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Epilepsy in paediatric patients with schizencephaly

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Abstract

Introduction. Schizencephaly is one of the rare congenital defects of the central nervous system (CNS), known as neuronal migration disorders. The etiology of schizencecephaly is unequivocal. Established etiologies include *in-utero* infections (cytomegalovirus and herpes simplex virus, HSV type I), toxic abuse (cocaine, alcohol), as well as drug use (warfarin).

Objectives. The aim of the study was to analyze the clinical presentation of schizencephaly with particular consideration of the course of epilepsy in paediatric patients.

Materials and method. The study group consisted of 38 children with schizencephaly (20 of them had seizure) and was retrospectively assessed. Data were analyzed using SAS version 9.4. U Mann-Whitney and χ^2 tests and logistic regression analysis were used in statistical analyses.

Results. Epilepsy was the most frequent in bilateral type II schizencephaly (p=0.033). In logistic regression analysis, the presence of bilateral open schizencephaly significantly increased the risk of seizures (OR=11.67; 95%CI 2.44–55.83; p=0.002). Drug-resistant epilepsy was observed in 9 children (45% of the children with epilepsy). Prevalence of both epilepsy and drug-resistant epilepsy in schizencephaly did not significantly depend on gender, stage of development, type or localization of schizencephaly, and other coexisting CNS defects or clinical presentation of schizencephaly at follow-up in the study group of patients.

Conclusions. The bilateral type of schizencephaly was identified as an independent risk factor for epilepsy in the analyzed children.

Key words

schizencephaly, bilateral, unilateral, central nervous system malformation, epilepsy, developmental delay

INTRODUCTION

Schizencephaly is a rare congenital malformation of the central nervous system (CNS) associated with cell migration disturbances where clefts extend through the hemisphere from the ventricles to the pial surface [1]. Closed and open schizencephaly (type I and type II, respectively) can be distinguished in dependence of the level of the morphological disturbances. These types can be uni- or bilateral. In type I schizencephaly, the cleft has no connection to the ventricular system, while in type II schizencephaly it is filled with cerebrospinal fluid from the lateral ventricle to the subarachnoid space [2]. The prevalence of schizencephaly was estimated in 1.48/100 000 births, and in other study in 0.54/10 000 births [1, 3]. In children with epilepsy and/or psychomotor, developmental delay the incidence of the defect is reported as 1 in 1,650 patients [4]. However, 5% of 109 children with cortical malformations had schizencephaly [5]. Schizencephaly belongs to the group of congenital CNS defects known as neuronal migration disorders. These also include lissencephaly, characterized by a paucity of gyri and sulci, and for this reason referred to as a 'smooth brain', in which heterotopias consisting of clusters of disorganized neurons occur in abnormal locations, and polymicrogyria when the gyri and sulci are numerous, narrow and crowded [6]. The clinical presentation of patients within the neuronal migration disorders is varied, ranging from very severe motor and mental disability and intractable epilepsy in children with lissencephaly, to mild forms in patients with some heterotopias where seizures are low in number and development is normal [6].

The causes of schizencephaly are heterogeneous and poorly investigated. The established etiologies include *in-utero* infections, toxic abuse or drug use [7], as well as young maternal age and lack of prenatal care [8]. On the other hand, thrombotic occlusion of the foetal brain vasculature in the region of distribution of the middle cerebral artery (MCA) is also taken into consideration [9]. Previously, genetic mutation of *EMX2* gene, which is a regulation gene for structural development of the pros encephalon, was also potentially related to schizencephaly [10].

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In some patients, the diagnosis of schizencephaly is made *in utero*. However, later diagnosis of schizencephaly can be made due to the presence of psychomotor developmental delay, haemiplegia (in patients with unilateral defect) or epileptic seizures commonly occurring in infancy. Thus, the outcome of epilepsy may differ in the patients with the same type of schizencephaly.

OBJECTIVES

Since psychomotor developmental delay and epilepsy are the most typical clinical presentations of schizencephaly [3], the aim of the study was to analyze the potential risk factors for seizures, as well as for drug resistant epilepsy in children with schizencephaly.

