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Risk factors for developing epilepsy in children with cerebral palsy

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Abstract

Aim. To identify the most important risk factors affecting the development of epilepsy in children with cerebral palsy.

Methods. The study included 160 cerebral palsy patients with and without epilepsy who received treatment at the Baku Children's Neurological Hospital. The patients were divided into 2 groups. The first group consisted of 110 (68.7%) patients with cerebral palsy and epilepsy, and the second group consisted of 50 (31.3%) patients with cerebral palsy. The age of children ranged from 1 to 14 years. Statistical data processing was performed by using the SPSS software version 16.0. The Chi-square test was used to compare categorical measurements. T-test for independent groups was used for comparison between groups of continuous measurements. Binary logistic regression was used for determining the risk factors. In all tests, the level of statistical significance was set at $p < 0.05$.

Results. There was no significant difference in age and gender distribution between groups ($p=0.492$ and $p=0.818$, respectively). 10 (9.1%) children in the main group had a positive family history of epilepsy (odds ratio 8.08, $p=0.028$). Neonatal seizures were observed in 25 (22.7%) children in the main group and 3 (6%) children in the control group (odds ratio 4.4, $p=0.010$). The presence of infection during pregnancy in the mother was found in both the main (39.1%) and control (20%) groups (odds ratio 2.6, $p=0.018$). Level IV of the Gross Motor Function Classification System (GMFCS) was the most frequent among patients with epilepsy (odds ratio 12.8; $p=0.035$). The incidence rate of epilepsy among cerebral palsy patients was 68.7%. The mean age of onset of seizures was 19.2±26.6 months. The most frequent epileptic seizures (55.5%) occurred in spastic quadriplegic cerebral palsy.

Conclusion. The presence of a positive family history of epilepsy, neonatal seizures, maternal infection during pregnancy and severe GMFCS level were identified as factors for the development of epilepsy in patients with cerebral palsy; premature birth, presence of hypoxic-ischemic injury, low birth weight, consanguineous marriage, multiple pregnancies, or gender were not identified as risk factors for the development of epilepsy in children.

Keywords: children, cerebral palsy, epilepsy, risk factors.

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Background. Infantile cerebral palsy (ICP) includes a group of chronic non-progressive symptom complexes of motor disorders secondary to lesions or anomalies of the brain that occur during early developmental stages [1]. The incidence of epilepsy in patients with ICP is 15%–90% [2]. Over the past decade, several publications have reported the prevalence and clinical characteristics of children with epilepsy and various forms of ICP [2–5]. It has also been consistently demonstrated that in most cases, such epilepsy develops at an early age. The most common risk factors for epilepsy in ICP are neonatal seizures and low birth weight.

In the development of epilepsy and ICP, several authors have highlighted great importance to factors with a role in the pre- and perinatal periods [5–8].

The aim of this study was to identify the most important risk factors affecting the development of epilepsy in children with ICP.

Materials and methods. The study included 160 patients with ICP who received treatment at the Children's Neurological Hospital in Baku from October 2017 to December 2019. Demographic information was recorded by collecting detailed history of parents, including birth weight, gestational age, seizures in the neonatal period, consanguinity of parents, and family history of epilepsy. The diagnosis of ICP was established in accordance with the recommendations of the modern classification of ICP [1]. According to the definition of ICP and its individual forms, the inclusion criteria were as follows: persistent impairment of motor function and

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posture caused by pathological high muscle tone, absence of disease progression, and exclusion of the hereditary nature of the disease. Movement disorders imply the presence of objective changes in tone, muscle strength, posture, reflexes, and motor skills during a neurological examination. The diagnosis was established by a pediatric neurologist.

The following forms of ICP were identified: spastic hemiplegic, spastic diplegic, double hemiplegia, hyperkinetic, atactic, and mixed. To determine the severity of movement disorders in children, we used the Gross Motor Function Classification System (GMFCS) [9].

Patients were classified according to the following main perinatal factors: prematurity (children born before the 37th week of pregnancy), birth weight (less than or more than 2500 g), head size (normocephaly, microcephaly, or macrocephaly), gestational age (full-term infants [38–41 weeks], premature [30–37 weeks], extremely premature [<30 weeks]), and delivery method (vaginal delivery or cesarean section). Epilepsy was defined as isolated cases of two or more unprovoked seizures [10].

