Comparison of Clinical Characteristics and Neuroimaging of Cerebral Palsy with and without Epilepsy in Children

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Abstract

Background: Cerebral palsy (CP) is one of the main causes of limited activity in children. The prevalence of CP ranges from 2.6 to 2.9 per 1000 live births. Most of children with CP have at least one comorbid, including epilepsy. Epilepsy in CP is difficult to control, and can increase the severity of motor impairment and cognitive function, therefore the prognosis is poor. The incidence of epilepsy in CP is associated with a specific clinical profile. This study aimed to analyze the comparison of clinical characteristics of cerebral palsy in children with and without epilepsy.

Methods: A cross-sectional study was conducted using medical record of children with cerebral palsy in pediatric neurology outpatient clinic in Dr. Soetomo Hospital Surabaya in March - May 2020. Children with CP who met the inclusion criteria were included in this study. The variables studied included sex, perinatal history (preterm birth, low birth weight, and neonatal asphyxia), neonatal seizures, spastic type, level of GMFCS, head circumference, neuroimaging features, hearing loss, and eye abnormalities. The study subjects were divided into two groups. Group 1 consisted of children with CP and epilepsy. Group 2 consisted of children with CP without epilepsy. Data analysis was performed using the Chi-square test and fisher's exact test using SPSS.

Result: Significant comparison of the characteristics were found in the history of neonatal seizures and the level of GMFCS. The percentage of neonatal seizures was higher in group 1 at 61.3% (p=0.049). The degree of GMFCS in group 1 was dominated by GMFCS III while in group 2 it was dominated by GMFCS IV (p=0.047). Subjects with GMFCS I and II levels were only found in group 2, while in group 1 with higher level of GMFCS, they were GMFCS III, IV, and V. More abnormal neuroimaging was found in group 1, namely 64.3%, while in group 2 it was 57.1%. There was no statistically significant difference of neuroimaging characteristics between the two groups (p= 0.911).

Conclusion: There were differences in clinical characteristics associated with neonatal seizures and GMFCS between CP with and without epilepsy.

Keyword: *Cerebral palsy, epilepsy, neuroimaging.*

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Background

Cerebral Palsy is a chronic disease affecting the center of movement control with clinical manifestations that are visible in the first few years of life and generally do not get worse at later ages. Based on data from NSCH and NHIS, it was reported that the prevalence of CP ranged from 2.6 to 2.9 per 1000 live births[1].

Children with CP suffer from motor problems and other disorders, such as intellectual problems, seizures, behavioral and emotional disorders, speech and language disorders, as well as eye and hearing problems[2]. Previous studies stated that epilepsy is most often found in children with spastic CP. Another study states that 39% of spastic CP in children have epilepsy[3]. The spastic types most often found in children with CP are hemiplegia, diplegia, and quadriplegia. In several studies, it is stated that the most common type of spastic in CP with epilepsy is quadriplegia[4-6].

Epilepsy is a major prognostic factor in mental and motor function in children with CP[7]. Gross Motor Function Classification System is a classification of children's motor abilities and limitations at home, school, and in the environment. GMFCS IV-V levels were found more frequently in CP accompanied by epilepsy[8-10]. Whereas in CP without epilepsy, the GMFCS level that was mostly obtained was level I-II[10].

Head circumference abnormalities, namely microcephaly, is one of the most common clinical manifestations of spastic CP patients[11]. Another study states that microcephaly is more common in CP patients with epilepsy, and microcephaly increases the risk of epilepsy in CP[12].

Other co-morbidities that often accompany CP patients are hearing loss and eye disorders. Children with CP had hearing loss in 10%, and 2% were bilateral deaf[13]. Another study states that nearly 20% of children with CP also have eye disorders, such as strabismus, amblyopia, nystagmus, cortical blindness, and visual abnormalities. Vision screening needs to be performed on children with CP so that these abnormalities can be detected early[14-16]. Children with CP and epilepsy are more likely to have abnormal brain imaging. Brain atrophy was also reported more frequently in CS with concomitant epilepsy and reached statistical significance in one study[17, 18]. The abnormality of the imaging features in CP is controversial. This study aimed to analyze the comparison of clinical characteristics and neuroimaging of cerebral palsy children with and without epilepsy.

