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Evaluation of the Frequency of Epilepsy in Pediatric Palliative Care Service

Çocuk Palyatif Bakım Servisinde Epilepsi Sıklığının Değerlendirilmesi

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Abstract

Objective: Epilepsy is a disorder characterized by sudden, repetitive, non-triggered seizures caused by abnormal and excessive electrical discharge in cortical neurons. There are no data regarding the palliative care needs of patients with epilepsy in Turkey. This study evaluates the frequency, etiology, clinical characteristics, and needs of children with epilepsy hospitalized in pediatric palliative care (PPC) services.

Methods: Following the approval of the local ethics committee, patients who received PPC services were retrospectively analyzed. Demographic data, primary diagnosis, device and technology used, duration and frequency of hospitalization, seizure type, electroencephalography, and magnetic resonance imaging findings of patients diagnosed with epilepsy were evaluated.

Results: Fifty-two (52%) of 100 patients included in the study had a diagnosis of epilepsy. The mean age of the patients with epilepsy was 4.8±0.8 years, and 53.6% (n=48) were male. It was found that 63.5% (n=33) of the patients diagnosed with epilepsy had cerebral palsy, and 26.9% (n=14) had inborn errors in metabolism. The most commonly used drug was levetiracetam, with 46.2%. Additionally, it was observed that patients with epilepsy had a statistically significantly more prolonged hospital stay than those without epilepsy and those with focal seizures than those with generalized seizures (p=0.004, p=0.023).

Conclusion: More than half of the patients needing palliative care had a diagnosis of epilepsy, and the presence of epilepsy prolonged hospital stay. The study may also be of interest to both pediatricians and pediatric neurologists in the field of PPC, which requires a multidisciplinary approach.

Keywords: Childhood, epilepsy, pediatric palliative care, neurological disease

Öz

Amaç: Epilepsi, kortikal nöronlarda anormal ve aşırı elektriksel deşarjın neden olduğu ani, tekrarlayan, tetiklenmeyen nöbetlerle karakterize bir hastalıktır. Türkiye'de epilepsi hastalarının palyatif bakım ihtiyaçları ile ilgili veri bulunmamaktadır. Bu çalışmada pediatrik palyatif bakım servisinde yatan epilepsili çocukların sıklığı, etiyolojisi, klinik özellikleri ve gereksinimlerinin değerlendirilmesi amaçlanmıştır.

Yöntem: Yerel etik kurul onayının ardından pediatrik palyatif bakım hizmeti alan hastalar retrospektif olarak incelendi. Epilepsi tanısı alan hastaların demografik verileri, birincil tanıları, kullandıkları cihaz ve teknoloji, hastanede kalış süresi ve sıklığı, nöbet tipi, elektroensefalografi ve manyetik rezonans görüntüleme bulguları değerlendirildi.

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Öz

Bulgular: Çalışmaya dahil edilen 100 hastanın 52'sinde (%52) epilepsi tanısı vardı. Epilepsili hastaların ortalama yaşı 4,8±0,8 yıldı ve %53,6'sı (n=48) erkekti. Epilepsi tanısı alan hastaların %63,5'inde (n=33) serebral palsi ve %26,9'unun (n=14) doğuştan metabolizma hataları olduğu tespit edildi. En sık kullanılan ilaç %46,2 ile levetirasetamdı. Epilepsili hastaların hastanede kalış sürelerinin epilepsi olmayanlara göre, fokal nöbeti olanların jeneralize nöbeti olanlara göre istatistiksel olarak anlamlı derecede daha uzun olduğu görüldü (p=0,004, p=0,023).

Sonuç: Palyatif bakıma ihtiyaç duyan hastaların yarısından fazlasında epilepsi tanısı vardır ve epilepsi varlığı hastanede kalış süresini uzatmaktadır. Çalışma aynı zamanda multidisipliner bir yaklaşım gerektiren pediatrik palyatif bakım alanında hem pediatristler hem de pediatrik nörologlar için ilgi çekici olabilir.

