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Correlation of neuroradiological, electroencephalographic and clinical findings in cortical dysplasias in children

Maria Mazurkiewicz-Bełdzińska, Marta Szmuda, Agnieszka Matheisel

Department of Developmental Neurology, Chair of Neurology, Medical University of Gdańsk, Gdańsk, Poland

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Abstract

Introduction: *Cortical dysplasias (CD) are defined as malformations of cortical development. They result from impairment of neuronal proliferation, migration and differentiation. CD are common pathological substrates in patients with early-onset childhood epilepsy and/or developmental delay as well as neurological signs. Recognition of the importance of cortical dysplasias has been shown in many studies when introducing structural MRI. The following study was performed in order to correlate the neuroimaging findings with the electroencephalographic and clinical picture of children with cortical dysplasias.*

Materials and methods: *46 patients with the presence of CD features in MRI were identified. There were 18 female and 28 male patients. The age ranged from 3 months to 12 years (mean age = 6.2, median age = 3.1). The objectives of the study were explained to the parents or legal representatives of children when possible and also informed consent was obtained.*

Multiple EEG recordings as well as detailed clinical analysis of all patients were performed. Statistical analysis was conducted in order to correlate the type of CD with clinical outcome and electrophysiological findings.

Results: *There were 31 patients with focal dysplasias, 6 with schizencephaly, 4 with heterotopias, 3 lissencephaly and 2 with band heterotopia. 80% presented epilepsy (60% of them drug-resistant).*

Additionally, we tried to elucidate the clinical characteristics of epilepsy. In 75% of epilepsy patients the electroencephalographic changes correlated with anatomical localization of CD. 74% of patients were mentally retarded and 30% had focal neurological deficits.

Conclusions: *There were no correlations between the type of CD and the severity of the clinical picture, especially the level of mental retardation and presence of drug-resistant epilepsy. Different age at epilepsy onset and various responsiveness to antiepileptic drugs in the majority of patients may reflect different dynamics in epileptogenicity of the underlying CD.*

Key words: *cortical dysplasias, children, epilepsy, MRI*

Introduction

Cortical dysplasia (CD) is a cortex development disorder associated with abnormal cellular proliferation, cellular migration or cortical organization during foetal growth [7]. This process occurs between the 8th and 16th week of intrauterine life. Cerebral cortex malfor-

Communicating author:

Maria Mazurkiewicz-Bełdzińska, MD, PhD, Department of Developmental Neurology, Chair of Neurology, Medical University of Gdańsk, ul. Dębinki 7, 80-952 Gdańsk, Poland, tel. +48 58 349 2396, fax + 48 58 349 23 95, Email: mmazur@amg.gda.pl

Table I. Classification of cortical malformations

Cortical dysplasias			
Diffuse dysplasias	**Bilateral cortical dysplasias**	**Focal dysplasias**	**Hemispheric**
– Agyria/Pachygyria	– Bilateral perisilvian dysplasia	– Focal cortical dysplasia	– Hemimegalencephaly
– Lissencephaly	– Heterotopias	– Heterotopias	
– Subcortical laminar heterotopia	– Schizencephaly		
– "Double cortex"			

mations may be genetically determined, e.g. chromosomal (ring-X, microdeletion 17p 13.3), gene mutations (autosomal, X-linked), they may be a consequence of detrimental exogenic factors that occur during development (intrauterine CMV infection, intrauterine blood circulation disturbances), or they may be unknown. As a result, subependymal primitive neuroblasts, primarily localized in the medial line, migrate pathologically and initiate the abnormal infolding that creates malformed sulci and gyri of the cortex. CD is the most common developmental disorder in patients with pharmacoresistant epilepsy. Some authors indicate that the prevalence of refractory epilepsy in this group of patients reaches 76% [4]. Moreover, abnormalities of the cerebral gyri are frequently associated with mental retardation, focal neurological deficits and other specific systemic features. According to the classification, cortical malformations include: diffuse dysplasias (e.g. agyria, pachygyria, lissencephaly), bilateral cortical dysplasias (e.g. schizencephaly), focal (e.g. heterotopias) and hemispheric dysplasias (Table I).

