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THE CLINICAL SPECTRUM OF MALFORMATIONS OF CORTICAL DEVELOPMENT IN A COHORT OF BULGARIAN PATIENTS

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Abstract

Malformations of cortical development (MCD) are a heterogeneous group of diseases, that cause epileptic seizures, motor deficit and mental retardation. We analysed the clinical course, seizure characteristics and neuroimaging data in patients with cortical malformations, treated between 2006 and 2021 in the Clinic of Child Neurology of MHATNP "St. Naum".

We studied 205 patients with MCD, 94 girls (45.9%) and 111 boys (54.1%), with a mean age of 7.7 years, ranging from one month to 18 years of age. According to the type of cortical malformation, patients were divided into five groups: 31 patients (15.12%) with heterotopia, 52 (25.3%) – with polymicrogyria, 47 (22.9%) – with lissencephaly, 59 (28.9%) – with cortical dysplasia and 16 (7.8%) – with schizencephaly.

Ninety-five (46.3%) of our patients were with intellectual disability. Motor deficit was reported in 122 children (59.5%) and 173 patients (84.4%) had epileptic seizures. The seizures were focal in 42 (20.57%) of the cases, with motor manifestation in 20 and secondary generalisation – in 7 of them. Forty-six patients experienced generalised seizures. Mixed type of seizures were registered in 83 patients. In two children, the seizures could not be classified. The seizures frequency varied significantly, but patients with cortical dysplasia had the highest rate of daily seizures – 52.5% ($n = 31$), followed by patients with polymicrogyria – 25% ($n = 13$).

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Malformations of cortical development are a heterogeneous group of disorders, associated with mental retardation, epilepsy and motor deficit in childhood. Our study provides phenotypic information that would be useful for future genotype-phenotype correlations.

Key words: malformations of cortical development, epilepsy, intellectual disability

Introduction. The development of the human brain is a complex process, during which distinct cell types must proliferate, differentiate, migrate and organize to form a highly complex structure, capable of complex cognition, language and emotions. The human cortex develops its basic structure during the first two trimesters of pregnancy. Disruptions in any of these processes lead to malformations of cortical development (MCD), which are a common cause of intellectual disability with or without epilepsy.

The paper presents the clinical picture, seizure characteristics, degree of intellectual disability and neuroimaging data in a cohort of Bulgarian patients with cortical malformations.

Patients and methods. The neuroimaging data and medical records of patients with cortical malformations, who were diagnosed, treated and followed up in the Clinic of Child Neurology at the St. Naum University Hospital for Active Treatment in Neurology and Psychiatry between 2006 to 2021, have been assessed. All children underwent MRI or CT scans of the brain, because of epilepsy, delayed motor and cognitive development or neurologic deficit. The classification of cortical malformations of Barkovich et al. has been used [1]. The most common epileptic cortical malformations (focal cortical dysplasia, lissencephaly, heterotopia, polymicrogyria and schizencephaly) have been included. The types of seizures have been defined and classified according to the ILAE (International League Against Epilepsy) classification of 2017.

Statistical methods (descriptive statistics, Kolmogorov–Smirnov test, the nonparametric Kruskal–Wallis test, Chi-Square test and Fisher's exact test) have been used to study relationships between descriptive (category) data with two or more categories. The accepted level of significance is $\alpha = 0.05$. Statistical significance is assumed when the p value is less than α ($p < 0.05$).

Results. The cases with MCD ($n = 205$) were divided into five groups, according to the type of cortical malformation. Thirty-one patients (15.1%) were diagnosed with heterotopia (HT), 52 (25.3%) – with polymicrogyria (PMG), 47 (22.9%) – with lissencephaly (LIS), 59 (28.9%) – with focal cortical dysplasia (FCD), and 16 (7.8%) – with schizencephaly (SCZ).

Figure 1 shows MRI of patients with the main types of cortical malformations.