Anahtar Kelimeler: Çocukluk çağı, epilepsi, pediatrik palyatif bakım, nörolojik hastalık

Introduction

Epilepsy is characterized by sudden, repetitive, non-triggered seizures caused by abnormal and excessive electrical discharge in cortical neurons[1]. According to the International League Against Epilepsy (ILAE), seizures that occur temporarily due to metabolic, toxic, structural, infectious, or inflammatory causes are considered acute symptomatic or situational seizures[1,2]. Epilepsy is a clinical diagnosis, and the most commonly used auxiliary methods to determine the etiology, treatment, and prognosis are electroencephalogram (EEG) and magnetic resonance imaging (MRI). EEG findings support the diagnosis of epilepsy, but its normality does not exclude the diagnosis of epilepsy. The approximate prevalence of epilepsy is 0.5-1%, and it is reported as the most common neurological disease of childhood and adolescence, requiring long-term medication[3]. Epilepsy is also frequent comorbidity in children with cerebral palsy (CP), inborn errors of metabolism, genetic diseases, and other congenital disorders, with reported frequencies between 15% and 60%[4-7].

Pediatric palliative care (PPC) is a high-level care system that increases the quality of life of children and their families with life-threatening/life-limiting diseases. The concept of PPC has come to the fore with oncology patients worldwide, and it has gained importance for children with neurological, metabolic, genetic, and other congenital disorders depending on the developments in medicine and technology[8,9]. PPC is a new area in Turkey, and no data are available on children requiring PPC with life-limiting/threatening disease and epilepsy. This study aimed to evaluate the frequency of epilepsy and accompanying diseases and current findings in children who applied to the PPC service for various reasons, and raise awareness for neurologists and clinicians working in PPC.

Materials and Methods

After the approval of the local ethics committee, the files of the patients hospitalized in the PPC unit between December 1, 2018, and December 1, 2019, were retrospectively reviewed. The data for this cross-sectional study were derived from this one-year experience. The center was established in November 2018 as the PPC clinic of a tertiary hospital and started admissions. Our clinic is the only PPC center serving the Aegean region of Turkey. Our unit is an example of teamwork consisting of 17 beds, three pediatricians, eight nurses and social workers, psychologists, clerical staff, physiotherapists, secretaries, and six assistant personnel. To our PPC clinic, a wide variety of patients such as oncology patients with no cure/treatment chance (brain tumor, neuroblastoma), care patients with severe neurological disease (CP, demyelinating diseases, muscle diseases), patients in need for post-traumatic care (traffic accident, hanging), patients of metabolic disorders without cure/treatment chance, including (carbohydrate, lipid, protein metabolism), genetic diseases (cystic fibrosis, Down syndrome, Haddad syndrome), cardiac diseases (single ventricle, advanced heart failure), and other (congenital cytomegalovirus infection) are admitted. In this study, all patients who were hospitalized in our clinic and had life-limiting/threatening diseases were included. The patients who were referred to the PPC unit due to a new symptoms and were admitted to our clinic for various reasons were previously evaluated and diagnosed by pediatric neurology and metabolic specialists treating disease. The demographic characteristics of the patients included in the study, the medical device and technology used (feeding tube, gastrostomy tubes, tracheostomy, non-invasive ventilation or mechanical ventilation), primary diagnoses, reasons for PPC admission, medications used, the duration of hospitalization, seizure type, EEG, and MRI findings were reviewed. Informed consent was obtained from all the participants. Seizure and epilepsy type were classified according to the ILAE 2017 criteria[6]. All children had at least one 20-minute awake and/or 20-minute sleep

EEG recordings with electrocardiogram monitoring, which was performed using an 18 channel digital recording system (Nihon Kohden EEG machine Irvine, CA, U.S.A) with electrode placement according to the international 10-20 system. EEGs were classified as "abnormal" when there were localized and/or generalized interictal epileptic discharges (IED), and/or a focal or generalized slow background activity and/or an abnormal response to either of the activation procedures (hyperventilation and photic stimulation). EEG abnormality was classified as mild and severe abnormality when the frequency of IEDs occurred less than once per 10 s and at least once per 10 s, respectively. MRI findings were classified as abnormal when cerebral abnormalities were relevant to the underlying etiology such as periventricular leukomalacia, a growing tumor, hydrocephalus, and normal when there were no abnormalities or non-specific findings. The ethical committee report prepared as per the World Medical Association Declaration of Helsinki-Ethical Principles for Medical Research Involving Human Subjects and Guide for the Care and Use of Laboratory Animals (16.09.2019/337).

