (19.6%) had malformations due to abnormal cortical organization (Group 3). We chose this classification because it allows patients to be categorized based on clinical and imaging findings, without the need for genetic or histopathological studies. Genetic tests in MCD are usually performed just for research purposes and are not common in clinical settings, even in developed countries.[26–28]

In our study, a comparative analysis of the 3 groups of MCD showed that there was not a significant difference in most of the clinical and epidemiologic features; however, a significant difference between these groups was noted in the presence of a focal deficit on the neurologic exam, which occurred more often in Group 3, in which PMG and schizencephaly are included. Some distinctive syndromes are well known in the spectrum of PMG. For instance, bilateral perisylvian syndrome (see Fig. 3) is characterized by pseudobulbar palsy, cognitive deficits, epilepsy and bilateral perisylvian polymicrogyria on MRI.[29] Other syndromes in PMG have also been described.[30–32] A high incidence of prenatal/perinatal insults as a probable etiology of PMG and schizencephaly has been reported in some studies.[33,34] These insults could also be the cause of the abnormalities found in the neurological exam.[35] However, we did not find a higher incidence of prenatal/perinatal insults in Group 3 compared to the other groups. Variation in localization or size of the lesions could be another reason for the differences found in the neurological examination. For instance, all of the 5 patients in Group 1 that presented with abnormal neurological examinations (3 had FCD and 2 had TS) had large lesions and multilobar involvement always affecting the perirolandic region, whereas 85.5% of the patients without neurological deficit in this group (excluding those with TS that usually have multifocal lesions) had a more circumscribed unilobar involvement affecting the temporal or frontal lobes.

Relatively few large studies of adult patients with a diagnosis of epilepsy and MCD have been reported. One example includes work by Raymond et al.[36] who analyzed 100 adults diagnosed with MCD, with a mean age of 27 years, all of whom had refractory epilepsy. In agreement with our findings, in this study, seizure onset was at a mean age of ten, and epilepsy started in adulthood in only 30 patients. In contrast with our study, in which 100% of cases were classified as having focal seizures, Raymond et al. described a partial syndrome in 84% of their cases. These differing results could be explained by the different classifications of seizures and syndromes that were applied in both studies. Raymond et al. found that 32% had a perinatal or prenatal insult, whereas in our series this was found in 15.2% of cases. Mental retardation and developmental delay were observed in 19% of cases, and neurological deficits were present in 14% in the Raymond patient population. These findings are lower than what we found (incidence of 31.9% and 21%, respectively) in our population.

Another study worth mentioning is Tinuper et al., which included 60 patients:[37] 28% of the cases could not be classified because of having a complex type of MCD (5 patients) or incomplete medical data (12 patients). As in our study, the Tinuper study used the BC to categorize the patients. To compare with our findings, we had to recalculate the frequencies of the subtypes described in this study, excluding the 17 patients that were not classified. Following recalculation, the distribution in the 3 groups was as follows: 48.8% (21 patients) with a disorder in proliferation, 39.5% (17 patients) with migration disorders, and 11.6% (5 patients) with abnormalities in organization. Likewise, the majority of patients in our study were classified into Group 1 and Group 3 was the least frequent category.

Pascual-Castroviejo et al.[38] presented 144 children classified with the BC scheme. In this study, unlike in our study, the majority (53.5%) of patients were included into Group 3, with 61 patients with polymicrogyria and 16 patients with schizencephaly, whereas they only found 9 cases with FCDs. They also included 22 patients with lissencephaly and 8 cases with hemimegalencephaly; we did not find lissencephaly cases in our adult series, and we found 3 probable cases of hemimegalencephaly. These differences in the distribution of the MCD subtypes could be explained because of the variance in the ages of populations included in the studies (pediatric vs. adults). Pediatric patient series of MCD are prone to having a higher proportion of cases presenting epilepsy and developmental delay and having more severe malformations such as lissencephaly, hemimegalencephaly and extensive polymicrogyria and schizencephaly, whereas adult series, such as ours, tend to include older patients with a higher percentage of focal cortical dysplasias, low grade tumors, heterotopias and less severe polymicrogyrias and schizencephalies. The usual coexistence of neurological signs in Group 3 likely leads to an earlier consultation, which could be one reason for the predominance of this group of MCD in the pediatric series. Moreover, patients with severe malformations like lissencephaly have a bad prognosis and usually do not reach adulthood. This is reflected by the absence of this subgroup in our study.

