Seizure 32 (2015) 92–99

Contents lists available at ScienceDirect

Seizure

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

Malformations of cortical development and epilepsy: A cohort of 150 patients in western China☆

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ARTICLE INFO

Article history:
Received 1 June 2015
Received in revised form 14 September 2015
Accepted 15 September 2015

Keywords:
Epilepsy
Malformations of cortical development
MRI

ABSTRACT

Purpose: Malformations of cortical development (MCDs) are abnormalities of the cerebral cortex that arise from abnormal formation of the cortical plate, and have become increasingly identified as an important etiology for refractory epilepsy. Little is known about the spectrum, distribution and clinical features of MCDs, especially in resource-limited regions. This study investigates the distribution of MCDs and compares the clinical features and long-term prognosis between the two forms of MCDs: Simple and Multiple.

Method: One hundred and fifty epilepsy patients (138 adults, 12 pediatric patients) with radiologically diagnosed MCDs were identified at a tertiary epilepsy center in western China. Patients were divided into three subtypes according to the Barkovich classification. They were further divided into either Simple or Multiple MCD forms based on whether they had a single type of MCDs or other co-existing developmental brain abnormalities.

Results: The most common type of MCD is focal cortical dysplasia. We found perinatal insults more common in group III patients. Multiple MCD was identified in 36 of 150 patients, and was associated with higher rates of delayed milestones ($p = 0.005$), cognitive impairment ($p = 0.023$) and neurological deficits ($p = 0.002$) compared to Simple MCD. Extra-temporal epilepsy was more commonly seen among individuals with Multiple MCD ($p = 0.017$). Participants with Multiple MCD were younger at time of seizure onset ($p = 0.003$) and at assessment ($p = 0.002$), had a lower seizure-free rate ($p = 0.033$) and had worse outcomes overall. Patients with heterotopias were more commonly associated with other abnormalities.

Conclusion: MCDs are a critical cause of epilepsy and pose a big challenge for resource-limited countries. Imaging techniques are crucial in diagnosing and classifying cortical deformities. Multiple malformations lead to more severe clinical features and worse prognosis. Identifying and classifying MCDs can help physicians to better estimate patient prognosis and seek the best, individualized therapeutic options.

1. Introduction

Malformations of cortical development (MCDs) have more recently become identified as a major etiology of drug-resistant epilepsy, motor delay, mental retardation, and a broad range of neurological deficits and developmental disorders [1–4]. Patients with MCDs have highly variable clinical presentations and differing degrees of disability and impairment. MCDs can be classified into three major groups based on the neurodevelopmental step which was disrupted [5,6]: Group I, 'abnormal neuronal and glial proliferation or apoptosis', e.g. focal cortical dysplasia (FCD) type II, tuberous sclerosis (TS); Group II, 'Abnormal Neuronal Migration', e.g. pachygyria, heterotopias; and Group III, 'Abnormal Post-Migrational Development', e.g. polymicrogyria, schizencephaly. This classification scheme is known as the Barkovich classification (BC). Interference with each of these three processes leads to different types of MCDs and displays varying degrees of epileptogenicity [4]. Though MCDs are heterogeneous, in practice only a few categories are used, including pachygyria, polymicrogyria, schizencephaly, FCD, and heterotopias [7].

☆ We confirm this manuscript has been thoroughly edited by a native English speaker from an editing company. Editing Certificate will be provided upon request.

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http://dx.doi.org/10.1016/j.seizure.2015.09.009
1059-1311/

The groups in the Barkovich classification scheme are not mutually exclusive. It is possible for an individual to have ongoing neuronal processes that result from impairment in more than one stage of development [8–12]. Additionally, cortical malformations may be associated with other extracortical neurodevelopmental deformities, such as abnormalities of the corpus callosum [13,14], hippocampus [15], midbrain, hindbrain, mega cisterna magna, occipital horns, or cerebellum [16–18]. Consequently, it can also be useful to refer to MCDs based on whether they occur in isolation (Simple MCD) or with co-existing neurodevelopmental abnormalities or another MCD (Multiple MCD).

Simple and Multiple MCDs have distinct clinical manifestations and outcomes, suggesting that this classification method can play a crucial part in patient management. Recognition of whether an individual has a Simple MCD or Multiple MCDs may allow physicians to better predict prognosis and make more individualized therapeutic decisions. Magnetic resonance imaging (MRI) is the best imaging modality to diagnose MCDs. Using MRI, physicians can describe the morphology and extension of the principal cortical malformation, as well as recognize any associated malformations. In a resource-limited region, the impressive advances in imaging and electrophysiological techniques are key methods to diagnose, classify and treat cortical malformations.