Statistical Analysis

The data were statistically analyzed using the SPSS 23.0 program (SPSS, Inc., Chicago, Illinois). Descriptive analysis was presented as frequency (%), mean, and standard deviation for variables with normal distribution. The median, minimum, and maximum values were used for variables that were not normally distributed. T-test or Pearson chi-square determined the comparisons between groups. A p-value of <0.05 was considered statistically significant.

Results

A total of 101 patients were admitted to the PPC service in one year, and one patient was excluded from the study because of the admission purposes other than palliative care. Of the 100 patients included in the study, 52% (n=52) had a diagnosis of epilepsy. The mean age was 4.8±0.8 years, and 53.8% (n=28) of the cases were male. Of the patients with a diagnosis of epilepsy, 34.6%, had CP, and 26.9% had inborn errors of metabolism (IEM). The etiological causes of patients with epilepsy are presented in Table 1. In our study group, the most common cause of epilepsy etiology was hypoxic ischemic encephalopathy (42.3%). The general characteristics of the study group are presented in Table 2. Patients with epilepsy were reviewed in terms of seizure and epilepsy type, EEG findings, and MRI findings. While 34.4% (n=18) of patients with epilepsy had focal seizures, 59.6% (n=31) had generalized seizures. Only three patients (5.8%) had mixed seizures. A comparison of patients with focal and generalized seizures is presented in Table 3. When clinical findings were analyzed between patients with mild and severe abnormalities in EEG, there was no difference except for the medications used (p<0.001) (Table 4). When clinical findings were analyzed between patients with and without abnormal MRI findings, there were no differences in the seizure types, medications, or severity of epilepsy (Table 5). MRI was performed in 80.7% of patients diagnosed with epilepsy and 52.3% of patients without a diagnosis of epilepsy. Of the patients with epilepsy, 19.3% did not have an MRI record. These patients had MRIs performed at other centers previously. Of all patients with epilepsy, 75% (n=39) had mild and 25% (n=13) had severe EEG abnormalities. While 36.5% of the patients received a single antiepileptic drug, 40.4%, 15.4%, and 7.7% were on two, three, and four antiepileptic medications, respectively. The most commonly used drug antiepileptic drug was levetiracetam (46.2%), followed by phenobarbital (32.7%). The most common hospitalization reason for patients with epilepsy was infectious diseases (61.5%), and the most commonly seen infection was pneumonia (71.2%). The hospitalization duration of patients with epilepsy was significantly longer than that of the other patient group

Table 1. Etiological causes of epilepsy cases

	n (%)
Idiopathic	8 (15.3%)
Structural causes	
Hypoxic ischemic encephalopathy	22 (42.3%)
Cotical malformations	5 (9.6%)
Congenital cytomegalovirus infection	1 (1.9%)
Cerebral hemorrhage	1 (1.9%)
Epileptic encephalopathies	
West syndrome	1 (1.9%)
Metabolic causes	
Urea cycle defect	1 (1.9%)
Tay-sachs disease	2 (3.8%)
Sulfite oxidase deficiency	1 (1.9%)
Saposin A deficiency	1 (1.9%)
Sandoff disease	1 (1.9%)
Pyruvate dehydrogenase	1 (1.9%)
Mitochondrial cytopathic	3 (5.7%)
Mitochondrial DNA depletion syndrome	1 (1.9%)
Krabbe	1 (1.9%)
GM2 protein activator	1 (1.9%)
Cell disease	1 (1.9%)

(p=0.004). The duration of hospitalization of patients with focal seizures was statistically significantly longer than those with generalized seizures (p=0.023). Regarding the reasons for hospitalization, no significant difference was found between patients with and without epilepsy (p=0.065).

