Interrelationship of Genetics and Prenatal Injury in the Genesis of Malformations of Cortical Development

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Context: Although the causes of some malformations of cortical development (MCD) have been established, others remain unclear. There are several lines of evidence supporting the theory of a complex mechanism that involves genetic and environmental factors.

Objective: To investigate the interrelationship of genetics and prenatal injury in the genesis of MCD.

Patients and Design: A series of 76 consecutive patients with MCD and their families were systematically questioned about their family histories of epilepsy or other neurological impairment and the occurrence of prenatal events. Whenever possible, magnetic resonance imaging was performed in other family members if MCD was suspected or in the presence of any neurological impairment. Patients were divided into 3 groups according to the type of MCD. Patients in group 1 had focal cortical dysplasia, group 2 had heterotopias (periventricular or subcortical) or agyria-pachygyria, and group 3 had polymicrogyria or schizencephaly. These findings were also compared with a disease-control group of 40 consecutive patients with epilepsy but without MCD.

Setting: Neurology clinic of a university hospital.

Results: Of the 76 patients with MCD, 21 (28%) had focal cortical dysplasia, 19 (25%) had heterotopias or agyria-pachygyria, and 36 (47%) had polymicrogyria or schizencephaly. There were 39 men and 37 women, aged 2 to 52 years (mean age, 13 years). In group 2, 6 patients (32%) had a family history of MCD, mental retardation, or miscarriages, suggesting a genetic predisposition. In group 3, family history of MCD was present in 5 patients (14%). Prenatal events occurred in 28 patients with MCD (37%) and 2 controls (5%) and were more frequent in patients with heterotopia or agyria-pachygyria and polymicrogyria (P < .001). Conversely, epilepsy occurred in all patients in group 1, in 17 patients (89%) in group 2, and in 17 patients (47%) in group 3. In group 3, epilepsy was less frequent (P < .001) and more easily controlled (P = .005) than in other forms of MCD.

Conclusions: Our findings support the idea of a spectrum among the different types of MCD. Focal cortical dysplasia (group 1) is associated with more frequent and severe epilepsy and less important genetic and prenatal events, heterotopias and agyria-pachygyria (group 2) are frequently associated with genetic predisposition, and polymicrogyria and schizencephaly (group 3) are less frequently associated with epilepsy but have a stronger association with genetic and detectable prenatal events.

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The migration of neuroblasts from the periventricular germinal matrix to their final destination and their organization within the cortical mantle may be disturbed by genetic or environmental factors. The interrelationship of genetics and prenatal events as contributors to malformations of cortical development (MCD) has been reported previously. However, few studies of large series are available.

The objective of this study was to investigate the occurrence of genetic predisposition and prenatal events and the interaction between these factors in a large series of patients with different types of MCD. We believe that this study may clarify the complex mechanisms involved in normal and abnormal cortical development.

DISEASE-CONTROL GROUP

Of 40 control subjects with epilepsy, 32 (80%) had temporal lobe epilepsy, 3 (8%) had frontal lobe epilepsy, and in 5 (13%) the localization was not established.
PATIENTS AND METHODS

This study was conducted at the neurology clinic of a university hospital. We evaluated 76 consecutive patients with a diagnosis of MCD confirmed by high-resolution magnetic resonance imaging (MRI). All patients were examined by at least 1 of us, and, whenever possible, an MRI was performed in other family members if cortical maldevelopment was suspected. We systematically investigated all patients and family members with any neurological disturbance, even when symptoms were mild, such as speech delay in early childhood. All patients signed an informed consent form approved by the ethics committee of the University of Campinas, Campinas, Brazil.

