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ORIGINAL ARTICLE

Risk factors associated with epilepsy development in children with cerebral palsy

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Abstract

Objectives Epilepsy is one of the most common and important comorbidity among patients with cerebral palsy (CP). The purpose of this study was to determine the risk factors predicting the development of epilepsy considering prenatal, perinatal, and natal characteristics; associated impairments; and cranial imaging findings in our patient population with cerebral palsy at a tertiary center in Istanbul, Turkey.

Methods This retrospective study consisted of 234 children aged between 3 and 18 years of age. Children were divided into two groups as CP patients with epilepsy (126 patients) and CP patients without epilepsy (108 patients). Demographic features and clinical and cranial magnetic resonance imaging (cMRI) findings were compared between the two groups.

Results Presence of family history of epilepsy, history of neonatal seizure especially in the first 72 h of life, quadriplegic type of CP, severe degree of gross motor function and fine motor disorders, and moderate to severe mental retardation or psycho-social developmental delay were determined as risk factors for the development of epilepsy in CP patients. Also, an increased risk of epilepsy was detected in term infants and appropriate for gestational age (2500–4000 g) infants. On the other hand, presence of parental consanguinity, being born from a primiparous mother, age of mother at birth, mode of delivery, presence of multiple gestation and labor problems, history of follow-up in neonatal intensive care unit and intubation, and cMRI findings were not significant risk factors for the development of epilepsy in CP.

Conclusion Predicting epilepsy development by determining the risk factors in patients with CP might be useful because knowing the risk factors could provide close follow-up of these patients for epilepsy.

Keywords Cerebral palsy · Epilepsy · Children · Risk factors

Introduction

Cerebral palsy is defined as a non-progressive disorder of posture, tone, and/or movement that occurred due to a damage in the developing brain [1]. Impairment of vision, hearing, sensation, perception, cognition, communication, and behavior and epilepsy often accompany cerebral palsy (CP) [1].

The incidence of epilepsy among CP patients varies with a wide range of 15–90% [2]. Since epilepsy is one of the most important problems that affects prognosis and mortality in patients with CP, the association of epilepsy and CP continues to be an interesting subject [2–4]. For these reasons, in recent years, many studies investigated the prevalence, characteristics, and prognosis of epilepsy in patients with CP but few studies investigated the risk factors considering prenatal, perinatal, and natal history for the development of epilepsy in these patients [3, 5–9]. In addition, most of the studies consisted of a small size of patient population, mostly less than 200 children [2, 5–7, 9]. Besides, knowing the risk factors could ensure these patients to be monitored carefully for the development of epilepsy.

In this study, our aim was to determine the risk factors predicting the development of epilepsy considering prenatal,

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perinatal, and natal characteristics; CP subtype; severity of CP; associated impairments, as well as cranial imaging findings in our large patient population with cerebral palsy at a tertiary center in Istanbul, Turkey.

Materials and methods

This retrospective study included patients being followed-up in Medeniyet University Göztepe Training and Research Hospital Child Neurology Department in Istanbul, Turkey, between December 2002 and December 2012 (within the last 10 years) with a diagnosis of cerebral palsy. Inclusion criteria were (1) patients with 3–18 years of age, (2) patients having at least one cranial magnetic resonance imaging (cMRI) above 1 year of age (1.5 Tesla). (3) For patients diagnosed with epilepsy, having at least one sleep and awake electroencephalogram (EEG). (4) Being followed-up for at least 1 year. (5) Patients who were called back in order to inquire whether they had a seizure after the last follow-up. The patients with missing information or laboratory findings in the files and who did not regularly come to follow-up were excluded from the study. Files of patients were screened and 234 patients (141 male; 93 female) who met the study criteria were included in the study.

Cerebral palsy was diagnosed according to the criteria of motor dysfunction which was caused by a non-progressive, static lesion in the developing brain [10] after metabolic and degenerative conditions have been ruled out. Epilepsy was defined as the occurrence of two or more unprovoked seizures beyond the neonatal period excluding febrile seizures [11].