Table 2. General characteristics of the working group (n=100)

	Patients with epilepsy n=52	Patients without epilepsy n=48	p-value
Age (years) (mean ± SD)	4.8±0.8	5.3±0.6	0.669
Gender, n (%)	-	-	0.860
Male	28 (53.8)	25 (52.1)	-
Female	24 (46.2)	23 (47.9)	-
Duration of stay, day (± SD)	30.2±4.2	16.1±1.9	0.004*
Primary diseases, n (%)	-	-	0.003*
Cerebral palsy	33 (63.5)	19 (39.6)	-
Metabolic disease	14 (26.9)	7 (14.6)	-
Genetic syndrome	1 (1.9)	2 (4.1)	-
Congenital infection	-	1 (2.1)	-
Muscular dystrophy	4 (7.7)	13 (27.1)	-
Other	-	6 (12.5)	-
Respiratory support, n (%)	-	-	0.163
Normal	34 (65.4)	27 (56.3)	-
Oxygen	5 (9.6)	4 (8.3)	-
CPAP/NIMV	-	4 (8.3)	-
MV	8 (15.4)	11 (22.9)	-
Tracheostomy	5 (9.6)	2 (4.2)	-
Nutritional support, n (%)	-	-	0.085
Oral	17 (32.7)	16 (33.3)	-
NG	17 (32.7)	24 (50.0)	-
PEG	18 (34.6)	8 (16.7)	-
Cranial MRI, n (%)	-	-	0.717
Normal	23 (54.8)	11 (50.0)	-
Abnormal	19 (45.2)	11 (50.0)	-

*p<0.05

CPAP: Continuous positive airway pressure, NIMV: Non-invasive mechanical ventilation, MV: Mechanical ventilation, NG: Nasogastric tube, PEG: Percutaneous enterostomy tube, MRI: Magnetic resonance imaging, SD: Standard deviation

Discussion

This study revealed that more than half of the patients hospitalized at the PPC unit had epilepsy, and patients with epilepsy stayed in the PPC for a more extended period. This research is the first study addressing the frequency of patients with epilepsy in the PPC unit in Turkey. Epilepsy is a frequent comorbidity accompanying genetic, metabolic, and neurological disorders and is mostly drug-resistant. CP is a static encephalopathy caused by various etiologies. Development in neonatal and pediatric intensive care units did not decrease the prevalence of CP, which is reported in 2.5/1,000 live births[7]. Although CP manifests a motor abnormality, mental retardation, epilepsy, vision and hearing loss, nutrition, and speech disorders accompany the picture[8,10]. One of the most common neurological problems in children with CP is epilepsy. In the literature, the frequency of epilepsy has been reported in 41.4% of patients with CP and

Table 3. Examination of epilepsy patients (n=52)

	Patients with epilepsy focal seizure	Patients with epilepsy generalized seizure	p-value
Age (years) (mean ± SD)	4.8±1.1	5.0±0.7	0.905
Gender, n (%)	-	-	0.196
Male	7 (38.9)	18 (58.1)	-
Female	11 (61.1)	13 (41.9)	-
Duration of stay, day (± SD)	44.4±9.4	23.6±4.0	0.023*
Primary diseases, n (%)	-	-	0.407
Cerebral palsy	10 (55.6)	22 (71.0)	-
Metabolic disease	6 (33.3)	8 (25.8)	-
Muscular dystrophy	2 (11.1)	1 (3.2)	-
Antiepileptic drug number, n (%)	-	-	0.618
1	5 (27.8)	13 (41.9)	-
2	9 (50.0)	10 (32.3)	-
3	3 (16.7)	5 (16.1)	-
4	1 (5.6)	3 (9.7)	-
Cranial MRI, n (%)	-	-	1.000
Normal	7 (53.8)	14 (53.8)	-
Abnormal	6 (46.2)	12 (46.2)	-