We used a semistructured questionnaire to ask patients and their families about family history of epilepsy or other neurological impairment in first-degree, second-degree, or third-degree relatives and the occurrence of any prenatal event during the first 24 weeks of gestation. Significant prenatal events included any abnormality reported by the mother or family during the first 24 weeks of gestation, such as a failed abortion attempt, drug addiction, physical abuse, a fall with abdominal trauma, hypertension, fever, skin rash, diabetes mellitus, exposure to x-rays, twin gestation, cytomegalovirus infection, and tonic-clonic seizure. Vaginal bleeding was not included as a significant prenatal event in this study because it is difficult to establish if the bleeding had any repercussion that led to vascular injury, such as in placental anomalies, or was already the result of a major malformation. In addition, we did not include the use of over-the-counter medications as a risk factor because, even though they are often used in the first 24 weeks of gestation, these drugs have not been associated with the pathogenesis of MCD. Because the occurrence of a prenatal event was retrospectively assessed, we directly interviewed the patients’ mothers and other available family members. In addition, we reviewed the clinical files of all patients.

The diagnosis of MCD was established according to MRI findings. The MRI was performed with a 2.0 T scanner (Elscint Prestige; Elscint Ltd, Haifa, Israel), using our epilepsy protocol: (1) sagittal T1-weighted spin-echo, 6 mm thick (repetition time [TR], 430; echo time [TE], 12) for optimal orientation of the subsequent images; (2) coronal T1 inversion recovery, 3 mm thick (flip angle, 200°; TR, 2800–3000; TE, 14; inversion time [TI], 840; matrix, 130×236; field of view [FOV], 16×18 cm); (3) coronal T2-weighted fast spin-echo, 3 to 4 mm thick. (flip angle, 120°; TR, 4800; TE, 129; matrix, 252×320; FOV, 18×18 cm); (4) axial images parallel to the long axis of the hippocampus; (5) T1 gradient echo, 3 mm thick (flip angle, 70°; TR, 200; TE, 5; matrix, 180×232; FOV, 22×22 cm); (5) axial T2 fast spin-echo, 4 mm thick (flip angle, 120°; TR, 6800; TE, 129; matrix, 252×328; FOV, 21×23 cm); and (6) volumetric (3-dimensional) T1 gradient echo, acquired in the sagittal plane for planar reconstruction, 1 to 1.5 mm thick (flip angle, 35°; TR, 22; TE, 9; matrix, 256×220; FOV, 23×23 cm). We performed planar reconstruction and curvilinear reformating in all 3-dimensional MRIs.23

Patients were divided into 3 groups according to the MRI findings of MCD. Patients in group 1 had focal cortical dysplasia, group 2 had heterotopias (periventricular or subcortical) or agyria-pachygyria, and group 3 had polymicrogyria or schizencephaly (Figure 1).

We also assessed a disease-control group and performed detailed interviews about the occurrence of prenatal events and family history of any neurological disturbance. The same semistructured questionnaire was used for patients with MCD and controls. The disease-control group consisted of 40 consecutive patients with epilepsy seen prospectively at our epilepsy clinic (26 women; age range, 6-54 years; mean age, 26.9 years) who underwent neuroimaging evaluation according to our epilepsy protocol and whose MRI findings excluded the presence of MCD. We excluded patients with major destructive lesions, such as porencephaly or hemispheric atrophy.

We used the χ² test to analyze differences in the frequency distribution of prenatal events, family history of epilepsy, family history of neurological impairment, and occurrence of epilepsy and seizure control among the different groups of patients with MCD and the control group, when appropriate. A P value of less than .05 was considered significant.

cause of epilepsy according to MRI findings was hippocampal sclerosis in 16 patients (40%), cavernous angioma in 3 (8%), low-grade tumor in 3 (8%), gliosis in 2 (5%), and cysticercosis in 2 (5%); 14 patients had normal findings on MRI. Family history of epilepsy was present in 13 patients (33%), mental retardation in 1 patient (3%), and history of miscarriage in 1 patient (3%). Two patients (5%) had a history of prenatal events during pregnancy. One reported fever in the first trimester of pregnancy, and the other reported amniotic bands, with multiple finger amputation.