Demographic characteristics and clinical manifestation in patients with MCD. The mean age of the patients with MCD in our cohort was 7.74 years ($\pm$5.67), ranging from 1 month to 18 years. Most of them were between 1 and

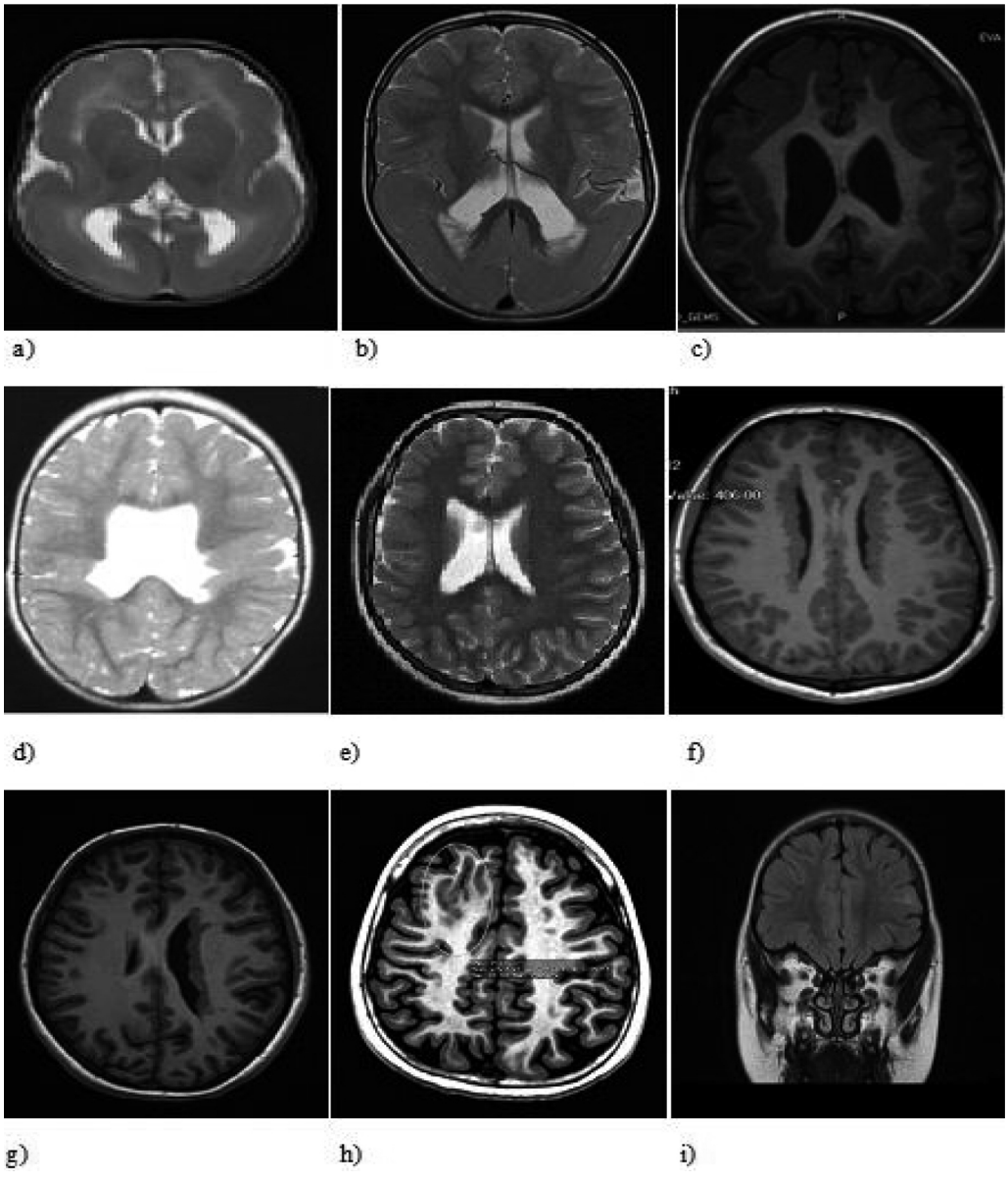

Fig. 1. MRI of cortical malformations: a) Axial T2-weighted MRI slice of diffuse agyria with few shallow sulci in the frontal area; b) Axial T2-weighted MRI slice of parieto-occipital agyria; c) Axial T1-weighted MRI slice of bilateral subcortical band heterotopia; d) Axial T2-weighted MRI slice of bilateral closed schizencephaly associated with septo-optic dysplasia; e) Axial T2-weighted MRI slice of right-sided polymicrogyria; f) Axial T1-weighted MRI slice of bilateral periventricular nodular heterotopia; g) Axial T1-weighted MRI slice of unilateral periventricular nodular heterotopia; h) Axial T1-weighted MRI slice of focal cortical dysplasia in the right frontal area; i) Coronal view of FLAIR MRI slice of cortical dysplasia in the area of the left lower frontal gyrus

10 years of age. Patients with LIS and PMG were diagnosed earlier compared to patients with FCD, HT and SCZ. In terms of gender distribution, 45.9% ($n = 94$) of the children were girls and 54.1% ($n = 111$) were boys.