Patients were divided into two groups: CP patients with epilepsy (126 patients) and CP patients without epilepsy (108 patients). Demographic information of both groups was noted including age, sex, parental consanguinity, parity, age of mother at birth, presence of multiple gestation, family history of epilepsy, mode of delivery, gestational age, birth weight, labor problems (prolonged labor, history of instrumental (forceps or vacuum-assisted) delivery, acute fetal distress, meconium aspiration, intrapartum asphyxia), postnatal problems including history of follow-up in neonatal intensive care unit and intubation, and presence of seizure history in the first 72 h and in the neonatal period. The gestational age of ≤ 37 weeks were described as prematurity. Gestational age was categorized into four groups as < 32 weeks, 32–37 weeks, 38–41 weeks, and ≥ 42 weeks. The birth weight was classified as < 1500 g, 1500–2499 g, 2500–4000 g, and > 4000 g. The groups of CP patients with epilepsy and CP patients without epilepsy were compared statistically for the demographic features listed above.

From a clinical point of view, types of CP were divided into four variants as spastic, dyskinetic (dystonic or choreoathetotic), ataxic, and mixed. Spastic, dyskinetic, and ataxic clinical types of CP were classified according to the classification of SCPE (European Cooperation on Surveillance of Cerebral Palsies in Europe) [12]. It was named as mixed type of CP when there was more than one type of CP in the same patient. Spastic CP was re-divided into three types according to topographical involvement of extremities as quadriplegia, hemiplegia, and diplegia.

The motor disorders were evaluated and classified according to the Gross Motor Function Classification System (GMFCS) into five levels [13, 14]. Levels I, II, and III were named as mild-moderate GMCFS level and levels IV and IV were named as severe GMCFS level. Fine motor disorders were classified according to Bimanual Fine Motor Function (BFMF) classification [15]. It was developed to evaluate each hand function separately and it has five levels. Levels I, II, and III were named as mild-moderate BFMF level and levels IV and IV were named as severe BFMF level.

The children's psychosocial development and intelligence were evaluated based on age-appropriate psychometric tests. The standardized, Turkish version of Denver Developmental Screening Test II was applied to evaluate cognitive development in children aged 6 years and below [16]. Children with developmental delay for age according to the developmental stages were diagnosed as developmental retardation. The standardized, Turkish version of Wechsler Intelligence Scale for Children-Revised (WISC-R) was used to assess intelligence quotient (IQ) for children above 6 years of age [17]. Children with a total intelligence score (IQ) level < 70 were diagnosed as intellectual disability. Children with an intelligence score of < 35 were diagnosed as severe intellectual disability, 49–35 were diagnosed as moderate intellectual disability, and 69–50 were diagnosed as mild intellectual disability [18].

Cranial magnetic resonance imaging (cMRI) findings were classified according to the MRI classification system proposed by the SCPE network: normal, primarily white matter injury (including periventricular leukomalacia, sequelae of intraventricular hemorrhage), primarily gray matter injury (including infarcts, basal ganglia/thalamus lesions or watershed lesions in parasagittal distribution), non-specific atrophy, hydrocephaly, and maldevelopments (including disorders of cortical formation) [19].

Clinical types of CP, types of CP according to topographical involvement of extremities, level of GMFCS, level of BFMF, level of intelligence/psychosocial development and findings of cMRI were compared statistically between the groups of CP patients with epilepsy and CP patients without epilepsy.

The study was approved by the local ethics committee (2012/25/D).

Statistical method

Statistical data were performed using NCSS 2007 program for Windows. Besides standard descriptive statistical methods

(mean ± standard deviation), unpaired *t* test was used in the comparison of groups, the chi-square test was performed during the evaluation qualitative data. Binary logistic regression was used for determining the risk factors for the development of epilepsy by using independent variables that were calculated as $p < 0.05$. Odds ratio and 95% confidence interval were calculated. Statistical significance was defined as $p < 0.05$.

Results

The mean age of children in group of CP patients with epilepsy was 9.7 ± 4.2 years and consisted of 58.7% boys. Similar results were obtained in the group of CP patients without epilepsy whose mean age was 8.7 ± 4.4 years and consisted of 62% boys. There was no significant difference according to mean age and gender distribution between both groups ($p = 0.078$ and $p = 0.606$ respectively). Also, there was no statistically significant difference between the two groups in terms of the mean age of mothers at birth (26.5 ± 5.5 years in CP patients with epilepsy; 27.4 ± 5.4 in CP patients without epilepsy) ($p = 0.21$).