PATIENTS WITH MCD

We evaluated 76 patients, 39 men and 37 women, whose ages ranged from 2 to 52 years (mean age, 13.8 years). Twenty-one patients (28%) had focal cortical dysplasia (52% men), 19 patients (25%) had heterotopias or agyria-pachygyria (26% men), and 36 patients (47%) had polymicrogyria or schizencephaly (67% men). Tables 1, 2, and 3 present the characteristics of patients in each group. Figure 2 shows the frequency of prenatal events, epilepsy, family history of neurological impairment, and family history of epilepsy, according to each group.

Patients in group 1 (Table 1; focal cortical dysplasia) had a lower frequency of prenatal events (5 [24%]) and family history of neurological impairment (3 [14%]) than the other 2 groups of patients with MCD and the disease-control group (P=.002). None of the patients in group 1 had a family history of MCD.

In group 2 (heterotopias or agyria-pachygyria), 8 patients (42%) had a history of a prenatal event that may have contributed to the pathogenesis of MCD (Table 2; patients 1-4, 7, 8, 11, and 14). Six patients (32%) had familial occurrence of MCD, mental retardation, or mis-
carriages, suggesting a genetic predisposition (Table 2; patients 1, 7, 9, and 11-13).

In group 3 (polymicrogyria or schizencephaly), 15 patients (42%) had a history of a prenatal event (Table 3; patients 1-15). Five patients (14%) had a family history of MCD in a first-degree relative (Table 3; patients 1, 18, 19, 27, and 33), and 8 (22%) had a family history of mental retardation, developmental delay, or miscarriage (Table 3; patients 5, 9-11, 20, 21, 31, and 32).

Family history of epilepsy was present in all groups of patients with MCD and in the disease-control group, and no significant differences in the frequency of a family history of epilepsy were detected among the groups (P = .18). Sixteen family members underwent MRI, and 5 (31%) had MCD (group 2, patient 13; and group 3, patients 18, 19, 27, and 33).

Epilepsy occurred in all patients with focal cortical dysplasia, and seizures were controlled with antiepileptic drugs in only 4 patients (19%). In group 2 (heterotopias or agyria-pachygyria), 17 patients (89%) had epilepsy, and only 1 (5%) had her seizures controlled with antiepileptic drugs. In group 3 (polymicrogyria or schizencephaly), 17 patients (47%) had epilepsy, and 9 of these (53%) were seizure-free after introduction of antiepileptic drugs. The frequency of epilepsy was lower (P<.001) and more easily controlled (P = .005) in group 3.

The development of human cerebral cortex can be divided into 3 overlapping stages: proliferation of stem cells into neuroblasts or glial cells, migration from the periventricular germinal matrix toward the developing cortex, and cortical organization within 6 layers associated with synaptogenesis and apoptosis.9,17-19 This is a dynamic process, and 1 or more stages may occur simul-

![Figure 1. A 2-dimensional curvilinear reconstruction (A) shows a focal cortical dysplasia with thickening of the left postcentral gyrus and blurring between gray and white matter (box; Table 1, patient 6). A coronal T1 image (B) shows diffuse subcortical band heterotopia/double cortex (Table 2, patient 2). An axial T1 image (C) shows bilateral perisylvian polymicrogyria (Table 3, patient 23). A curvilinear reconstruction of the same patient as in Figure 1C (D) shows the extension of the polymicrogyria from the sylvian fissure until the parieto-occipital regions.](https://archneur.jamanetwork.com/)

<table>
<thead>
<tr>
<th>Table 1. Characteristics of Patients With Focal Cortical Dysplasia (FCD; Group 1)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient No./ Age, y/Sex</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>1/9/F</td>
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<tr>
<td>2/6/M</td>
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<tr>
<td>3/2/M</td>
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<td>6/24/F</td>
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<tr>
<td>15/19/F</td>
</tr>
<tr>
<td>16/7/M</td>
</tr>
<tr>
<td>17/3/F</td>
</tr>
<tr>
<td>18/4/F</td>
</tr>
<tr>
<td>19/41/F</td>
</tr>
<tr>
<td>20/38/M</td>
</tr>
<tr>
<td>21/10/M</td>
</tr>
</tbody>
</table>

*MR indicates mental retardation; AED, antiepileptic drugs; and ellipses, not applicable.
†Cognitive status was assessed during neurological examination.