Methods and Materials

A cross-sectional study was conducted using medical record of children with cerebral palsy in pediatric neurology outpatient clinic in Dr. Soetomo Hospital Surabaya in March - May 2020. Children with CP with epilepsy and without epilepsy who met the inclusion criteria were included in this study. Children with multiple congenital anomalies, genetic syndromes, and incomplete medical record (age, sex, body weight, head circumference, perinatal and postnatal history, spastic type, level of GMFCS) were excluded. The study subjects were divided into two groups. Group 1 consisted of children with CP and epilepsy. Group 2 consisted children with CP without epilepsy.

The variables studied included sex, perinatal history (preterm birth, low birth weight, and neonatal asphyxia), neonatal seizures, spastic type, level of GMFCS, head circumference, neuroimaging features, hearing loss, and eye abnormalities.

Data analysis was performed using the Chi-square test and Fisher's exact test with a significant significance value of $p < 0.05$. All statistical analyzes were conducted using SPSS version 25.

Result

There were 50 subjects included in this study. The characteristics of the subjects were showed in table 1.

Table 1. Subject characteristics

Subject characteristics	n=50	%
Age (year) (mean ± SD)	5,66 ± 2,84	
Sex Male Female	 20 30	 40% 60%

Cont... **Table 1. Subject characteristics**

Preterm birth	17	34%
Low birth weight	15	30%
Neonatal asphyxia	19	38%
Neonatal seizure	26	52%
Spastic type		
Hemiplegia	2	4%
Diplegia	17	34%
Quadriplegia	31	62%
Level of GMFCS		
GMFCS I	2	4%
GMFCS II	2	4%
GMFCS III	16	32%
GMFCS IV	17	34%
GMFCS V	13	26%
Head circumference		
Microcephaly	25	50%
Normocephaly	21	42%
Macrocephaly	4	8%
Neuroimaging features (n=42)		
Abnormal	26	61,9%
Hearing examination (n=41)		
Hearing problem	7	17,07%
Ophtalmological examination (n=41)		
Eye abnormalities	8	19,5%

In this study, the characteristics were compared between cerebral palsy with epilepsy and without epilepsy included sex, spastic type (quadriplegia, diplegia, and hemiplegia),level of GMFCS, perinatal history, neonatal seizures, head circumference, neuroimaging features, hearing problem, and eye abnormalities. Neuroimaging examination was performed on 42 of the total study subjects. ENT examination was performed on 41 of the total subjects. The comparison of these characteristics was described in table 2.

Tabel 2. Comparison of subject characteristics between cerebral palsy children with and without epilepsy

Subject characteristics	Group 1 (%) n=31	Group 2 (%) n=19	P
Sex Male Female	 12 (38,7) 19 (61,3)	 8 (42,1) 11 (57,9)	1.000*
Preterm birth Low birth weight Neonatal asphyxia	9 (29,0) 8 (25,8) 12 (38,7)	8 (42,1) 7 (36,8) 7 (36,8)	0.522* 0.611* 1.000*
Neonatal seizure	19 (61,3)	7 (36,8)	0,049*
Spastic type Hemiplegia Diplegia Quadriplegia	 1 (3,2) 10 (32,3) 20 (64,5)	 1 (5,3) 7 (36,8) 11 (57,9)	0.885**
Level of GMFCS GMFCS I GMFCS II GMFCS III GMFCS IV GMFCS V	 0 0 12 (38,7) 9 (29) 10 (32,3)	 2 (10,5) 2 (10,5) 4 (21,1) 8 (42,1) 3 (15,8)	0.047**
Head circumference Microcephaly Normocephaly Macrocephaly	 15 (48,4) 14 (45,2) 2 (6,5)	 10 (52,6) 7 (36,8) 2 (10,5)	1.000**
Neuroimaging features (n=42) Abnormal	n=28 18 (64,3)	n=14 8 (57,1)	0.911*
Hearing examination (n=41) Hearing problem	n=25 4 (16)	n=16 3 (18,7)	1.000*
Ophthalmology examination (n=41) Eye abnormalities	n=25 5 (20)	n=16 3 (18,7)	1.000*