When average birth weight (2717 ± 815 g) and gestational age (37.5 ± 4 weeks) in CP-patients with epilepsy were compared with average birth weight (2297 ± 943 g) and gestational age (35 ± 4.9 weeks) in CP-patients without epilepsy; the differences between the groups were found statistically significant ($p = 0.0001$; $p = 0.0001$ respectively). Birth weight between 2500 and 4000 g was more frequent in CP patients with epilepsy. Out of 134 term infants, 89 (66%) had developed epilepsy whereas out of 100 preterm infants, 37 (37%) had developed epilepsy (Table 1).

In CP patients with epilepsy, 13% of patients had positive family history of epilepsy while none of the patients had family history of epilepsy in the group of CP patients without epilepsy. Both presence of history of seizure in the first 72 h and in the neonatal period were more frequent in CP patients with epilepsy. But the results of the other demographic features such as mode of delivery, presence of multiple gestations, and labor problems were not statistically significant between two groups (Table 2).

Table 1 Birth weight and gestational age in CP patients with epilepsy and CP patients without epilepsy

	CP patients with epilepsy *N* (%)	CP patients without epilepsy *N* (%)	*p*
Birth weight (g)			0.005
< 1500	14 (11.1)	31 (28.7)	
1500–2499	27 (21.4)	24 (22.2)	
2500–4000	82 (65.1)	50 (46.3)	
4000	3 (2.4)	3 (2.8)	
Gestational age (weeks)			0.0001
< 32	15 (11.9)	32 (29.6)	
32–37	22 (17.4)	31 (28.7)	
38–41	84 (66.7)	44 (40.7)	
42 and above	5 (4)	1 (0.9)	

When topographical types of CP were evaluated in both groups, quadriplegic type of CP was more common in CP patients with epilepsy whereas diplegic type of CP was more common in CP patients without epilepsy ($p = 0.0001$). Both GMFCS and BFMF levels were more severely impaired in the epileptic group ($p = 0.0001$) (Table 2). When intelligence or psychosocial development was assessed in both groups, it was observed that severe intellectual disability was four times more frequent in epileptic patients than in non-epileptic patients ($p = 0.0001$) (Table 2). The cMRI findings in epileptic and non-epileptic patients with CP were not statistically different (Table 3). Demographic features of the patients with a history of follow-up in NICU and no history of follow-up in NICU are shown in Table 4.

Discussion

In this retrospective study, we compared epileptic and non-epileptic patients with CP according to demographic, clinical, neuroimaging features, and etiological aspects to find out the risk factors predicting the development of epilepsy. Positive family history of epilepsy, positive seizure history in 72 h and in neonatal period, quadriplegic type of CP, severe degree of gross and fine motor disorders, and moderate-severe intellectual disability were determined as risk factors for the development of epilepsy in CP patients. On the other hand, epilepsy was found to be rare in CP patients with a history of low birth weight and prematurity.

European CP register suggested that the lowest age of patient with CP should be 3 years due to the changing clinical picture in young children with motor disorders [12]. Also, epileptic seizures in patients with CP mostly occur during the first 2 years [5]. For these reasons, we included patients above 3 years of age in order to make definite diagnosis of CP and epilepsy. And also, there was no difference in terms of age and sex between CP patients with epilepsy and CP patients without epilepsy.