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Normal cortical development depends on many interacting components such as trophic factors, cell-adhesion molecules, cell-cell contact-dependent signals, and possibly other currently unrecognized factors. Its association with several genetically determined syndromes, such as neurofibromatosis 1, tuberous sclerosis, hypomelanosis of Ito, Walker-Warburg, Aicardi, Zellweger, Miller-Diecker, and many others, and the occurrence of familial cases of MCD (X-linked lissencephaly and filamin 1 in lissencephaly and transmantine in agryria-pachygyria) strongly indicate a genetic component in the processes leading to different extremes within the spectrum of the same disease, which has an X-linked pattern of inheritance.

There are several reports indicating that harmful prenatal events are likely to be involved in the pathogenesis of some MCD. However, to our knowledge, no study has systematically evaluated the influence of genetic or prenatal events in each of the 3 different stages of MCD.

The division of MCD into different groups is a major challenge because many important aspects, such as association with a specific genetic syndrome and pathological and neuroimaging findings, should be considered. In our study, the diagnosis of MCD was based on well-established MRI findings, and the classification of patients into 3 groups was consistent with imaging findings. Heterotopias (subcortical or periventricular) and agryria-pachygyria (group 2) and polymicrogyria and schizencephaly (group 3) were grouped together because there is strong evidence that, in many cases, these lesions represent different ends within the spectrum of the same disease.

In group 1 (focal cortical dysplasia), the frequency of family history of neurological impairment (3 patients [14%]) and the occurrence of a prenatal event (5 patients [24%]) were significantly lower compared with the other forms of MCD. In addition, none of these patients had a family history of MCD. To our knowledge, there is no description of familial cases of focal cortical dysplasia.

### Table 2. Characteristics of Patients With Heterotopias or Agyria-Pachygyria (Group 2)*

<table>
<thead>
<tr>
<th>Patient No./Age, y/Sex</th>
<th>Imaging Findings</th>
<th>Prenatal Event</th>
<th>Family History (No. of Relatives)</th>
<th>Age at First Seizure</th>
<th>Clinical Outcome</th>
<th>Cognitive Status†</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/12/M 2/12/F 3/12/F 4/4/M 5/22/F 6/25/F 7/28/F 8/3/M 9/7/M 10/3/M 11/10/F 12/30/F 13/29/F 14/34/F 15/6/6/F 16/19/F 17/4/F 18/52/F 19/29/F</td>
<td>High blood pressure Exposure to x-rays Cyto-meagolovirus infection Fever and skin rash</td>
<td>Stillbirth (1); MR (1) Epilepsy (2) ... Epilepsy (1) ... Epilepsy (1)</td>
<td>MR (1); multiple malformations (1)</td>
<td>3 mo 11 y 3 d 2 mo 4 y 2.5 y 4 y 3 mo 5 mo</td>
<td>Daily seizures MR Daily seizures MR Daily seizures MR Daily seizures MR Daily seizures MR Daily seizures MR Daily seizures MR Daily seizures MR</td>
<td>Pachygyria Pachygyria Epilepsy (1) PNH (1); 5 spontaneous abortions PNH (1)</td>
</tr>
<tr>
<td>11/10/F 12/30/F 13/29/F 14/34/F 15/6/6/F 16/19/F 17/4/F 18/52/F 19/29/F</td>
<td>Lissencephaly Subcortical band heterotopia Bilateral PNH Bilateral PNH</td>
<td>Fever and skin rash MR (6) MR (1) PNH (1); 5 spontaneous abortions</td>
<td>MR (6) MR (1) MR (1); 5 spontaneous abortions</td>
<td>2.5 y 7 y 4 y</td>
<td>Daily seizures MR Weekly seizures MR Daily seizures MR</td>
<td>Pachygyria Abortion attempt Abortion attempt Abortion attempt Abortion attempt</td>
</tr>
<tr>
<td>15/7/6/F 16/19/F 17/4/F 18/52/F 19/29/F</td>
<td>Agyria/pachygyria Agyria/pachygyria Agyria/pachygyria Agyria/pachygyria</td>
<td>Abortion attempt (transmantine) Abortion attempt (transmantine) Abortion attempt (transmantine) Abortion attempt (transmantine)</td>
<td>... ... ... ...</td>
<td>9 y 11 y 2 y 36 y</td>
<td>Weekly seizures MR Weekly seizures MR Weekly seizures MR Weekly seizures MR</td>
<td>Agyria/pachygyria Agyria/pachygyria Agyria/pachygyria Agyria/pachygyria</td>
</tr>
</tbody>
</table>