All patients underwent routine electroencephalography (EEG) using a NeuroSpectrum apparatus, in which 16 channels with electrodes were applied according to the international 10/20 system. In some cases, when it was difficult to diagnose the type of seizures, a video EEG recording was performed. To detect latent epileptiform activity, EEG recordings were obtained during and after sleep deprivation. The type of seizures was determined according to the classification of the International League Against Epilepsy [10].

All patients underwent magnetic resonance imaging or computed tomography of the brain, and the results were described by radiologists.

The study was approved by the Ethics Committee of the Azerbaijan Medical University (Protocol No. 11 dated December 29, 2019).

Statistical data processing was conducted using the SPSS program version 16.0. Categorical measurements are analyzed as numbers and percentages and continuous measurements as means and standard deviations (median and minimum–maximum where appropriate). The $\chi 2$ test was used to compare categorical measurements. Logistic regression was used to identify risk factors. The *t*-test for independent groups was used to compare continuous measurements between groups. In all tests, the level of statistical significance was set to $p < 0.05$; thus, the minimum significance of differences was 95%.

Results. To study the effect of epilepsy on the course of ICP, two comparison groups were created and compared. The first group (main) comprised 110 (68.7%) patients with ICP and epilepsy; the second group (control) comprised 50 (31.3%) patients with ICP. The age of children ranged from 1 to 14 years. In the main group, 35 (31.8%) patients were girls, 75 (68.2%) were boys, and the mean age was 4.7 ± 3.3 years. In the control group, 35 (70%) patients were boys, and 15 (30%) were girls; the average age was 4.3 ± 3.5 years. There was no significant differences in age and sex distribution between the groups ($p = 0.492$ and $p = 0.818$, respectively). In addition, there was no statistically significant difference between the two groups in terms of the average age of the mother at the time of childbirth (25.4 ± 4.5 years in patients with ICP with epilepsy; 25.4 ± 5.6 years in patients with ICP without epilepsy) ($p = 0.953$).

Table 1 shows the main characteristics of patients in the main and control groups.

Hypoxic-ischemic brain damage was one of the most frequent types of pathology in children in both groups, to varying degrees. It was diagnosed in 97 (88%) children with epilepsy and 46 (92%) without epilepsy.

Differences between groups were not statistically significant ($p > 0.05$) in terms of preterm labor, delivery method, low birth weight, multiple pregnancies, and baby head size.

In both the main (39.1%) and control (20%) groups, infections were present during pregnancy in the mother. Most of them were TORCH infections[1]. Statistical analysis showed that infectious diseases in the mother during pregnancy increased the risk of epilepsy among patients with LC by >2.5 times (odds ratio [OR] = 2.6, 95% confidence interval [CI]: 1.2–5.6, $p = 0.018$).

Notably, 24 (21.8%) parents of children with cerebral palsy (CP) and epilepsy and 8 (16%) parents of children with CP were consanguineous (cousins and second cousins). In addition, in the main group, 10 (9.1%) children had a family history of epilepsy (OR = 8.08, $p = 0.028$).

Neonatal convulsions were recorded in 25 (22.7%) children in the main group and 3 (6%) in the control group. There was a statistically significant difference between the groups for these indicators ($p < 0.05$). Factor analysis revealed that neonatal seizures increased the risk of epilepsy (OR = 4.4, 95% CI: 1.2–15.3, $p = 0.010$).

The mean age of seizure onset was 19.2 ± 26.6 months: 12.6 ± 2.24 months in patients with tetraplegic seizure type, 29 ± 8.68 months in patients

[1] TORCH (from English Toxoplasmosis, Other viruses, Rubella, Cytomegalovirus, Herpes simplex viruses) — a group of congenital infections including toxoplasmosis, other viral infections, rubella, cytomegalovirus, and herpes simplex virus infections.