Prenatal pathology was reported in 50.0% ($n = 26$) of the cases with PMG, in 46.8% ($n = 22$) of the cases with LIS, in 43.8% ($n = 7$) of the cases with SCZ and in 25.8% ($n = 8$) of the patients with HT. Fewer cases with cortical dysplasia ($n = 13$, 22.0%) mentioned prenatal pathology. Perinatal pathology was most common in cases with SCZ ($n = 8$, 50%) and PMG ($n = 22$, 42.3%). Microcephaly prevailed in children with LIS (46.8%), SCZ (43.8%) and PMG (26.9%).

Neurological examination showed varying degree of pyramidal changes in 54.6% of the patients ($n = 112$). Statistically significant correlation between the severity of the motor deficit and the type of MCD has been established. Quadriparesis prevailed in LIS, SCZ and PMG cases, while patients with FCD and HT rarely had severe motor deficit, but mainly pyramidal reflex changes (Table 1).

T a b l e 1

Quadriparesis in MCD

Quadriparesis		HT	SCZ	PMG	LIS	FCD	Total	p
No	N	31	11	41	31	58	172	<0.001
	%	100.0	68.8	78.8	66.0	98.3	83.9	
Yes	N	0	5	11	16	0	32	
	%	0.0	31.3	21.2	34.0	0.0	15.6	
Total	N	31	16	52	47	59	205	
	%	100.0	100.0	100.0	100.0	100.0	100.0	

Other changes in the neurological status such as extrapyramidal syndrome, ataxia and hypotonia were rarely observed. Extrapyramidal symptoms were registered in 12/205 patients (5.9%), with the highest percentage in PMG cases (13.5%).

We established a statistically significant correlation between the degree of intellectual disability and the type of the MCD, as most of our patients with LIS ($n = 37$, 78.7%) and PMG ($n = 36$, 69.2%) had mild to severe mental retardation, but patients with HT ($n = 7$, 22.6%) and FCD ($n = 17$, 28.8%) rarely experienced cognitive problems.

Epileptic seizures occurred in 84.4% of MCD ($n = 173$) cases. All patients ($n = 59$) with FCD had epileptic seizures. In the other MCD cases, the percentage of epilepsy occurrence was also high, as 83.9% ($n = 26$) of the HT cases, 78.7% ($n = 37$) of the LIS cases, 78.8% ($n = 41$) of the PMG cases and 62.5% ($n = 10$) of the SCZ cases experienced epileptic seizures. This observation highlights the pronounced epileptogenicity of the MCD (Table 2).

Table 2

Epilepsy in MCD

Epilepsy		HT	SCZ	PMG	LIS	FCD	Total	p
No	N	5	6	11	10	0	32	
	%	16.1	37.5	21.2	21.3	0.0	15.6	
Yes	N	26	10	41	37	59	173	
	%	83.9	62.5	78.8	78.7	100.0	84.4	<0.001
Total	N	31	16	52	47	59	205	
	%	100.0	100.0	100.0	100.0	100.0	100.0	

The age of seizure onset in patients with MCD varied between 0 to 16 years (mean age 3.95 years). The earliest manifestation (mean age of seizure onset 2.4 years) was observed in LIS patients, with onset in the neonatal period in 3 of them. Later age of seizure manifestation was reported in HT (mean age of 5.45 years) and FCD (mean age 5.12 years) patients.

Depending on the type of the seizures, we divided our patients into four groups: cases with focal seizures, cases with generalized seizures, with mixed seizures (focal, generalized and epileptic spasms), and unclassified seizures. Focal seizures were reported in 42 (20.57%) of the children. Focal seizures predominated in FCD cases ($n = 24$, 40.7%). Forty-six patients experienced generalised seizures – generalized non-motor (absence) seizures were presented in 14 (30.4%) cases and generalized tonic-clonic seizures – in 32 of them, (69.6%). Mixed type of seizures was registered in 83 patients (40.5%). In two children, the seizures could not be classified.