*MR indicates mental retardation; PNH, periventricular nodular heterotopia; and ellipses, not applicable.†Cognitive status was assessed during neurological examination.‡This patient also had neurofibromatosis 1.
plasia, other than those associated with specific syndromes, such as tuberous sclerosis.

In group 2, 8 patients (42%) reported a prenatal event that might have contributed to the pathogenesis of their cortical malformation, and 6 (32%) had a family history of neurological disturbances, suggesting a central nervous system lesion. However, 3 of these patients (16%) had a family history of neurological impairment and a prenatal event. Although there are several reports correlating prenatal events such as those reported by our patients and the occurrence of MCD because of abnormal migration,18,25 it is well established that the majority of patients with the so-called migration disorders (bilateral periventricular nodular heterotopia, subcortical laminar heterotopia, agryria-pachygryria, and lissencephaly) have mutations in specific genes: LIS-1, DCX, and filamin 1.3, 7, 8,10-12 We believe that MCD because of abnormal migration is mainly genetically determined, either as a familial trait or a de novo mutation; however, prenatal events could be acting in conjunction with the genetic predisposition to determine the final phenotype.

### Table 3. Characteristics of Patients With Polymicrogyria or Schizencephaly (Group 3)*

<table>
<thead>
<tr>
<th>Patient No./Age, y/Sex</th>
<th>Imaging Findings</th>
<th>Prenatal Event</th>
<th>Family History (No. of Relatives)</th>
<th>Age at First Seizure</th>
<th>Clinical Outcome</th>
<th>Cognitive Status†</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/13/M 13/M CBPS</td>
<td>High blood pressure</td>
<td>CBPS (4)</td>
<td>. . .</td>
<td>. . .</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>2/3/F 3/F</td>
<td>Focal unilateral</td>
<td>Drug addiction</td>
<td>. . .</td>
<td>. . .</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>3/15/M 3/M Schizencephaly</td>
<td>CBPS</td>
<td>Abortion attempt</td>
<td>. . .</td>
<td>. . .</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>4/6/M 4/M CBPS</td>
<td>Twin gestation</td>
<td>Developmental delay (1)</td>
<td>. . .</td>
<td>. . .</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>6/9/M 9/M CBPS</td>
<td>Fever; physical abuse</td>
<td>. . .</td>
<td>. . .</td>
<td>. . .</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>7/5/F 5/F CBPS</td>
<td>Abortion attempt</td>
<td>NA</td>
<td>3 y</td>
<td>Seizures controlled with AED</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>8/13/M 13/M Schizencephaly</td>
<td>Abortion attempt</td>
<td>. . .</td>
<td>. . .</td>
<td>. . .</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>9/17/M 17/M Schizencephaly</td>
<td>Abortion attempt</td>
<td>Fever and skin rash</td>
<td>Epilepsy (2); stillbirth (1)</td>
<td>4 y</td>
<td>Seizures controlled with AED</td>
<td>Normal</td>
</tr>
<tr>
<td>10/3/M 3/M Schizencephaly</td>
<td>Abortion attempt</td>
<td>Developmental delay (1)</td>
<td>. . .</td>
<td>. . .</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>11/5/F 5/M CBPS</td>
<td>Fall during 12th/16th weeks</td>
<td>Developmental delay (2)</td>
<td>. . .</td>
<td>. . .</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>12/5/M 5/M Schizencephaly</td>
<td>Abortion attempt;</td>
<td>. . .</td>
<td>5 mo</td>
<td>Seizures controlled with AED</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>13/11/M 11/M CBPS</td>
<td>Exposure to x-rays</td>
<td>. . .</td>
<td>. . .</td>
<td>. . .</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>14/3/M 3/M CBPS</td>
<td>Bilateral schizencephaly</td>
<td>Poor prenatal care; patient put up for adoption</td>
<td>NA</td>
<td>4 mo</td>
<td>Daily seizures</td>
<td>MR</td>
</tr>
<tr>
<td>15/8/M 8/M CBPS</td>
<td>. . .</td>
<td>Abortion attempt</td>
<td>9 y</td>