MATERIALS AND METHOD

Study sample. The research was retrospective and based on patients' records. Finally, 38 children with schizencephaly: mean age at the time of schizencephaly diagnosis 2.2±3.6 years; mean age 4.7±4.8 years at follow up, were enrolled. The following inclusion criteria were accepted: age between one month to 18 years of life, hospitalization for developmental problems or need for seizure outcome/anti-epileptic therapy. Exclusion criteria were as follows: age below one month of life and over 18 years of life, lack of neuroimaging results confirming schizencephaly, and defects other than schizencephaly found on imaging. All patients were white Polish Caucasians hospitalized at the Department of Paediatric Neurology in the Medical University of Silesia in Katowice. Diagnosis of schizencephaly (any type) was confirmed by neuroimaging results. Magnetic resonance imaging (MRI) was performed in 33 children, computed tomography (CT) in one patient, and both MRI and CT in 4 children. Permission for the study was granted by the Local Ethics Committee.

Classification of epilepsy. The classification of the seizures was quoted after Berg et al. [11]. Epilepsy was defined as a disorder of the brain characterized by an enduring predisposition to generate at least one epileptic seizure, and by the neurobiological, cognitive, psychological, and social consequences of this condition [12]. Drug-resistant epilepsy may be defined as the failure of adequate trials of two tolerated and appropriately selected schedules and antiepileptic drugs (AED) used, whether as monotherapies or in combination, to achieve sustained seizure freedom [13].

Data analysis. Data were analyzed using SAS version 9.4 (SAS Institute Inc., Gary, NC, USA). Mean values (M) with standard deviations (SD) were estimated for continuous variable (age), and absolute (n) and relative numbers (%) of occurrence of items for categorical variables. U Mann-Whitney test was used to compare age between children with and without drug-resistant epilepsy. $\chi 2$ test with Yates's correction was used to compare prevalence of epilepsy and prevalence of drug resistant epilepsy vs. gender, stage of development, type and anatomical localization of schizencephaly, and other coexisting CNS defects or clinical presentation of schizencephaly. The odds ratios (ORs) as well as the 95% confidence intervals (CI) were computed in logistic regression to analyze whether the type or localization of schizencephaly determined the occurrence of seizures. The value of $p<0.05$ was considered as a significant difference.

RESULTS

Epilepsy in schizencephaly patients. The general characteristics of analyzed schizencephaly patients is presented in Table 1. Epileptic seizures developed in 20 children with schizencephaly (52.6%). The first seizures occurred between the ages of 2 months and 11 years, mean 2.5±3.7 years. The differences between the age of the seizures occurrence and the age of schizencephaly diagnosis were from -6 to +3 years in the analyzed patients. The age at the occurrence of seizures and diagnosis of schizencephaly was the same in 9 children with epilepsy (45% of the epilepsy patients). Epilepsy appeared before the schizencephaly diagnosis in 5 of the children (25%). In turn, epilepsy developed after the diagnosis of schizencephaly in 6 cases (30%).

Epilepsy was found to affect both genders with similar frequency and was not related to the stage of development or other coexisting CNS defects. It was observed that epilepsy was associated with the type of schizencephaly, as well as its localization, and was the most prevalent in cases with bilateral type II schizencephaly, compared to other types and localizations of schizencephaly (82% vs 29%, respectively). In logistic regression, it was found that both the open type and the bilateral localization of schizencephaly increased the risk of seizures when analyzed separately (OR=6.09 95%CI 1.23–30.09; p=0.027 and OR=4.53 95%CI 1.07–21.14; p=0.049, respectively). Moreover, when type and localization of schizencephaly was considered together, the risk of the appearance of seizures was observed to be greater in the presence of bilateral open schizencephaly (OR=11.67 95% CI 2.44–55.83; p=0.002).

Epilepsy occurred significantly more often in children with spastic tetraparesis as the clinical presentation of schizencephaly, compared to children without spastic tetraparesis. In contrast, epilepsy occurred only in children without right-sided spastic hemiparesis, not in children with right-sided spastic hemiparesis. Prevalence of epilepsy in analyzed patients did not differ in case of other clinical presentations of schizencephaly.

