Polymicrogyria: the bigger the malformation, the worse the epilepsy, is that true?

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Abstract

Polymicrogyria (PMG) is a common malformation of cortical development (MCD) related to cortical organization defects, resulting in overfolding and abnormal lamination of the cortex. Epilepsy is one of the main clinical features of this syndrome, although frequency, severity and long-term outcome of seizures in these patients are not known. We describe three patients with polymicrogyria-related epilepsy: clinical, electroencephalographic and neuroimaging data have been analyzed. Interestingly the severity of the malformations was not correlated to the severity of epilepsy: indeed in the patient with isolated PMG the long-term outcome was poor, with severe drug-resistant epilepsy and cognitive decline, while in the patients with widespread malformations (PMG associated to nodular heterotopia, focal cortical dysplasia and other malformations of cortical development) the epilepsy outcome resulted excellent. Future studies of prognostic data in large cohorts of patients with PMG and epilepsy are needed.

KEY WORDS: polymicrogyria, drug-resistant epilepsy, malformation of cortical development.

Introduction

Polymicrogyria (PMG) is a common malformation of cortical development (MCD) due to the overfolding and abnormal lamination of the cortex (1, 2). It is classified as the result of post-migrational abnormalities occurring during early cortical organization (3-5). Etiology is not fully understood: exogenous noxae such as hypoxic-ischemic insults during the perinatal period or infectious diseases (in particular Cytomegalovirus, Toxoplasmosis, Syphilis infections) have been correlated to this malformation. At the same time, the recent discovery of genetic mutations in these patients (mutations identified in the following genes: TUBB2B, TUBB3, COL18A1, PAX6, KIAA1279, AH1, TEMEM216, TUBA8, TBR2, SRPX2, RAB3GAP1, RAB3GAP2, RAB18, NSDHL) and the presence of PMG in genetic syndromes, supports the hypothesis that the pathogenesis of polymicrogyria is multifactorial (5).

PMG diagnosis is based on neuroimaging data, specifically brain MRI leads to the identification of an irregular surface of the cortex, which appears thickened and overfolded, while the grey-white interface looks stippled and irregular (4). PMG is extremely heterogeneous both in radiological and clinical features, and although different radiological subtypes have been identified (4), a clear association with the clinical phenotypes is still lacking. In particular, epilepsy is frequently associated to PMG, but seizure long-term outcome in these patients is not known. We describe three patients who have completely different neuroradiological patterns of PMG, and different outcomes in terms of seizures recurrence. The patients gave informed consent to participate in the current report; details that might disclose the identity of the subjects have been omitted.

Case reports

Patient 1

K. is a 26-years-old woman with epilepsy related to right perisylvian polymicrogyria. She was born preterm at 32 weeks of pregnancy for placental abruption, with no sequelae and subsequent normal developmental milestones. A history of febrile seizures or familiarity for epilepsy was absent. She underwent surgery at the age of 9 years for left clubfoot (congenital talipes equinovarus). Her clinical history started at the age of 11 years with sporadic and brief episodes of oral deviation towards the left, but no medical investigations were performed until she was 20, when she had her...
first generalized tonic-clonic seizure. Brain MRI showed isolated right temporo-insulo-parietal polymicrogyria (Fig. 1). During EEG, frequent epileptiform abnormalities such as high amplitude poli-spikes and wave were observed in fronto-temporal-parietal regions, with tendency of synchronization during sleep. Her neuropsychological evaluation was normal. She started antiepileptic treatment initially with one drug, then with an association of two antiepileptic drugs for seizure recurrence. At first seizures were partially controlled by the pharmacological treatment, presenting every 3-4 months. Over the time the seizures occurred more frequently on a monthly base; the patient also experienced few episodes of non-convulsive status epilepticus during which she appeared absent, with continuous generalized spikes-and-wave on EEG (Fig. 2). The patient was given an association of multiple antiepileptic drugs (Sodium Valproate 750 mg/die, Lamotrigine 100 mg/die, Lacosamide 400 mg/die, Phenobarbital 75 mg/die), but nonetheless, in the last two years she developed a progressive worsening of epilepsy in terms of seizure frequency (multiple seizures per week), seizure manifestation (longer duration, ictal falls), incremented EEG abnormalities, and cognitive decline. Neuropsychological assessment highlighted impairment in verbal fluencies, executive functions and anterograde memory. Her quality of life has dramatically decreased, as she is now unable to stand by herself, to study or to get a job. Although the region of her malformation is near to eloquent areas, she has started a presurgical workup in order to consider any possible optional treatment.