It is known that prenatal and perinatal problems are the major cause of CP but there is little known about the effect of these factors on the development of epilepsy. So, we determined the detailed history of prenatal problems including postnatal problems. It was detected that higher age of mother at birth increased the risk of antenatal and perinatal problems, therefore increasing the risk of CP [20]. High maternal age at birth as well as presence of multiple gestations were found to be associated with an increased risk of epilepsy both in

Table 2 Demographical and clinical features in CP patients with epilepsy and CP patients without epilepsy

Parameters	CP patients with epilepsy *N* (%)	CP patients without epilepsy *N* (%)	*p*	OR (95% CI for OR)
Parental consanguinity			0.338	
Yes	26 (20.6)	28 (25.9)		
No	100 (79.4)	80 (74.1)		
Parity			0.385	
Primiparous	57 (45.2)	55 (50.9)		
Multiparous	69 (54.8)	53 (49.1)		
Age of mother at birth (years)			0.09	
18–34	117 (92.9)	93 (86.1)		
≥ 35	9 (7.1)	15 (13.9)		
Number of gestations			0.07	
Multiple	7 (5.6)	13 (12)		
Singleton	119 (94.4)	95 (88)		
Family history of epilepsy			0.0001	34.7 (2–84.9)
Yes	17 (13,5)	0 (0)		
No	109 (86.5)	108 (100)		
Mode of delivery			0.6	
Normal SVD	62 (49.2)	56 (51.8)		
Cesarean section	64 (50.8)	52 (48.2)		
Presence of labor problems			0.56	
Yes	85 (67.5)	69 (63.9)		
No	41 (32.5)	39 (36.1)		
Follow-up in NICU			0.59	
No	44 (34.9)	31 (28.7)		
Yes, intubation (−)	22 (17.5)	20 (18.5)		
Yes, intubation (+)	60 (47.6)	57 (52.8)		
History of seizure in 72 h			0.005	3.57 (1.48–8.63)
Yes	25 (19.8)	7 (6.4)		
No	101 (80.1)	101 (93.5)		
History of neonatal seizure			0.006	4.51 (1.89–10.75)
Yes	30 (23.8)	7 (6.4)		
No	96 (76.1)	101 (93.5)		
Clinical types of CP			0.754	
Spastic	100 (79.4)	89 (82.4)		
Dyskinetic	4 (3.2)	4 (3.7)		
Ataxic	7 (5.5)	3 (2.8)		
Mix	15 (11.9)	12 (11.1)		
Types of CP—topographical			0.0001	
Diplegia	12 (10.4)	41 (40.6)		
Hemiplegia	27 (23.5)	27 (26.7)		
Quadriplegia	76 (66.1)	33 (32.7)		2.76 (1.88–4.05)
GMFCS			0.0001	2.56 (1.5–4.35)
Mild-moderate	54 (42.9)	71 (65.7)		
Severe	72 (57.1)	37 (34.3)		
BFMF			0.0001	3.44 (1.92–6.18)
Mild-moderate	67 (53.2)	86 (79.6)		
Severe	59 (46.8)	22 (20.4)		
Intelligence/psychosocial development				
Normal	22 (17.4)	44 (40.7)		
Mild disability	16 (12.7)	34 (31.5)	0.999	
Moderate disability	30 (23.8)	17 (15.7)	0.002	3.53 (1.61–7.74)
Severe disability	58 (46)	13 (12)	0.0001	8.92 (4–19.66)

OR odds ratio, *CI* confidence interval, *SVD* spontaneous vaginal delivery, *NICU* neonatal intensive care unit, *GMFCS* Gross Motor Function Classification System, *BFMF* bimanual fine motor function

Table 3 The cMRI findings in CP patients with epilepsy and CP patients without epilepsy

Parameters	CP patients with epilepsy *N* (%)	CP patients without epilepsy *N* (%)	*p*
Imaging findings			
Normal	12 (9.5)	7 (6.5)	
P. white matter injury	82 (65.1)	83 (76.8)	0.252
P. gray matter injury	14 (11.1)	6 (5.5)	0.999
Non-specific atrophy	2 (1.6)	2 (1.8)	0.584
Maldevelopments	12 (9.5)	7 (6.5)	0.651
Hydrocephaly	4 (3.2)	3 (2.8)	0.998

children and in adult patients with idiopathic epilepsy [21–23]. For these reasons, we wondered if maternal age at birth, multiparity, or multiple gestation status affected the risk of epilepsy development in CP patients but we did not find any relation. Also, we could detect no association between these prenatal, perinatal, or postnatal problems except neonatal seizures and risk for epilepsy development. Even though it is known that these perinatal and postnatal problems increased the risk for the development of CP, we found that they did not have an effect on epilepsy development in CP patients.