Epilepsy was treated with polytherapy in 14 children (70%) and in 6 children (30%) with monotherapy (67% of them were treated with valproic acid, 33% with vigabatrin).

Morphology of seizures. Table 2 shows morphology of seizures in the analyzed patients at onset and during follow-up. In most of the children (70%), the seizures occurred at infancy (from above 1 month of age to 2 years of age) and were characterized by various morphology. In follow-up, the evolution of the seizures was observed to be focal, primarily or secondarily generalized tonic-clonic seizures, tonic seizures, and atypical absence o0f seizures.

Drug-resistant epilepsy. Drug-resistant epilepsy was observed in 9 children (45%) with epilepsy. Children with drug-resistant epilepsy were aged from 2 years to 15 years, mean 7.1±4.6 years, and their age was not significantly

Table 1. Characteristics of patients, prevalence of epilepsy and drug resistant epilepsy

Variable	Category	Total No. in group n (%1)	Prevalence of epilepsy n (%2)	p*	Prevalence of drug-resistant epilepsy n (%3)	p**
	Total	**38 (100.0)**	**20 (52.6)**		**9 (45.0)**	
Gender	female	11 (28.9)	5 (45.5)	0.572	3 (60.0)	0.437
	male	27 (71.1)	15 (55.6)		6 (40.0)	
Stage of development	normal	7 (18.4)	2 (28.6)	0.154	1 (50.0)	0.881
	delayed	31 (81.6)	18 (58.1)		8 (44.4)	
Type of schizencephaly	type I (close)	11 (28.9)	3 (27.3)	0.031	2 (66.7)	0.281
	type II (open)	23 (60.5)	16 (70.0)		6 (37.5)	
	both types	4 (10.5)	1 (25.0)		1 (100.0)	
Localization of schizencephaly	unilateral	11 (28.9)	3 (27.3)	0.043	1 (33.3)	0.656
	bilateral	27 (71.1)	17 (63.0)		8 (47.1)	
Type and localization of schizencephaly	bilateral type I	6 (15.8)	2 (33.3)	0.033	1 (50.0)	0.583
	bilateral type II	17 (44.7)	14 (82.4)		6 (42.9)	
	right-sided type I	3 (7.9)	1 (33.3)		1 (100.0)	
	right-sided type II	4 (10.5)	1 (25.0)		0 (0.0)	
	left-sided type I	2 (5.3)	0 (0.0)		0 (0.0)	
	left-sided type II	2 (5.3)	1 (50.0)		0 (0.0)	
	right-sided type I and left-sided type II	2 (5.3)	0 (0.0)		0 (0.0)	
	right-sided type II and left-sided type I	2 (5.3)	1 (50.0)		1 (100.0)	
Complex defect (schizencephaly and other accompanying CNS defects)	yes	18 (47.4)	10 (55.6)	0.732	5 (50.0)	0.653
	no	20 (52.6)	10 (50.0)		4 (40.0)	
Clinical presentation of schizencephaly at follow-up	Spastic tetraparesis – yes	17 (44.7)	12 (70.6)	0.044	6 (50.0)	0.581
	no	21 (55.3)	8 (38.1)		3 (37.5)	
	Left-sided spastic haemiparesis – yes	7 (18.4)	3 (42.9)	0.566	1 (33.3)	0.656
	no	31 (81.6)	17 (54.8)		8 (47.1)	
	Right-sided spastic haemiparesis – yes	3 (7.9)	0 (0.0)	0.029	0 (0.0)	1.000
	no	35 (92.1)	20 (57.1)		9 (45.0)	
	Microcephaly – yes	24 (63.2)	13 (54.2)	0.804	6 (46.2)	0.889
	no	14 (36.8)	7 (50.0)		3 (42.9)	
	Generalised hypotonia – yes	11 (28.9)	5 (45.5)	0.572	2 (40.0)	0.795
	no	27 (71.1)	15 (55.6)		7 (46.7)	
	Cerebellar component – yes	1 (2.6)	1 (100.0)	0.253	1 (100.0)	0.197
	no	37 (97.4)	19 (51.4)		8 (42.1)	
	Left central facial nerve palsy – yes	1 (2.6)	1 (100.0)	0.253	0 (0.0)	0.266
	no	37 (97.4)	19 (51.4)		9 (47.4)	

* with epilepsy vs without epilepsy; ** with drug resistant epilepsy vs without drug resistant epilepsy;
1 % of total group; 2 % in rows, of schizencephaly; 3 % in rows, of epilepsy in schizencephaly.