* Chi-square; **Fisher's exact test

Significant comparison of the characteristics were found in the history of neonatal seizures and the level of GMFCS. The percentage of neonatal seizures was higher in group 1 at 61.3% (p=0.049). The degree of GMFCS in group 1 was dominated by GMFCS III while in group 2 it was dominated by GMFCS IV, where there was a significant difference for the clinical characteristics of GMFCS (p = 0.047). Subjects with GMFCS I and II levels were only found in group 2, while in group 1 with higher GMFCS level, they were GMFCS III, IV, and V (Table 2).

In this study, data on EEG examination results were reported only in children of CP with epilepsy. There were 70.9% subjects with abnormal EEG and 29.1% subjects with normal EEG. The most common type of EEG abnormality was sharp waves (16.1%).

Neuroimaging examinations in the form of head MRI and head CT scan were performed on 42 subjects. More abnormal neuroimaging was found in group 1, namely 64.3%, while in group 2 it was 57.1% (p=0.911). The description of neuroimaging abnormalities found in the two groups is presented in Table 3.

Table 3. Comparison of the neuroimaging features of cerebral palsy children with epilepsy and without epilepsy

Neuroimaging features	Group 1 (%) (n=28)	Group 2 (%) (n=14)
Brain atrophy	5 (17,8)	4 (28,6)
Periventricular leucomalacia	0 (0)	1 (7,1)
Cystic encephalomalacia	1 (7,1)	0 (0)
Hydrocephalus	4 (14,3)	2 (14,3)
Infarct	2 (7,1)	0 (0)
Schizencephaly	0 (0)	1 (7,1)
Subdural hygroma	1 (3,5)	0 (0)
Ventriculomegaly	1 (3,5)	0 (0)
Infection	2 (7,1)	0 (0)
Calcification	2 (3,5)	0 (0)
Normal	10 (35,7)	5 (42,9)

Discussion

In the study of all subjects with cerebral palsy, the percentage was higher in the cerebral palsy group with epilepsy, which was 62%. A study conducted found that 89.9% of cerebral palsy patients developed epilepsy[19]. A meta-analysis study showed the prevalence of epilepsy in CP children of 36% -62%[16]. There is a close relationship between epilepsy and cerebral palsy. Epilepsy is considered to be one of the most common

neurological disorders that accompany patients with CP. It is estimated that about 20% of cases of childhood epilepsy are the result of brain lesions that also cause CP[20]. The CP patients in this study were predominantly female, both in the CP group with epilepsy and without epilepsy, namely 61.3% and 57.9%, respectively, and there was no significant difference between the two groups (p = 1,000). This result is different from the results of another study that male sex dominated both in the CP group with epilepsy and the CP group without epilepsy with a percentage of 57.6% and 60.3% respectively, but there was no significant difference between the two sex-related group (p = 0.673)[12].

In the perinatal history, the characteristics assessed include preterm birth, low birth weight infants, and neonatal asphyxia. In preterm birth, the percentage was higher in the CP group without epilepsy, namely 42.1% compared to the CP group with epilepsy, which was 29.0% (p = 0.522). Previous study stated that 20.9% of patients with CP were diagnosed with preterm birth, with most details in the CP group with epilepsy (21.6%) compared to the CP group without epilepsy (44.7%)[11]. Other study reported that a higher frequency of epilepsy in term infants with CP similar to this study, but there was no correlation was found between gestational age and risk of epilepsy in other studies[21].