Previous studies reported that history of neonatal seizure in patients with cerebral palsy is a risk factor for epilepsy development [2, 4, 5, 7, 9]. In all related studies, there is a consensus on this issue, and a contrary finding has not been asserted yet. Zelnik et al. reported that 22 out of 27 (81.5%) children with a history of neonatal seizure subsequently developed epilepsy [9]. Similar to the literature, in our study, epilepsy developed in 30 out of 37 (81%) children with a history of neonatal seizure. Besides, seizures started in the first 72 h in 25 out of 30 (83.3%) CP patients with epilepsy that had a

Table 4 Demographic features of the patients with a history of follow-up in NICU and no history of follow-up in NICU

	History of follow-up in NICU (*N*:159) *N* (%)	No history of follow-up in NICU (*N*:75) *N* (%)
CP patients with epilepsy (*N*:126)	82 (51.6)	44 (58.7)
CP patients without epilepsy (*N*:108)	77 (48.4)	31 (41.3)
GA < 32 weeks	47 (29.5)	0
GA 32–37 weeks	41 (25.8)	12 (16)
GA ≥ 38 weeks	71 (44.7)	63 (84)
BW < 1500 g	44 (27.7)	1 (1.3)
BW 1500–2499 g	43 (27)	8 (10.7)
BW ≥ 2500 g	72 (45.3)	66 (88)
CP patients with epilepsy (*N*:126)	(*N*:82)	(*N*:44)
GA < 32 weeks	15 (18.3)	0
GA 32–37 weeks	19 (23.2)	3 (6.8)
GA ≥ 38 weeks	48 (58.5)	41 (93.2)
BW < 1500 g	14 (17.1)	0
BW 1500–2499 g	23 (28)	4 (9.1)
BW ≥ 2500 g	45 (54.9)	40 (90.9)
CP patients without epilepsy (*N*:108)	(*N*:77)	(*N*:31)
GA < 32 weeks	32 (41.5)	0
GA 32–37 weeks	22 (28.6)	9 (29)
GA ≥ 38 weeks	23 (29.9)	22 (71)
BW < 1500 g	30 (39)	1 (3.2)
BW 1500–2499 g	20 (26)	4 (12.9)
BW ≥ 2500 g	27 (35)	26 (83.9)

NICU, neonatal intensive care unit, *CP* cerebral palsy, *GA* gestational age (weeks), *BW* birth weight (g)

seizure history during neonatal period. Therefore, we determined that neonatal seizure especially beginning in the first 72 h was a major risk factor for epilepsy development.

In our study, family history of epilepsy was observed in 13% of epileptic cases while none in non-epileptic cases. Our study is compatible with the literature detected that a family history of epilepsy increased the risk for epilepsy development in CP patients [2, 5, 7]. Although it is known that the etiology of idiopathic epilepsy is genetic [24], we emphasized that genetic predisposing factors might play an important role in the pathogenesis of epilepsy development even in patients with CP, one of the causes of symptomatic epilepsy.

The results from various studies determining the relation between gestational age or birth weight and epilepsy development in CP patients were conflicting. Mert et al. found that both prematurity and low birth weight were not related to epilepsy development [7]. Kulak et al. did not find any relation between gestational age and the risk of epilepsy development. But they determined an increased risk of epilepsy in patients with low birth weight [2]. On the other hand, Zelnik et al. demonstrated that epilepsy was more frequent in term infants than in premature infants whereas they found no relation between birth weight and risk of epilepsy development [9]. Gruraj et al. also reported that term delivery had an increased association with epilepsy development [5]. Sellier et al. determined association between epilepsy development and term and ≥ 2500 g infants in 17 European registers [4]. In our study from a developing country, similar to the latest studies, epilepsy is found to be more common both in term infants, and appropriate for gestational age (2500–4000 g) infants. Periventricular leukomalacia, affecting primarily white matter in the brain, is the most common etiologic factor for CP in preterm infants by causing spastic diplegia [25–27]. Since epilepsy is less common in CP patients with spastic diplegia [27] and in patients with white matter insult [28], this can explain why epilepsy is rarely seen in premature infants in our patient population.