<td>Weekly seizures</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>16/15/M 15/M Schizencephaly</td>
<td>Focal unilateral</td>
<td>. . .</td>
<td>3 d</td>
<td>Weekly seizures</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>17/20/M 20/M Schizencephaly</td>
<td>CBPS</td>
<td>. . .</td>
<td>Consanguinity, epilepsy (2); CBPS (1)</td>
<td>. . .</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>18/6/F 6/F CBPS</td>
<td>. . .</td>
<td>Epilepsy (2); CBPS (1)</td>
<td>. . .</td>
<td>. . .</td>
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<td>Normal</td>
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<tr>
<td>19/7/F 7/F Schizencephaly</td>
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<td>Spontaneous abortion (1)</td>
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<td>Normal</td>
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<tr>
<td>20/7/F 7/F CBPS</td>
<td>Spontaneous abortion (2)</td>
<td>. . .</td>
<td>. . .</td>
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<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>21/6/F 6/F Schizencephaly</td>
<td>Epilepsy (1)</td>
<td>. . .</td>
<td>5 y</td>
<td>Seizures controlled with AED</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>22/9/M 9/M Schizencephaly</td>
<td>Consanguinity</td>
<td>. . .</td>
<td>4 mo</td>
<td>Daily seizures</td>
<td>Normal</td>
<td>Normal</td>
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<tr>
<td>23/10/M 10/M CBPS</td>
<td>Focal unilateral</td>
<td>Consanguinity</td>
<td>12 y</td>
<td>Weekly seizures</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>24/18/F 18/F Schizencephaly</td>
<td>Epilepsy (2); speech delay (1)</td>
<td>. . .</td>
<td>. . .</td>
<td>. . .</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>25/3/M 3/M CBPS</td>
<td>. . .</td>
<td>Epilepsy (2); speech delay (1)</td>
<td>. . .</td>
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<td>Normal</td>
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<tr>
<td>26/10/F 10/F CBPS</td>
<td>Focal unilateral</td>
<td>Consanguinity</td>
<td>2 y</td>
<td>Seizures controlled with AED</td>
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<td>Normal</td>
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<tr>
<td>27/9/M 9/M CBPS</td>
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<td>CBPS (4)</td>
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<td>Normal</td>
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<td>28/8/F 8/F CBPS</td>
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<td>. . .</td>
<td>. . .</td>
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<td>Normal</td>
</tr>
<tr>
<td>29/19/M 19/M Polymicrogyria</td>
<td>Epilepsy (1)</td>
<td>. . .</td>
<td>4 y</td>
<td>Monthly seizures</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>30/2/F 2/F Schizencephaly</td>
<td>MR (2)</td>
<td>. . .</td>
<td>1 wk</td>
<td>Seizures controlled with AED</td>
<td>Normal</td>
<td>Normal</td>
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<tr>
<td>31/25/F 25/F Polymicrogyria</td>
<td>MR, microcephaly (1)</td>
<td>. . .</td>
<td>2 mo</td>
<td>Monthly seizures</td>
<td>Normal</td>
<td>Normal</td>
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<tr>
<td>32/13/M 13/M Schizencephaly</td>
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<td>33/3/M 3/M CBPS</td>
<td>. . .</td>
<td>CBPS (4)</td>
<td>. . .</td>
<td>. . .</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>34/13/M 13/M Schizencephaly</td>
<td>Consanguinity</td>
<td>1.5 y</td>
<td>Seizures controlled with AED</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>35/37/M 37/M Schizencephaly</td>
<td>Epilepsy (1)</td>
<td>18 y</td>
<td>Weekly seizures</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>36/2/F 2/F Bilateral</td>
<td>. . .</td>
<td>. . .</td>
<td>. . .</td>
<td>. . .</td>
<td>Normal</td>
<td>Mr</td>
</tr>
</tbody>
</table>