Discussion. Malformations of cortical development are a heterogeneous group of diseases that lead to epileptic seizures, motor deficit and intellectual disability. In our cohort of Bulgarian patients, children with FCD and PMG prevail, an observation that is similar to that of Montenegro et al. [2], but their group includes also adult patients. In the study of Mathew et al. [3] the prevalence of HT cases is high, but they reported a small number of patients that were followed up for a shorter period of time. The differences between the published data depend on the selected case groups and the type of the chosen cortical malformations.

We observed a statistically significant higher percentage of microcephaly in LIS and SCZ cases, in contrast to the study of Güngör et al. [4], who reported microcephaly in all groups of MCD, mostly in LIS patients.

Patients with cortical dysplasia usually do not have severe neurological deficit and the main clinical manifestation is epilepsy. According to Lee et al. [5] FCD is the most common cause of refractory focal epilepsy in childhood. In approximately 25% of patients with FCD the epilepsy will progress to drug-resistant form [6, 7]. We observed therapeutic resistance in 23 (39%) cases, with seizure onset in infancy

in 7 patients. Patients with a high daily frequency of seizures have a higher risk for therapeutic resistance. Seventeen (73.9%) of our patients with drug-resistant epilepsy experienced daily seizures. In these cases, the predominant localization of FCD was in the frontal and temporal lobe.

The clinical presentation of polymicrogyria is highly variable, depending on the size and location of the PMG, as well as the presence of other brain malformations. According to the literature, the most common localisation of PMG is in the perisylvian (60–70%), frontal (70%) and parietal cortex (63%). In our study the localisation varied, but cases of unilateral PMG with a localisation other than in the perisylvial area (n = 18, 34.6%) prevailed. Our observation showed that PMG is the second most frequent MCD (25.3%) that leads to epileptic seizures, motor deficit and intellectual disability.

The incidence of mental retardation in LIS patients ranges from 56% [9] to 84% [2] and 92% [10]. In our LIS group, 78.7% of the cases had mental retardation that was severe in 38.3% of them. In the study of Guerrini et al. [8] most of the cases (90%) had an early age of seizure onset and severe developmental delay. In our LIS cases the mean age of seizure onset was 2.4 years, which was the earliest manifestation compared to the other MCD. In 26 patients with LIS (55.3%), epilepsy started before the age of 1 and in the neonatal period in three of them. Therapeutic resistance was observed in 7/26. In 42.6% of LIS cases, the mixed seizures prevailed.

Heterotopia is a rare MCD in our group (n = 31, 15.12%) with an almost equal gender distribution. Most of the cases were unilateral and consisted of a single or multiple nodules (n=17, 54.8%). Rarely bilateral periventricular HT was diagnosed (n = 6, 23%). In three patients (12%) MRI showed subcortical HT, combined with other brain pathology, such as SCZ and FCD. In these cases, the diagnosis was made usually before 6 months of age, because of the clinical manifestation of epileptic spasms, drug resistant seizures and severe mental retardation. In cases of periventricular HT without other brain pathology the main clinical manifestation is epileptic seizures. In the study of Budisteanu et al. [11] intellectual disability was described in 8 out of 15 patients and most of them were with mild mental retardation, results that are similar to our observations. Normal development was reported in 20 (64.5%) of our patients.

Schizencephaly often occurs in combination with other brain malformations, such as PMG and HT. The combination between SCZ and abnormalities of the fornices and septum pellucidum, part of the spectrum of septo-optic dysplasia, was found in 3 of our children. One third of our patients had bilateral SCZ, while almost half of the pediatric patients of Barkovich and Raybaud [12] had bilateral schizencephaly. The clinical manifestation of SCZ varies significantly. Hung et al. [13] found that patients with unilateral SCZ had hemiparesis and mild mental retardation, while patients with bilateral clefts had quadriparesis and severe mental retardation. Motor deficit was presented in most of our patients,

81.2% had different type of paresis that was more severe in the open type of SCZ. Ten children (62%) experienced epileptic seizures – generalized in 25% of our patients and mixed – in 6.3% of them.

Conclusion. MCD are among the most important causes of mental retardation, epilepsy and motor deficit in childhood. Overall, 78% of our patients with MCD had epilepsy, which is the main clinical manifestation of cortical malformations. Our study provides detailed phenotypic information that would be useful for future genotype-phenotype correlations.

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