In the characteristics of low birth weight babies, a higher percentage was also found in the CP group without epilepsy (36.8%) compared to the CP group with epilepsy (25.8%) with p= 0.611. This is also in line with research conducted by El-Tallawy et al., Which did not get a significant difference in terms of birth weight in the two groups[4,12].

Neonatal asphyxia was found in 38% subjects. The percentage was more in CP with epilepsy (38.7%) compared to CP without epilepsy (36.8%) and there was no significant difference with p = 1,000. In a previous study the highest percentage of low apgar scores was in the CP group with epilepsy compared to the group without epilepsy (24.4% vs 6.9%) with p<0.02[21]. Asphyxia is a condition that can cause the brain to go into hypoxia, ischemia, and hypercapnia, which can cause brain damage. Brain damage causes CP at a later date and when it hits certain areas such as the cerebral cortex and temporal lobe, it will cause epilepsy[22].

Neonatal seizure was found in 52% subjects, and most were found in the CP group with epilepsy (61.3%) compared to the CP group without epilepsy (36.8%) with p = 0.049. A study was found that there were more patients with neonatal seizures in the CP group with epilepsy than those without epilepsy (38.1% vs 17.2%) and there was a significant difference with a value of p = 0.000[12]. In line with the study it was found that neonatal seizures in CP with epilepsy compared to CP without epilepsy were 48.4% vs 7.9% (p<0.004)[19]. Some literature states that neonatal seizures increase the risk of death and the occurrence of neurological sequelae in neonates in the form of epilepsy. In various previous studies it was reported that neonatal seizures are a risk factor that plays a role in the occurrence of epilepsy in CP patients[3,18]. Widiastuti's research conducted at 3 teaching hospitals in Jakarta found a neonatal seizure mortality rate of 47.4%. Neonatal seizure mortality is related to the degree of clinical condition of the neonate after birth. This study did not find subjects who had neonatal seizures in the CP group with epilepsy. This may be related to the high mortality in neonatal seizures[23]. Neonatal seizures result in intrinsic lesions in the brain that have the potential to produce epileptogenicity, and epileptogenesis is a process of neural tissue that will develop into recurrent epileptic seizures[24]. In addition, neonatal seizures will produce more extensive brain damage, and when it hits certain areas such as the cerebral cortex and temporal lobe, it will cause epilepsy[22].

In this study, when compared between the CP group with and without epilepsy, it was found that in the two groups the most common types were quadriplegia (64.5% vs 57.9%), then diplegia (32.3% vs 36.8%), and hemiplegia (3, 2% vs 5.3%) with p=0.885. In line with another study mentioned that the CP group with epilepsy and without epilepsy were both dominated by the spastic quadriplegia type, but the percentages between the two were quite different (58.3% vs 34%) with p <0.05[4]. Cerebral palsy with spastic quadriplegia is common in patients who have a high incidence of seizures, ranging from 50 to 94%, which, in turn, may be a reflection of the severity of damage to the brain[25, 26]. Another study states that the most common type of CP with epilepsy is the type of quadriplegia, which causes the most severe motor disorders and involves all extremities and is associated with mental retardation due to brain damage that is relatively greater than the type of CP without

epilepsy[5, 18].

In this study, the highest level of GMFCS in all study subjects was GMFCS IV. In the CP group with epilepsy, there were no GMFCS levels I and II, only GMFCS levels III, IV, V. In the CP group without epilepsy, all GMFCS degrees were obtained. The level of GMFCS describes the severity of motor disturbances in CP. Some previous studies have reported that GMFCS degrees IV and V are dominated by CP patients with epilepsy[8, 9]. The same results were also obtained in a study, where GMFCS grade IV-V was found the most in the CP group with epilepsy and grade I-II was mostly found in the CP group without epilepsy, and there were significant differences between the two groups[10]. These studies are in line with this study that obtained a high degree of GMFCS which illustrates the severity of the dominant motor function found in CP accompanied by epilepsy. The literature states that there is a straight relationship between epilepsy and the degree of motor impairment, as well as a relationship with mental disorders[27]. Epilepsy is the main prognostic factor in mental and motor function in children with CP[7].