Table 1. Main test parameters of study groups

Parameter	Patients with ICP and epilepsy, n (%)	Patients with ICP, n (%)	p	OR (95% CI for OR)
Sex: Boys Girls	 75 (68.2%) 35 (31.8%)	 35 (70%) 15 (30%)	0.818	—
Intermarriage of parents	24 (21.8%)	8 (16.0%)	0.394	—
Mean age of mother, years	25.4	25.4	0.417	—
Gestation: In term Premature (<37 weeks)	 70 (63.6%) 40 (36.4%)	 30 (60%) 20 (40%)	0.661	—
Gestosis	26 (23.6%)	10 (20.0%)	0.611	—
Infectious diseases in the mother during pregnancy	43 (39.1%)	10 (20.0%)	0.018	2.6 (1.2–5.6)
Hypoxic-ischemic brain damage at birth	97 (88%)	46 (92%)	0.015	—
Delivery: Vaginal delivery Caesarian section	 85 (77.3%) 25 (22.7%)	 37 (74%) 13 (26%)	0.653	—
Body weight at birth: >2500 g <2500 g	 74 (65%) 36 (35%)	 34 (68%) 16 (32%)	0.989	—
Microcephalia	17 (15.5%)	5 (10%)	0.355	—
Epilepsy in family history	10 (9.1%)	0	0.028	8.08
Typical febrile seizures	21 (19.1%)	5 (10%)	0.150	
Neonatal seizures	25 (22.7%)	3 (6.0%)	0.010	4.4 (1.2–15.3)
ICP forms: Spastic diplegia Spastic hemiplegia Double hemiplegia Extrapyramidal Ataxic	 16 (14.5%) 24 (21.8%) 61 (55.5%) 4 (3.6%) 5 (4.5%)	 3 (6%) 15 (30%) 24 (48%) 5 (10%) 3 (6%)	0.368	—
Changes in neuro-visualization: Lesions of white matter Gray matter lesions Malformations Combined changes Hydrocephalus Normal	 45 (40.9%) 23 (20.9%) 7 (6.4%) 22 (20.9%) 2 (1.8%) 11 (10%)	 20 (40%) 5 (10%) 3 (6%) 5 (10%) 0 9 (18%)	0.42	—
Total	110	50	160	—

Note: ICP — infantile cerebral palsy; OR — odds ratio; CI — confidence interval.

with hemiplegic seizure type, and 22 ± 6.65 months in patients with diplegic seizure type. In patients with myoclonus and tonic spasms, episodes began much earlier, usually during the first year of life ($p < 0.05$).

A comparison was made between the groups of the results obtained with neuroimaging. However, there was no statistical difference between patients with and without epilepsy ($p = 0.42$).

In 80 patients, the level of lesions of large motor functions was determined according to the GMFCS scale. In patients with epilepsy, the most common level of involvement of large motor functions was IV. This difference was statistically significant (OR = 12.8; $p = 0.035$).

Changes in groups according to the GMFCS scale are shown in Fig. 1.

Discussion. It is known that prenatal and perinatal problems are one of the main reasons for the development of CP, but little is known about the influence of various factors on the development of epilepsy [2, 11]. We attempted to study the influence of possible factors by comparing children with CP who had epilepsy and did not have epilepsy. Current literature describes the influence of various factors on the development of epilepsy in CP.

Thus, Sadowska et al. (2020) found that maternal hypertension was a significant risk factor and that delivery by caesarean section doubled the likelihood of developing epilepsy in patients with CP

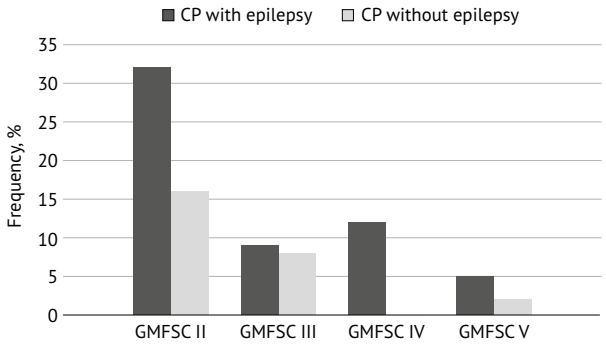

Fig. 1. Distribution of lesions of large motor functions in patients according to the Gross Motor Function Classification System (GMFCS) scale by groups; CP - cerebral palsy

[12]. Results from a Swedish study of term-born infants showed that the risk of epilepsy appeared related to the child's 10-min Apgar score [13]. Zelnik et al. (2010) proved the relationship between a low Apgar score (0–3 points) at the 1st and 5th min and further development of epilepsy [8].

Although in our study there was a difference between the groups in the degree of hypoxic-ischemic brain damage in children, it is difficult to judge it as a risk factor because of the retrospective assessment of obstetric history.

The results of various studies that determined the relationship between gestational age or birth weight and the development of epilepsy in patients with CP are contradictory. Mert et al. (2011) found that prematurity and low birth weight were not associated with the development of epilepsy [7]. Kulak et al. (2003) identified an increased risk of epilepsy in patients with low birth weight [5]. In contrast, Zelnik et al. (2010) demonstrated that epilepsy was more common in infants born at term than in preterm infants, while they found no association between birth weight and the risk of epilepsy [8]. Gururaj et al. (2003) also found a link between the development of epilepsy and term birth [4]. Sellier et al. (2012), when analyzing data from 17 European registries, found a definite relationship between the development of epilepsy and the degree of maturity in infants [2]. Our study did not find an association between the term, birth weight, and the further development of epilepsy in children with CP.