Table 2. Morphology of seizures in 20 epileptic children with schizencephaly

Morphology of seizures	Presence at onset n (%)	Presence at follow-up n (%)	Presence at both onset and follow-up n (%)	Presence neither at onset nor at follow-up n (%)	Presence at onset, but not at follow-up n (%)	Presence at follow-up, but not at onset n (%)
Focal	4 (20.0)	5 (25.0)	3(15.0)	14 (70.0)	1 (5.0)	2 (10.0)
Infantile spasms	9 (45.0)	2 (10.0)	2 (10.0)	11 (55.0)	7 (35.0)	0
Generalised tonic-clonic	5 (25.0)	6 (30.0)	4 (20.0)	13 (65.0)	1 (5.0)	2 (10.0)
Tonic	1 (5.0)	1 (5.0)	0	18 (90.0)	1 (5.0)	1 (5.0)
Atypical absence	1 (5.0)	4 (20.0)	1 (5.0)	15 (75.0)	1 (5.0)	3 (15.0)
Myoclonic	3 (15.0)	6 (30.0)	3 (15.0)	14 (70.0)	0	3 (15.0)
Atonic	1 (5.0)	1 (5.0)	0	18 (90.0)	1 (5.0)	1 (5.0)

Classification of the epileptic seizures according to ILAE 2010, Berg et al. [10]

different from children without drug- resistant epilepsy (from 3 months to 18 years, mean 5.3±6.4 years; p=0.147).

The prevalence of drug-resistant epilepsy did not significantly depend on gender, stage of development, type or localization of schizencephaly, coexisting other CNS defects or clinical presentation of schizencephaly at follow-up in the study group of patients (Tab. 1).

DISCUSSION

The problem of epilepsy concerns a large number of children with schizencephaly. In the patients analyzed in the current study it was found that epilepsy is significantly more frequent in bilateral type II (open) schizencephaly than in other types of the defect. In regression analysis, bilateral type II

schizencephaly significantly increased the risk of seizures (OR=11.67).

Similarly, in a recent study on 21 patients with schizencephaly from Taiwan, epilepsy was more common in children with bilateral defect, compared to those with a unilateral defect. Moreover, the onset of seizures occurred earlier in children with bilateral schizencephaly and the course of epilepsy was more severe in these patients. Additionally, in 4 out of 5 children with bilateral schizencephaly (80%), intractable epilepsy was diagnosed [14].

In research by Stopa et al., the study group was slightly smaller and younger compared to the presented study, which seems to be the most important, and different in respect of the type of brain defect [15]. Contrary to the presented study, Stopa et al. observed unilateral closed schizencephaly to be the most prevalent; however, certain symptoms occurred more often in the group of children with bilateral type II schizencephaly. Similarly to data in the current study, epileptic seizures were observed in 50% of patients in the study by Stopa et al., additionally, the bilateral type of defect was related to a higher risk of seizures [15]. In turn, the closed type was more frequent in epileptic patients than the open type (53% vs 44%), which again is contrary to the current study data. In an other study from northern Poland, most of the patients with schizencephaly had epilepsy, and bilateral schizencephaly was observed in children with spastic diplegia and tetraplegia; however, patients with spastic haemiplegia only had unilateral schizencephaly [16].

In a group of children with schizencephaly described by Packard et al., epilepsy was diagnosed in 57%, and in two-thirds of them the seizures were satisfactorily controlled [17]. The children with the unilateral and closed form of the defect presented a much more favourable outcome when those with the open type of schizencephaly presented more commonly with seizures. The age of the patients described by Packard et al. [17] was similar to those in the current (nearly 4 years of age). The authors suggested that some of schizencephaly patients start the seizures later on, even in the third decade of life, thus a longer follow-up would be very instructive for learning the natural history of epilepsy in schizencephaly patients [17]. Similarly, seizures were observed in 50% of Spanish patients with schizencephaly [18].