There are some neurological syndromes particularly associated with cortical dysplasia presence. Among these are the following: Dandy-Walker syndrome (focal cortical dysplasias, heterotopias), Miller-Dieker syndrome (lissencephaly, agyria, pachygyria), Walker-Warburg syndrome (lissencephaly, agyria), etc [2].

Table II. Neurological syndromes associated with cortical dysplasias

• Dandy-Walker s.,
• Miller-Dieker s.,
• Walker-Warburg s.,
• Fukyama congenital muscular anomalies, congenital muscular dystrophy, myopathy, myotonic dystrophy,
• Cerebellar hypoplasia, corpus callosum agenesis,
• Tuberous sclerosis, NF-1, Hypomelanosis Ito, Incontinentia pigmenti, Klippel Trenaunay syndrome,
• Aicardi, Angelman, Waardenburg, Ehlers-Danlos s.

Classification schemas and diagnosis of CD is based on the combination of neuropathological, aetiological and radiological findings. Accessibility to magnetic resonance imaging (MRI) has allowed neuronal migration deficits to be identified in an increasing number of patients. This has also allowed radiological features to be associated with epileptic seizure presence and other neurological deficits. In accordance with this, the purpose of our study was to assess the correlation between the severity of clinical and electroencephalographic findings with the neuroradiological picture of patients with CD.

Materials and methods

Patients

46 patients with the presence of CD features in MRI were identified. They were hospitalized at the Department of Developmental Neurology at the Medical University of Gdańsk (Poland) in years 2000–2005. There were 18 females and 28 males. The age ranged from 3 months to 12 years (mean age = 6.2 years, median age = 3.1 years). The objectives of the study were explained to the parents or legal representatives of children when possible and also informed consent was obtained.

Methods

Every patient was assessed according to the neurological symptoms present, which included: (1) motor function, especially presence of cerebral palsy, (2) vision and hearing disability, (3) focal neurological deficits, (4) mental retardation, (5) presence of epileptic seizures.

According to the findings mentioned above, clinical disability scores were estimated: normal – 0, mild impairment – 1, severe impairment – 2. On the basis of the clinical features (medical history and neurological

Table III. CD differentiation in the study group patients

Type of CD	No of patients	%
Schizencephaly	6	13
Lissencephaly	3	6.5
Focal cortical dysplasias	31	67
Heterotopias	4	8.5
Band heterotopias	2	4

examination), the child underwent comprehensive evaluation including EEG and MRI of the brain.

EEG recordings were also divided into classes: when they were normal they were classified as score 1, when abnormal background activity was found – score 1, when the presence of ictal or interictal epileptiform activity was present – score 2.

In the MRI examination, the following sequences were acquired: transverse double-echo spin-echo of the entire brain; T1-weighted coronal inversion recovery (IR), T2-weighted coronal turbo spin-echo (TSE) and T2-weighted coronal TSE fluid-attenuated inversion recovery (FLAIR). The MR data were reviewed by a neuroradiologist. The following characteristics were specifically looked for on each patient's MR images: gyration anomalies, focal thickenings of the cortex, increased signal intensity of grey matter and subcortical white matter, blurring of the grey-white matter junction, focal brain hypoplasia and shrinkage of the white matter core.

On the basis of these characteristics, we assigned each of the 46 patients to one of three categories: mild changes (restricted) – score 1, moderate changes (not restricted) – score 2, and severe changes – score 3.