In the present study, infectious diseases in the mother during pregnancy were more often associated with CP and epilepsy (39.1%) than with only CP (20%) ($p = 0.018$).

Similar data were obtained by Wu et al. (2003), who identified an increased risk of CP and epilepsy if the mother had an infection before or during pregnancy [14].

A family history of epilepsy can also influence the risk of developing epilepsy in children with CP [11, 13, 15, 16]. Many studies have demonstrated that a family history of epilepsy increases the risk of epilepsy in patients with CP [4, 5, 7]. In our study, a positive family history of epilepsy was noted in 9.1% of cases, while none in non-epileptic cases, and this history was also associated with an increased risk of epilepsy ($p < 0.05$).

Neonatal seizures are a significant factor in the development of epilepsy. Several early studies conducted on children with LC have shown that the risk of developing epilepsy is greater in patients with a history of neonatal seizures [2, 5–8]. Kulak and Sobaniec (2003) indicated that neonatal seizures were present in 14 (17%) children and that they may have been associated with a significant risk of epilepsy in children with CP [5]. Zelnik et al. (2010) observed 132 patients with CP and 65 patients with CP and epilepsy to determine the risk factors for the development of epilepsy. Of 27 patients with CP and a history of neonatal seizures, 22 (81.5%) developed epilepsy [8]. El-Tallawy et al. (2014) reported that neonatal seizures were strong predictors of epilepsy in CP [17]. When analyzing the available literature, we found that no studies refuted these data. In our study, epilepsy later occurred in 25 (22.7%) children with neonatal seizures.

It is known [8, 11, 13] that perinatal and postnatal factors increase the risk of developing CP. However, we could not find a connection between them ($OR < 1$), with the exception of neonatal seizures ($OR = 4.4$), as well as previous infectious diseases in the mother during pregnancy ($OR = 2.6$) and the risk of developing epilepsy.

The incidence of epilepsy among patients with CP was 68.7%. Similar data were found in the works of Polish and Turkish researchers [7, 11].

In our study, we did not find a significant correlation between CP type and the development of epilepsy ($p = 0.368$). However, when analyzing patients with CP and epilepsy, as in our previous studies [4–7], we found that epilepsy was more common in children with tetraplegic (61, 55.5%) form of CP, followed by hemiplegic (24, 21.8%), diplegic (16, 14.5%), ataxic (5, 4.5%), and extrapyramidal (4, 3.6%) forms. Carlsson et al. studied 148 children with CP in Sweden and revealed that epilepsy most often developed in children with tetraplegic CP [3]. Similar data have been reported by Sadowska (2020), with epilepsy occurring in 42% of children with tetraplegia [11].

In our patients, a severe level of damage to motor functions according to the GMCFS (IV) scale was identified as a risk factor for the development of epilepsy ($OR = 12.8$; $p = 0.035$). Previous studies have also shown that the severity of brain damage,

rather than the form of CP, increases the risk of developing epilepsy [6, 11].

In the present study, changes in neuroimaging were observed in 90% of patients with epilepsy and 82% of patients without epilepsy. The difference was not statistically significant (p = 0.420). Gururaj et al. in their work revealed changes in brain images in 95% of cases with CP and epilepsy and in 97% of cases with CP without epilepsy [4]. Similarly, Mert et al. found no connection between changes in magnetic resonance imaging and the development of epilepsy [7]. According to the literature, damage to the gray matter of the brain is associated with greater incidence of epilepsy [4, 8] than changes in the white matter of the brain [12]. In our study, gray matter changes were detected more often in patients with epilepsy (20.9%) than in patients without epilepsy (10%) (p = 0.092). The frequency of damage to the white matter did not differ between the groups (40.9% and 40%; p = 0.91).

CONCLUSIONS

1. A family history of epilepsy, neonatal seizures, infectious diseases in the mother during pregnancy, and a severe level of damage to motor functions have been identified as risk factors for the development of epilepsy in patients with infantile CP.

2. Mode of delivery, head size, birth weight, febrile seizures, and changes in neuroimaging were not recognized as risk factors for the development of epilepsy in children with CP.

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