Contrarily, seizures (early or late remote) were observed in less than 26% of children suffering from arterial ischemic stroke [19]. On-third of the schizencephaly patients in the current study were treated with monotherapy. However, in a previously published study on a large group of epileptic patients aged ≥4 years, almost 61% of them were on monotherapy [20]. The treatment of epilepsy in children with schizencephaly should be considered based on the nature of the seizures they suffered. For the treatment of focal seizures in children, oxcarbazepine is the AED of first choice, and for generalized seizures – carbamazepine, phenytoin, phenobarbital, topiramate, and valproate. As epilepsy in children with congenital brain defects has a symptomatic character, there is a high probability of its drug-resistance; therefore after the first seizure in schizencephaly patients, AED should be administered without delay.

In a study by Lopes et al. [21], the type of schizencephaly (open vs. close) did not correlate with the presence of epilepsy and seizure control. Surprisingly, the better seizures control was in the patients with open schizencephaly, compared to the close form [21]. The clinical course of epilepsy in schizencephaly is very variable. Some authors describe a mild course of seizures in schizencephaly patients, and indicate no relationship between epilepsy and development of the patients [15, 22].

In the presented study, epilepsy was observed in 56% of children with a complex defect, whereas drug resistant epilepsy occurred in 50% of epileptic patients with complex defect. Thus, the co-existence of other defects was not the factor determining the course of epilepsy in the current group. In the case of stage of development, epilepsy was present in 58% of delayed children, of whom 44% showed drug-resistant epilepsy. However, the results of the developmental test are difficult to compare due to the variety of ages of the children in the current study (from very early infancy to almost adults). Most of the children were admitted to hospital because of the intensification of seizures, and evaluation of the level of development was not performed in all of them. In the study byu Pascual-Castroviejo et al., a degree of developmental delay was observed in all patients with schizencephaly, which was very mild in cases of closed schizencephaly [20]. On the other hand, in some patients with schizencephaly, seizure onset may be late, even in late adulthood [23].

Some observations suggest that rufinamide would be a treatment option for patients with drug-resistant epilepsy due to neuronal migration defects [24]. The authors described a group of patients at the very wide range of age (3years up to 43 years of life) of which 62% presented a reduction in the number of seizures between 50% – 99%, and 3% were seizures-free. On the other hand, nearly a half of the presented group of patients showed side-effects of the treatment [24]. Other small case-series on 3 patients with schizencephaly aged 7.2 – 10.1 years, the treatment of drug-resistant seizures with rufinamide was very successful [25]. In turn, the American Academy of Neurology indicates that rufinamide was more effective than placebo in seizure-reduction action with over 50% of responders. In conclusion, the add-therapy of rufinamide in Lennox-Gastaut syndrome is effective although the benefits of the therapy are modest [26]. The European Medicines Agency allows the use of rufinamide in Europe for the treatment of patients older than one year of age and diagnosed with Lennox-Gastaut syndrome. According to this European recommendation, the research in children between 1 and 4 years of age treated with rufinamide were inconclusive. Because of the young age of patients in the current study (much younger than these presented by Cusmai et al. [24]), and the above recommendations, the patients were not treated with rufinamide.

Due to the rarity of the schizencephaly, the recruitment of large enough group of patients from one medical centre is very difficult, as shown in the cited data. In addition, the wide age range of patients may affect a proper assessment of development.

CONCLUSIONS

In the presented group of patients, the type of schizencephaly was the only proven risk factor for epilepsy. The risk of the occurrence of seizures was especially high in the presence of bilateral open schizencephaly. The children diagnosed with the mentioned defects should remain under special care for high risk of seizure outcome, especially when the diagnosis of the defect is established early, even in the premature period,

and the most typical seizure onset is earlier than 6 months of age. Early diagnosis and proper treatment may enable these patients to attain better developmental achievements.

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