Statistical analyses

Statistical analysis of the data was performed with Statistica® 6.0 for Windows® and Microsoft Excel®. Chi--square analyses were used for discrete data and Fisher exact test for analysis of 2 x 2 tables with small frequencies. For continuous variables, comparisons of two independent groups were performed using the Student *t*-test, when distributions were normal or approximately normal, and the Mann-Whitney test, the nonparametric counterpart of the *t*-test, when distributions were skewed. For multivariate analysis logistic regression was performed. Spearman's correlation was used to assess the strength of the relationship between the pairs of the variables. $P<0.05$ was considered statistically significant.

Results

MRI review

There were a total of 46 patients with radiologically confirmed diagnosis of CD. The main characteristics of MRI findings are presented in Table III.

The localization of the cerebral cortex malformations was: temporal (24), extratemporal (10) and multilobar (12). However, approximately one-quarter of cases had more diffuse structure.

Regarding MRI scores: There were 10 patients (22%) included in the first (score 1), 25 (54%) in the second (score 2) and 11 (24%) in the third category (score 3).

Electroencephalographic findings

The mean age of seizure onset was 14 months and the mean duration of epilepsy was 3.5 years (ranged from 3 months to 7 years). The mean seizure frequency was 8 per month.

Of the entire group, 37 (80%) suffered from active epilepsy and in 28 cases (60%) seizures were pharmacoresistant.

Performed surface electroencephalography (EEG) revealed a normal record in 11 (25%) cases. Nonetheless, in the majority of patients (35; 75%) EEG records demonstrated abnormalities, such as

Table IV. Neuroimaging characteristics of CD according to which the patients were divided into one of the following categories

Mild changes	Moderate changes	Severe changes
Focal cortical dysplasia (unifocal)	Focal cortical dysplasia (multifocal)	Bilateral Lissencephaly
Heterotopia	Unilateral Lissencephaly	Bilateral Schizencephaly
	Unilateral Schizencephaly	
	Band heterotopia	

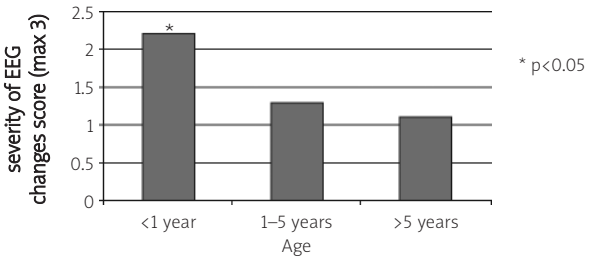

Fig. 1. Correlation between the severity of EEG changes and the age of seizure onset

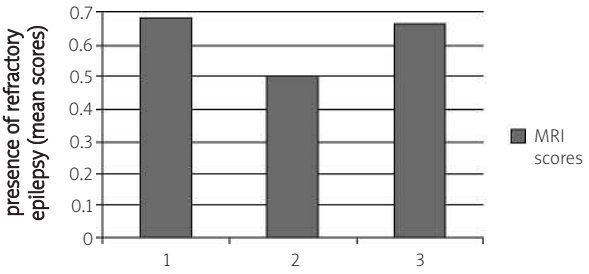

Fig. 2. Correlation between the presence of refractory epilepsy and MRI changes (p>0.05)

pathological background (28; 60%), interictal (27; 59%) or ictal epileptiform activity (30; 65%). In all "ictal" cases the EEG alterations correlated with localization of CD. Severity of EEG changes, described according to the 3-score system, were assessed in each of the following age groups: below 1st year of life, between 1 to 5 years, and more than 5 years. The analysis has shown that the highest severity of changes strongly correlated with the age of onset below 1 year (Fig. 1).

The electroencephalographic and imaging characteristics revealed that there was no specific correlation between refractory epilepsy occurrence and the severity of MRI changes (Fig. 2).

Clinical functions

14 of the study patients (30%) demonstrated neurological deficits (including cerebral palsy) and 34 (74%) presented mental retardation.