Montenegro et al. presented a study in a developing country that took place in a center in Brazil,[39] and Güngör et al. have presented a study based on patients in Turkey.[40] Montenegro et al. presented 100 patients with a diagnosis of MCD in a neuroimaging study, but not all of the patients had epilepsy (epilepsy was present in 77% of cases). Their most relevant finding was that epilepsy in patients with polymicrogyria and schizencephaly had a better control of seizures compared to the other groups. Similarly, Güngör et al. described 101 patients (of a pediatric population), in which 71.3% of cases with epilepsy. In this last study, it was also observed that patients with polymicrogyria and schizencephaly had a better control of their seizures. In contrast with these two last reports, our study only included patients who had a confirmed diagnosis of epilepsy; our study did not find a difference in seizure control between the 3 groups of MCD. The high incidence of refractory epilepsy in the 3 groups possibly reflects the fact that our study was performed in a referral epilepsy center and that difficult cases

are prone to be transferred to our center for their treatment and follow up.

With regard to seizure types, all of our patients were considered to have focal seizures. Just 6 patients had experienced epileptic spasms or a diagnosis of West syndrome in their early infancy developing focal seizures later during disease evolution. The semiology of seizures was extremely variable. Temporal and frontal lobe seizures seem to predominate in accordance with what is published for focal epilepsies in the general population[41] and were observed in 29.7% and 28.3% of cases, respectively. Seizures corresponding to more than one lobe occurred in 19.6% of the cases. In Group 2, 35% of the cases (14 out of 40) showed seizures with different onset corresponding to more than 1 lobe, whereas this happened in only 9 out of 71 (12.7%) G1 cases and in only 4 out of 27 G3 cases (14.8%). With respect to the localization and extent of the lesions, multilobar involvement was higher in group 2 (71%; 10 out of 14 excluding PNH in which this concept cannot be applied) and group 3 (62%; 17 out of 27), compared to group 1 (28%; 20 out of 71). We observed that seizure semiology depended on the localization of the lesion and not on the type of MCD, as different types of lesions in a given location showed the same semiology.

EEG showed epileptiform discharges in 72.5% of all cases with bilateral distribution in 54.9% of them. Bilateral discharges were present in the following distribution: 46.5% of patients with anomalies in proliferation, 40% of the patients with anomalies in migration and 22.2% of patients with abnormalities in organization. The differences found in the distribution of EEG discharges in the different groups were not of statistical significance. Video EEG was performed in 29 patients (21%), and in 6 others (4.3%), video EEG has been ordered but not performed yet. Patients that were not considered good candidates for resective epilepsy surgery did not have this test performed.

Most of the patients had medically refractory epilepsy; only 8 patients (5.7%) underwent epilepsy surgery. All the operated patients belonged to Group 1, and there was agreement between the presurgical image and the histopathological diagnosis. Many developing countries have created epilepsy surgery programs in recent years.[42] However, a report from the year 2000 revealed that only 26 out of 142 (18%) economically disadvantaged nations had at least one center that regularly conducted epilepsy surgery, compared with 18 out of 24 (75%) in developed countries.[43] Moreover, epilepsy surgery centers in resource-poor countries, like Argentina, lack the full range of state-of-the-art technologies to perform presurgical evaluation and surgery techniques that are usually available in developed countries.[44] Very few patients in resource-poor countries have access to or can afford the cost of the intracranial electrodes that are used in invasive evaluation. In our center, it is usual to perform surgery in patients with unilateral mesial temporal lobe epilepsy or well-circumscribed lesions, which do not need invasive or expensive techniques in the presurgical evaluation, but this is not the case in the majority of MCD patients. Nevertheless, MCD surgical outcome, even in the developed world, is worse than that reported for HS and for other focal pathologies. Large MCD studies with at least 2 years of follow up suggest a 50–60% seizure-free outcome compared with 70–85% in surgery for HS.[45] This may reflect the incomplete understanding of MCD biology and other non-biological issues that complicate presurgical evaluation of these patients or the inadequate surgical techniques applied. Completeness of resection, a key factor for successful surgery, might be difficult, especially in proximity to eloquent cortex.[46] Furthermore, there are cases in which surgery is precluded beforehand, without even having an ordinary presurgical evaluation, as some subtypes of MCD are thought to be bad candidates for surgery. This is the case for patients with bilateral, extensive malformations or lesions localized in non-resectable eloquent areas. In our study, video EEG was not performed in these cases, even if this technique was available, as they were not considered for surgery. Regarding the different subtypes, FCD is undoubtedly the most common MCD in surgical series. MCD subtypes included in Group 2 and 3 are less likely to be considered for surgery even in developed countries.[45] Many of our cases in Group 2 and 3 had bilateral or diffuse lesions in MRI.