It was reported that the frequency of epilepsy varied according to CP subtype. Indeed, in many previous studies, epilepsy was reported to be particularly more common in patients with quadriplegic CP ranging from 50 to 94% of the cases and relatively rare in children with dyskinetic or ataxic CP [5, 9, 27]. In the study data on 9654 children with CP in 17 European registers, epilepsy had been reported more frequent in children with dyskinetic or bilateral spastic type [4]. They reported that epilepsy was found to be more common in children with bilateral spastic CP that were unable to walk (likely to be similar to tetraplegic CP) than those able to walk (similar to diplegic CP) [4]. In our study, we found no significant correlation between the type of CP and development of epilepsy. But when type of CP was analyzed topographically, we found that epilepsy was more common in patients with quadriplegic CP, whereas diplegic CP was more common in the group of CP patients without epilepsy. Since CP is a heterogeneous disease containing different etiological groups, we thought that different results may be related to heterogeneous etiological groups. More detailed studies evaluating homogeneous groups classified according to etiology and imaging finding are needed.

On the other hand, similar results were observed when motor disorders were evaluated from a severity of functional point of view. Severe GMCFS level and BFMF level were major risk factors for epilepsy development in our patient population. Both our study and previous studies showed that the relationship between epilepsy and CP is associated with severity rather than type of CP. We agreed with the previous studies which reported that the severity of the injury in the brain influenced the clinical manifestations and increased the risk of epilepsy development [8, 27].

Previous studies indicated that patients with CP and epilepsy had lower intelligence levels compared to patients with CP only [2, 4, 7, 27]. In the present study, intellectual disability or psychosocial developmental delay was observed in 88.5% of CP patients with epilepsy versus 59.2% of CP patients without epilepsy. This difference is more pronounced in patients with severe intellectual disability (as 8.9-fold). Mert et al. also found moderate to severe intellectual disability was four times more in patients with CP and epilepsy [7]. We concluded that severity of intellectual disability increased the risk of epilepsy development in CP patients. Again, this may be due to the severity of the brain damage in these patients [8].

In previous studies, cMRI abnormality among CP patients was reported as 84–88% [7, 29]. In our study, cMRI abnormality was 91.9% among all CP patients. We have a slightly higher ratio in our study because all of our patients had undergone cMRI whereas in other studies either CT or cMRI was evaluated. We detected cMRI abnormality in 90.5% of CP patients with epilepsy and 93.6% of CP patients without epilepsy. There was no statistically significant difference between the two groups. Gruraj et al. determined abnormal brain imaging in 95% of patients with CP and epilepsy and 97% in patients with CP without epilepsy but they could not explain this [5]. Similar to our study, Mert et al. did not find relation between abnormal cMRI findings and epilepsy development [7]. In patients with gray matter insult, epilepsy is an expected finding [9, 30]. Epilepsy reported to be less common in patients with CP and white matter insult [28]. In our study compatible with the literature, white matter insult was detected in 165 CP patients, only half of them developed epilepsy whereas, gray matter insult was detected in 20 CP patients and 14 (70%) of them developed epilepsy.

There are some limitations of this study. One of the most important limitations is due to the retrospective design of the study. Also, we only aimed to determine the risk factors associated with epilepsy development. We did not investigate the epilepsy type or syndrome in patients that developed epilepsy.

Conclusion

Presence of family history of epilepsy, history of neonatal seizure especially in the first 72 h of life, quadriplegic type of CP, severe degree of gross and fine motor dysfunction, and moderate-severe intellectual disability was determined as risk factors for the development of epilepsy in CP patients. Term born and appropriate for gestational age infants were also more frequent among CP patients with epilepsy. Predicting epilepsy development by determining the risk factors in patients with CP might be useful because knowing the risk factors could provide close follow-up of these patients like evaluating these patients more frequently in an outpatient clinic, informing the families about the seizures, advising to record video in case of suspicion of seizure and if necessary, requesting early EEG.

Compliance with ethical standards The study was approved by the local ethics committee (2012/25/D).

Conflict of interest The authors declared no conflict of interest.

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