The clinical state of each patient was estimated according to symptoms or deficits he or she presented (Table IV). On the basis of examination results, the severity of clinical disability was classified into one of the 3 following categories. There were 11 (24%) patients with no deviation in clinical functions (neurological and mental) (score 0), patients with mild impairment – 26 (56%) (score 1), and 9 (20%) with severe impairment (score 2). The relationship between the clinical disability score and MRI lesions was not statistically significant (Fig. 3).

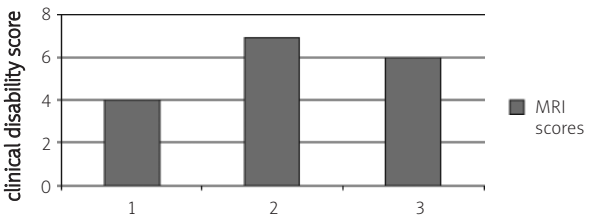

Fig. 3. Clinical disability score and MRI lesions

The comprehensive evaluation of the MRI changes, motor disability, presence of seizures and mental retardation revealed no correlation between CD presence and features mentioned above (Spearman's correlation; Table V).

Discussion

The study directly assessed electroencephalographic and clinical features in paediatric patients with neuroradiologically confirmed CD. In this research we conducted recommended MRI acquisition techniques and sequences for older and younger (below 2 years) children, whose white matter is either immature or marginally mature [7]. The same refers to the EEG evaluation. All the conclusions were based on the integral assessment of clinical findings, including neuropsychological tests, EEG data and MRI features. In controversial or unclear cases, further procedures were performed in order to exclude different causes of brain damage. Only distinct neuroradiological CD features were included in the study.

It has been proved that epilepsy is present or will develop in the majority of patients with CD and

Table V. Assessment of clinical functions impairment in the study population

Type of disability	No of patients	[%]
Motor function impairment	18	40
Presence of seizures	37	80
Vision and/or hearing disability	5	11
Focal neurological deficits	14	30
Cerebral palsy	4	9
Mental retardation	34	74

Table VI. Spearman's correlation estimating the MRI changes, motor disability, seizure presence and mental retardation

Scores	MRI	Motor disability	Presence of seizures	Mental retardation
MRI	–	0.599	0.233	0.750
Motor distability	0.599	–	0.100	0.137
Presence of seizures	0.233	0.100	–	0.137
Mental retardation	0.375	0.750	0.137	–

in about two-thirds of cases the seizures will be pharmacoresistant. Our results also unequivocally suggest that there is a strong relationship between localization of cerebral cortex malformations and severe localized changes in the EEG in a group of patients with active epilepsy. These conclusions are in agreement with previous reports that showed straight dependence of CD on refractory epilepsy [9]. However, the severity of CD does not play a role in the severity of epilepsy.

A complex assessment indicates that mental retardation and neurological deficits are expected clinical findings in cases of cortex abnormalities. 74% of the children in the study group had been classified as mentally retarded, and only 30% demonstrated a neurological deficit. This probably reflects the phenotypic heterogeneity of CD, and reiterates the fact that some patients with these disorders are neurologically or sometimes cognitively unimpaired.

Our study demonstrated no specific correlation between the simultaneous neuroradiological, electroencephalographic and clinical abnormalities. We did not find a relationship between neurodevelopmental outcome and extent of our patients' malformations, which is not in agreement with previous authors [10] who have shown that children with diffuse malformations were more clinically disabled than those with focal abnormalities. It agrees with their statement that there were no certain abnormalities in EEG patterns that apply to children with diffuse CD and severe clinical disability.

The weakness of this study was the inability to perform neuropathological work because of the lack of surgical treatment in this particular group of patients.

Patients with CD represent a heterogeneous group. This study proves that children with mental retardation and presence of intractable epilepsy pose a particular challenge for interdisciplinary diagnosis and treatment. Different age at epilepsy onset and transient responsiveness to antiepileptic drugs may reflect different dynamics in epileptogenicity of the underlying CD. It will be interesting to see the neuropsychological development and the course of epilepsy in this particular group of patients after some years, possibly in some of them already after epilepsy surgery.

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