The matters discussed above (limitations of presurgical resources and poor risk-benefit balance in determined cases) explain the low proportion of patients in our study that underwent surgery, even though the majority of our population was refractory to medical treatment.

The present article is concerned with the clinical characteristics found in a consecutive series of patients with epilepsy secondary to MCD. It has to be considered that this is one of only a few studies on this entity that have been carried out in a developing country. The incidence rate that we found was similar to that reported in other studies and does not differ from reports from developed countries.

Our study also reflects the usefulness of Barkovich et al.'s classification scheme in clinical practice, as we were able to divide all patients in its 3 principal groups and make a comparison between them. The only difference that we observed, when we compared patients in the 3 groups, was that the presence of a neurological deficit was higher in patients belonging to Group 3 (cases with polymicrogyria and schizencephaly). When MCD is suspected in an epileptic patient with an abnormal neurological exam, these subtypes have to be thought as the first diagnostic possibility.

In a country with limited resources, the possibility of classifying individual cases with imaging and electro clinical criteria alone, without the need for genetic tests, is crucial for early diagnosis and treatment. We think that the Barkovich classification can be used for correct categorization of patients with MCD and allows physicians to make a prognosis and seek the best therapeutic option for each case. For example, some cases with bilateral pathology such as bilateral periventricular heterotopia, bilateral perisylvian polymicrogyria or unilateral but extended malformations are not good surgical candidates. In this case, optimizing medical treatment or other alternative therapeutic options (vagus nerve stimulation, corpus callosotomy surgery or hemispherectomy) might be beneficial.

References

1. Koehn MA, Duchowny M. Preoperative clinical evaluation and noninvasive electroencephalogram in cortical dysplasia. *Neurosurg Clin N Am* 2002;**13**(1):35–9.
2. Guerrini R, Holthausen H, Parmeggiani L, Chiron C. Epilepsy and malformations of cerebral cortex. *Epileptic syndromes in infancy, childhood and adolescence*. London: John Libbey and Co Ltd.; 2002. p. 457–79.
3. Chung CK, Lee SK, Kin KJ. Surgical outcome of epilepsy cause by cortical dysplasia. *Epilepsia* 2005;**46**(suppl 1):25–9.
4. Sisodiya SM. Malformation of cortical development: burdens and insights from important causes of human epilepsy. *Lancet Neurol* 2004;**3**:29–38.
5. Kuzniecky RI, Barcovich AJ. Malformations of cortical development and epilepsy. *Brain Dev* 2001;**23**:2–11.
6. Palmini A, Lüders HO. Classification issues in malformations caused by abnormalities of cortical development. *Neurosurg Clin N Am* 2002;**37**(1):1–25.
7. Vigevano F, Fusco L, Lo Russo G, Broggi G. Epilepsy and malformations of cortical development: Editorial. *Epileptic Disord* 2003;**5**(Suppl. 2):S7–S8.
8. Barkovich AJ, Kuzniecky RI, Dobyns WB, Jackson GD, Becker LE, Evrard P. A classification scheme for malformations of cortical development. *Neuropediatrics* 1996;**27**:59–63.
9. Barkovich AJ, Kuzniecky RI, Jackson GD, Guerrini R, Dobyns WB. Classification system for malformations of cortical development. Update 2001. *Neurology* 2001;**57**:2168–78.
10. Barkovich AJ, Kuzniecky RI, Jackson GD, Guerrini R, Dobyns WB. A developmental and genetic classification for malformations of cortical development. *Neurology* 2005;**65**:1873–87.
11. Berg AT, Berkovic SF, Brodie MJ, Buchhalter J, Cross JH, Van Emde Boas W, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE commission of classification and terminology 2005–2009. *Epilepsia* 2010;**51**(April (4)):676–85.

12. Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. *Epilepsia* 1989;**30**(4):389–99.
13. Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Allen Hauser W, Mathern G, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. *Epilepsia* 2010;**51**(6):1069–77.
14. Glauser T, Ben-Menachem E, Bourgeois B, Cnaan A, Chadwick D, Guerreiro C, et al. ILAE treatment guidelines: evidence-based analysis of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. *Epilepsia* 2006;**47**(7):1094–120.
15. Blümcke I, Thom M, Aronica E, Armstrong DD, Vinters HV, Palmini A, et al. The clinicopathologic spectrum of focal cortical dysplasias: a consensus classification proposed by an ad hoc Task Force of the ILAE Diagnostic Methods Commission. *Epilepsia* 2011;**52**(1):158–74.
16. Najm I, Avanzini G, Guerrini R, Foldvary-Schaefer N, Jackson G, Lüders HO, et al. Terminology and classification of cortical dysplasias. *Neurology* 2004;**62**(6 Suppl. 3):S2–8.
17. Barkovich AJ, Kuzniecky RI. Neuroimaging of focal malformations of cortical development. *J Clin Neurophysiol* 1996;**13**(6):481–94.
18. Barkovich AJ, Kuzniecky RI, Bollen AW, Grant PE. Focal transmantle dysplasia: a specific malformation of cortical development. *Neurology* 1997;**49**(4):1148–52.
19. Li LM, Fish DR, Sisodiya SM, Shorvon SD, Alsanjari N, Stevens JM. High resolution magnetic resonance imaging in adults with partial or secondary generalized epilepsy attending a tertiary referral unit. *J Neurol Neurosurg Psychiatry* 1995;**59**:384–7.
20. Semah F, Picot MC, Adam C, Broglin D, Arzimanoglou A, Bazin B, et al. Is the underlying cause of epilepsy a major prognostic factor for recurrence? *Neurology* 1998;**51**:1256–62.
21. Everitt AD, Birnie KD, Stevens JM, Sander JW, Duncan JS, Shorvon SD. The NSE MRI study: structural brain abnormalities in adult epilepsy patients and healthy controls (abstract). *Epilepsia* 1998;**39**(Suppl 6):140.
22. Mathern GW. Epilepsy surgery patients with cortical dysplasia: present and future therapeutic challenges. *Neurology* 2009;**72**:206–7.
23. Tassi L, Colombo N, Garbelli R, Francione S, Lo Russo G, Mai R, et al. Focal cortical dysplasia: neuropathological subtypes, EEG, neuroimaging and surgical outcome. *Brain* 2002;**125**:1719–32.
24. Bast T, Ramantani G, Seitz A, Rating D. Focal cortical dysplasia: prevalence, clinical presentation and epilepsy in children and adults. *Acta Neurol Scand* 2006;**113**:72–81.
25. Fausser S, Schulze-Bonhage A, Honegger J, Carmona H, Huppertz GP, Rona S, et al. Focal cortical dysplasias: surgical outcome in 67 patients in relation to histological subtypes and dual pathology. *Brain* 2004;**127**:2406–18.
26. Bahi-Buisson N, Boddaert N, Saillour Y, Souville I, Poirier K, Léger PL. Epileptogenic brain malformations: radiological and clinical presentation and indications for genetic testing. *Rev Neurol (Paris)* 2008;**164**(12):995–1009.
27. Leventer RJ, Guerrini R, Dobyns WB. Malformations of cortical development and epilepsy. *Dialogues Clin Neurosci* 2008;**10**(1):47–62.
28. De Wit MC, Lequin MH, de Coo IF, Brusse E, Halley DJ, Van de Graaf R, et al. Cortical brain malformations: effect of clinical, neuroradiological, and modern genetic classification. *Arch Neurol* 2008;**65**(3):358–66.