*CBPS indicates congenital bilateral perisylvian syndrome; MR, mental retardation; AED, antiepileptic drugs; NA, not available; and ellipses, not applicable.
†Cognitive status was assessed during neurological examination.
may play an important role as a contributor to the genesis of polymicrogyria and schizencephaly. A pathologic finding of a necrotic layer in patients with layered polymicrogyria supports the traditional theory that, in many cases, these abnormalities are a form of destructive lesion. A family history of neurological impairment, suggesting a central nervous system lesion, was also relatively common in this group (14 patients [39%]), including 5 patients (14%) who had a first-degree relative with congenital bilateral perisylvian syndrome. It is interesting to note that in this family only 1 patient had a history of prenatal injury, and he had a more severe phenotype.

Our data clearly show that prenatal events are very frequently linked to MCD. One possible limitation of this finding is the fact that information on the occurrence of prenatal events was ascertained retrospectively, and precise recollection of events that may have occurred many years before is difficult. Prenatal events, such as placental dysfunction, may be asymptomatic in the mother, which could cause a substantial underestimation of the occurrence of this kind of event. Although difficult to perform, a prospective study on the association between prenatal events and MCD would be the best way to address this issue.

We are well aware that MRI does not always detect focal cortical dysplasia and that it may be associated with other types of lesions. On the other hand, it is not known if people without epilepsy may have focal cortical dysplasia that cannot be detected with MRI. This is quite possible, judging from the fact that other types of MCD may not be associated with epilepsy. We believe that a disease-control group with epilepsy helped to differentiate factors that could be related to the seizure disorder itself and not necessarily to MCD. For example, family history of epilepsy was not significantly different among groups, but family histories of neurological impairment and prenatal events were significantly less frequent in the disease-control group. If the control group consisted of healthy subjects, there would also be a significant difference for family history of epilepsy.

Epilepsy due to MCD probably depends on many factors such as size, localization, and type of MCD lesion. The frequency of epilepsy was significantly lower and the disease was more easily controlled in group 3. These findings are in agreement with previous studies in which epilepsy was present in 57% to 87% of patients with polymicrogyria or schizencephaly. In these studies, the epileptic spectrum was wide, and most patients had their seizures controlled with antiepileptic drugs.

In conclusion, we believe that environmental factors, such as prenatal events, may act in conjunction with genetic predisposition to determine the variable phenotypes seen in the different forms of MCD. Our findings support the idea of a clinical spectrum among the different types of MCD. Focal cortical dysplasia (group 1) is associated with more frequent and severe epilepsy and less important genetic and prenatal events, heterotopias and agria-pachygyria (group 2) are frequently associated with genetic predisposition, and polymicrogyria and schizencephaly (group 3) are less frequently associated with epilepsy but have a stronger association with genetic and detectable prenatal events.

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