**Patient 2**
A. is a 24-years-old man with a complex cortical malformation of the right hemisphere, characterized by right hemispheric polymicrogyria, parietal focal cortical dysplasia, periventricular and subcortical nodular heterotopia (Fig. 1). He was born from a term physiological twin pregnancy and presented normal developmental milestones. His twin is healthy. At the age of 22 years he experienced a first focal seizure, followed by a second one a few hours later. Brain 3T MRI led to the diagnosis of a complex cortical malformation, and antiepileptic treatment was started. EEG was unremarkable. Since then no other seizures occurred, he has now been seizure-free for 2 years. He is currently a university student with good advancement.

**Patient 3**
M. is a 25-years-old man who has had an unremarkable physiological history. He suffered from a febrile convulsion at 12 months receiving no antiepileptic therapy. His sister presented febrile convulsions too. In his pathological history obesity and high blood pressure were found at young age. He experienced a first afebrile generalized tonic-clonic seizure at the age of 22 years, followed by the discovery of a complex mal-
formation of cortical development on brain MRI, characterized by right focal frontal PMG, right subcortical nodular heterotopia and partial agenesis of corpus callosum (Fig. 2). Scalp EEG showed frequent abnormalities such as slow wave, high-amplitude spikes and wave, low-voltage fast activity and bi-synchronization during sleep. Antiepileptic treatment was started. Two seizures recurred a few months later so therapy was incremented and since then (4 years follow-up) he has been seizure free.

Discussion

The clinical outcome of epilepsy in three patients with polymicrogyria has been addressed. The first patient is a 26-years-old woman with a right isolated perisylvian polymicrogyria, who developed a severe form of drug-resistant epilepsy associated to acquired cognitive decline in the adult age. The second case is a young man who experienced only two focal seizures and has instead a widespread complex malformation of cortical development, including polymicrogyria associated to focal cortical dysplasia, periventricular and subcortical heterotopia. Also in the third case, despite a complex cortical malformation, there was a positive outcome.

An interesting point of discussion of the illustrated cases regards the discrepancy between the clinical phenotype and the anatomic pattern of the MCD. In contrast to what we expected, the isolated and simplest form of PMG (patient 1) was associated with the worse outcome both in terms of epilepsy and neurological decline, while a very extended and complex malformation of almost an entire hemisphere (patient 2) or MCD with subcortical heterotopia and partial agenesis of corpus callosum (patient 3) were associated with an excellent outcome, seizure freedom and absence of neurological impairment. Since the extension or the anatomical complexity of the cortical malformation does not seem to be so relevant in the epilepsy outcome, the research of other factors is essential. Clinical data obtained by physiological and familiar history, and neuropsychological data obtained by scalp EEG, could help us in this research. Physiological antecedents such as prematurity and placental abruption, twin pregnancy, and history of febrile convulsions, were present in the illustrated cases. It is now established that an exogenous insult at early stages of brain maturity is a risk factor of neuronal migration or post-migrational defects, which lead to MCD (6). No correlation of these factors with outcome has however been observed. Moreover, frequent and typical EEG epileptiform abnormalities have been observed in the first and third patient, one with poor outcome, the other with an excellent one. As reproduced in other studies (7, 8) it appears that EEG abnormalities represent an electrophysiological marker of the cortical malformation per se, rather than a predictive factor of the epilepsy outcome.

A few studies on polymicrogyria are available in the current literature: the biggest series have focused on the neuroradiological picture, phenotype-genotype correlations, or clinical features of patients with PMG, but long-term outcome studies of epilepsy in the adult age are lacking (4, 9). Moreover, many studies on PMG-related epilepsy include patients with drug-resistant forms, who participate in work-ups for epilepsy surgery, therefore a selection bias is present, being these series probably not representative of the whole spectrum of PMG-related epilepsy (10, 11). Future studies of prognostic data in large cohorts of patients with PMG and epilepsy are needed.

References

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