29. Kuzniecky R, Andermann F, Guerrini R. The epileptic spectrum in the congenital bilateral perisylvian syndrome. *Neurology* 1994;**44**:379–85.
30. Montenegro M, Guerreiro M. Bilateral posterior parietal polymicrogyria: A mild form of congenital bilateral perisylvian síndrome? *Epilepsia* 2001;**42**(7):845–9. 2001.
31. Guerrini R, Genton P, Bureau M, Parmeggiani A, Salas-Puig X, Santucci M, et al. Multilobar polymicrogyria, intractable drop attack seizures, and sleep-related electrical status epilepticus. *Neurology* 1998;**51**:504–12.
32. Caraballo R, Cersosimo R, Fejerman N. A particular type of epilepsy in children with congenital hemiparesis associated with unilateral polymicrogyria. *Epilepsia* 1999;**40**:865–71.
33. Pascual-Castroviejo I, Pascual-Pascual SI, Viaño J, Martínez V, Palencia R. Unilateral polimicrogyria: a common cause of hemiplegia of prenatalorigin. *Brain Dev* 2001;**23**:216–22.
34. Mejía L, Gómez JC, Carrizosa J, Cornejo JW. Phenotypic characterisation of 35 Colombian children with an imaging diagnosis of schizencephaly. *Rev Neurol* 2008;**47**(2):71–6.
35. Krsek P, Jahodova A, Maton B, Jayakar P, Dean P, Korman B, et al. Low-grade focal cortical dysplasia is associated with prenatal and perinatal brain injury. *Epilepsia* 2010;**51**(December (12)):2440–8.
36. Raymond AA, Fish DR, Sisodiya SM, Alsanjari N, Stevens JM, Shorvon SD. Abnormalities of gyration, heterotopias, tuberous sclerosis, focal cortical dysplasia, microdysgenesis, dysembryoplastic neuroepithelial tumor and dysgenesis of the archicortex in epilepsy: clinical, EEG and neuroimaging features in 100 adult patients. *Brain* 1995;**118**:629–60.
37. Tinuper P, D' Orsi G, Bisulli F, Zaniboni A, Piracci A, Bernardi B, et al. Malformation of cortical development in adult patients. *Epileptic Disord* 2003;**5**(Suppl 2):S85–90.
38. Pascual-Castroviejo I, Pascual-Pascual SI, Viaño J, Martínez V, Palencia R. Malformaciones del desarrollo cortical y su repercusión clínica en una serie de 144 casos. *Rev Neurol* 2003;**37**(4):327–34.
39. Montenegro MA, Cendes F, Lopes-Cendes I, Guerreiro CA, Li LM, Guerreiro MM. The clinical spectrum of malformations of cortical development. *Arq Neuropsiquiatr* 2007;**65**(June (2A)):196–201.
40. Güngör S, Yalnizoğlu D, Turanli G, Saatçi I, Erdoğan-Bakar E, Topçu M. Malformations of cortical development and epilepsy: evaluation of 101 cases (part I and II). *Turk J Pediatr* 2007;**49**(April–June (2)):120–40.
41. Manford M, Hart YM, Sander JW, Shorvon SD. National General Practice study of Epilepsy (NGPSE): partial seizure patterns in a general population. *Neurology* 1992;**42**(10):1911–7.
42. Radhakrishnan K. Challenges in the management of epilepsy in resource-poor countries. *Nat Rev Neurol* 2009;**5**:323–30.
43. Wieser H, Silfvenius H. Overview: epilepsy surgery in developing countries. *Epilepsia* 2000;**41**(4):S3–9.
44. Sylaja PN, Radhakrishnan K. Surgical management of epilepsy. Problems and pitfalls in developing countries. *Epilepsia* 2003;**44**(1):48–50.
45. Sisodiya SM. Surgery for malformation of cortical development causing epilepsy. *Brain* 2000;**123**:1075–91.
46. Guerrini R, William B, Dobyns WB, Barkovich AJ. Abnormal development of the human cerebral cortex: genetics, functional consequences and treatment options. *Trends Neurosci* 2008;**31**(3):154–62.