In western China, sophisticated imaging like high-resolution MRI and invasive procedures like stereoelectroencephalogram are not always accessible. As a result, the true prevalence and distribution of MCDs and the subtypes of MCDs in these regions are unknown. While many recent papers have described cortical malformations, in depth evaluation of the clinical features and long-term follow up of these patients has often been neglected. No studies have compared Simple MCDs with Multiple MCDs in a large and heterogeneous cohort of patients. Additionally, there have been little data to relate the particular types of MCDs to the likelihood of the patient developing epilepsy or the severity of their epilepsy.

The current study involves patients from western China and aims to investigate the distribution of Simple and Multiple MCDs in this population and to compare the clinical characteristics of these two separate but related entities.

2. Materials and methods

2.1. Patients

A total of 150 patients (71 females, 79 males) were recruited into the study between April 2012 and December 2014 from a single center (Department of Neurology at West China Hospital affiliated with Sichuan University). One hundred and thirty eight patients were adults (92%), while twelve patients (8%) were pediatric patients under the age of 18 years. The mean age of the participants was 25.5 years (range 4–67). All patients were diagnosed by an experienced epileptologist under ILAE criteria [19] with radiologically identified MCDs. Exclusion criteria included individuals with radiological identified MCDs with no history of seizure activity and individuals with tuberous sclerosis or dysembryoplastic neuroepithelial tumors (DNT). Cases with incomplete or missing clinical data were also excluded. One hundred thirty-three of the 150 patients (87%) were referred to West China Hospital for the diagnosis and management of epilepsy. This cohort had been closely monitored by the Epilepsy Center at West China Hospital for periods ranging from 1 to 18 years (mean 5.9 years). The remaining seventeen patients included in the study (13%) had been followed for less than one year.

Clinical data including age at enrollment, age at seizure onset, ante- and perinatal events, congenital abnormalities, developmental delay, current neurological and cognitive status, and location of epileptic discharges on electroencephalography (EEG) were collected. Each patient's clinical course and response to different antiepileptic drugs were prospectively monitored. All patients had at least two standard EEG recordings. One hundred and seven patients underwent extended video EEG monitoring for at least 24 h. Cognitive function was evaluated using the Wechsler Intelligence Scale for Children-Revised (WISC-R) or the Wechsler Adult Intelligence Scale-Revised (WAIS). Autism was diagnosed by the DSM-IV criteria.

2.2. Imaging

All patients had MRI scan with a 3.0 T (EXCITE, General Electric, Milwaukee, USA) or 1.5 T (Philips Achieva, Holland & Sonata, Siemens, Germany) image system with standard 3D (sagittal, axial, and coronal) images. MRI studies included conventional T1/T2-weighted studies, as well as MRI with inversion recovery and coronal fast fluid-attenuated inversion recovery. All images were evaluated by two independent physicians: an experienced epileptologist and a skilled neuroradiologist. In cases where there was a dispute regarding the categorization of the cortical malformation, a third neuroradiologist was consulted.

Brain MRI for all patients were reviewed for the following: localization of the lesion; hippocampal morphology; appearance and shape of the corpus callosum; ventricular shape and size; cerebral cortical gyral pattern; presence of posterior fossa cyst; white matter volume and cerebellar morphology. Lateral ventricles were assessed for colpocephaly, defined as dilation of the trigones and occipital horns.

2.3. Definition of terms; criteria for Simple and Multiple MCDs

Diagnostic criteria of focal cortical dysplasia (FCD) were in line with the literature [20–25]: cortical thickening, blurring of the white matter-gray matter junction, altered white matter signal with or without the penetration through cortex (transmantal sign), and abnormal sulcal or gyral pattern. MR imaging, however, can also be normal for certain subtypes of FCD type I [23–25]. Heterotopia is defined as groups of normal neurons in an inappropriate location. Lissencephaly was considered if the brain surface appeared smooth with areas of absent gyri (agyria) and abnormally wide gyri (pachygyria). Polymicrogyria is characterized by microscopic overfolding and irregular lamination. In schizencephaly, abnormal clefts in the grey matter occur; and the cortex edges can seem to fuse (closed lips) or stay at a distance (open lips) [7].

A detailed assessment of MRI features allowed us to classify participants based on MCD subtype into three groups according to the Barkovich classification [5,6]. Imaging also allowed us to further classify participants into groups based on whether more than one kind of MCD existed or whether the patient had a single MCD. The Simple MCD group consisted of participants with a deformity of a single characteristic MCD in the absence of other malformations; and participants in the Multiple MCD group had an MCD that was associated with additional cortical or cerebral malformations.

2.4. Statistical analysis

Statistical analysis was performed using SPSS 20 (IBM, Armonk, New York, USA). Categorical data were analyzed using Chi-square test or Fisher's exact test. Continuous data were analyzed by means of ANOVA followed by multiple comparisons (performed using Dunnett's *t*-test) or Mann–Whitney *U* test where data were nonparametric (e.g., seizure frequency per year). Univariate ANCOVA and multinomial logistic regression tests were performed