In this study, microcephaly is slightly more common in in CP group without epilepsy compared with epilepsy (50% vs 48.4%) but there was no statistically significant difference between these two groups. In previous study was found the distribution in the CP group with epilepsy and without epilepsy were almost the same[21]. Another study states that microcephaly increases the risk of epilepsy in CP[12]. According to Wibowo and Saputra, in their research, the incidence of head circumference is inversely proportional to the incidence of preterm gestational age and low birth weight. This suggests that head circumference abnormalities in cerebral palsy may occur in the post-natal period, which is caused by disorders when brain development has not been completed, namely at the age of less than 3 years and the most likely cause in this study is CNS infection (72%)[11]. According to literature, CNS infection can cause head circumference abnormalities by destroying brain mass causing microcephaly[28].

Of the 41 study subjects, 17.07% were found with hearing loss, and 16% were found in the group with epilepsy and 18.7 % in the group without epilepsy. There was no statistically significant difference between the two groups (p = 1,000). Research conducted by Delacy et al. mentioned as many as 12% of research subjects with CP have hearing loss[29]. Research conducted by Zafeiriou et al., Obtained hearing loss as much as 19.1% in the CP group with epilepsy and 12.7% in the CP group without epilepsy[30]. Although it is different from this study which states that hearing loss is more common in the CP group without epilepsy, there is no statistically significant difference between the two groups.

Approximately 12% of children with CP experience hearing loss. The incidence of hearing loss is higher when the etiology of CP is associated with low birth weight, kernicterus, neonatal meningitis, or hypoxic-ischemic encephalopathy. Hearing loss is generally a neurogenic abnormality in high-pitched perception, making it difficult for children to grasp words. In addition, CP children are prone to recurring chronic ear infections which will impair their hearing. Hearing loss also has a negative impact on language development. CP children with intellectual disabilities and abnormal radiological examinations are at high risk for hearing loss. Hearing loss is often diagnosed late, and research shows that more than half of children with severe hearing loss are diagnosed when the child is almost 3 years old[14,15].

In the CP group with epilepsy, there were 20% with eye abnormalities and 18.7% in the CP group without epilepsy. There was no significant difference between the two groups regarding eye abnormalities. Research conducted by Zafeiriou et al., found 19.1% eye abnormalities in the CP group with epilepsy and 12.7% in the CP group without epilepsy[30]. The eye disorders in this study were refractive errors, strabismus, and decreased vision. Although the study found a significant relationship between eye disorders and epilepsy, there is no data in the literature on the relationship between eye problems and epilepsy[12].

Neuroimaging in this study was performed using head CT scan and head MRI. There were 64.3% of the neuroimaging features were abnormal in the CP group with epilepsy, and 57.1% in the CP group without epilepsy and there were no significant differences between the two groups. In line with the study conducted by Senbil et al., It was stated that the abnormal neuroimaging picture was found as much as 74.2% in the CP group with epilepsy and 48.8% in the CP group without epilepsy,

and there was no significant difference between the two groups[5]. The most neuroimaging features found in the two groups were brain atrophy. Other types of disorders found are maldevelopment, encephalomalacia, ventriculomegaly, periventricular leucomalacia, cystic lesion, hydrocephalus, and cerebral infarction[5]. The same results were obtained in this study. Most of the cases with cerebral atrophy are the end result of prenatal or perinatal ischemia globally with extensive neurological damage possibly due to seizure[21]. The effects of imaging abnormalities on CP are controversial. In one study, MRI abnormalities were recorded in 86.7% of patients, and abnormal findings on MRI did not significantly affect epilepsy progression and seizure outcome[2].

Conclusion

There were no differences in sex, perinatal history (prematurity, LBW, neonatal asphyxia), head circumference, spastic type, hearing loss, eye abnormalities, and neuroimaging features between CP with and without epilepsy. There were differences in clinical characteristics associated with neonatal seizures and GMFCS between CP with and without epilepsy.

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