*p<0.05, SD: Standard deviation, MRI: Magnetic resonance imaging

75% of children with congenital metabolic diseases[11-13]. It has been shown that the frequency of epilepsy was higher, and seizures were more resistant in patients with poor functional status, diffuse EEG abnormalities, and cerebral atrophy[14,15]. Especially in patients with the tetraplegia phenotype, epilepsy rates have been reported to be even higher[16,17]. The frequency of seizures in palliative care for adults has been reported to be 13%. However, it remains unknown in patients with PPC patients[18]. In our study, the frequency of epilepsy was 52%. This result may be due to the lack of PPC units in our country and the hospitalization of patients with advanced neurological and congenital metabolic diseases (90.4%). A single type of seizure is determined in 90.2% of patients with epilepsy, and the most common type is focal seizures[18]. The prevalence of generalized epilepsy in CP was 62%, and the frequency of generalized seizures was 63.3%[19]. Although Singhi et al.[20] reported the highest frequency of epilepsy in children with spastic hemiplegia, the most common seizure type in children with CP in the literature was generalized seizures, and it was reported that the frequency of epilepsy was higher in tetraplegic CP[21,22]. Kułak and Sobaniec[14] reported the rate of generalized epilepsy and drug-resistant epilepsy as 41.1% and 51.2%, respectively, and the rate of epilepsy increased to 51.2% and drug-resistant epilepsy to 60% in tetraplegic children. In CP patients diagnosed with epilepsy, an epilepsy pattern with remission and relapses was reported in 43.9%[23]. Similar to previous

Table 4. MRI findings of epilepsy patients (n=42)

	Patients with epilepsy MRI normal	Patients with epilepsy MRI abnormal	p-value
Age (years) (mean ± SD)	4.2±0.9	5.5±0.8	0.317
Gender, n (%)	-	-	1.000
Male	14 (60.9)	11 (57.9)	-
Female	9 (39.1)	8 (42.1)	-
Duration of stay (days)	29.7±6.0	28.3±7.7	0.890
Primary diseases, n (%)	-	-	0.187
Cerebral palsy	12 (52.2)	13 (68.4)	-
Metabolic disease	10 (43.5)	3 (15.8)	-
Genetic syndrome	-	1 (5.3)	-
Muscular dystrophy	1 (4.3)	2 (10.5)	-
Antiepileptic drug number, n (%)	-	-	0.566
1	10 (43.5)	5 (26.3)	-
2	9 (39.1)	8 (42.1)	-
3	2 (8.7)	4 (21.1)	-
4	2 (8.7)	2 (10.5)	-
Seizure type, n (%)	-	-	0.912
Focal	7 (30.4)	6 (31.6)	-
Generalized	14 (60.9)	12 (63.2)	-
Combined	2 (8.7)	1 (5.3)	-
EEG, n (%)	-	-	0.468
Mild	19 (82.6)	13 (68.4)	-
Severe	4 (17.4)	6 (31.6)	-

SD: Standard deviation, MRI: Magnetic resonance imaging, EEG: Electroencephalogram

Table 5. EEG findings of epilepsy patients (n=52)

	Patients with epilepsy mild EEG findings	Patients with epilepsy severe EEG findings	p-value
Age (years) (mean ± SD)	5.0±0.7	4.3±1.0	0.585
Gender, n (%)	-	-	0.521
Male	22 (56.4)	6 (46.2)	-
Female	17 (43.6)	7 (53.8)	-
Duration of stay (days)	30.9±5.3	27.9±6.2	0.765
Primary diseases, n (%)	-	-	0.932
Cerebral palsy	25 (64.1)	8 (61.5)	-
Metabolic disease	10 (25.6)	4 (30.8)	-
Genetic syndrome	1 (2.6)	-	-
Muscular dystrophy	3 (7.7)	1 (7.7)	
Antiepileptic drug number, n (%)	-	-	<0.001*
1	18 (46.2)	1 (7.7)	-
2	21 (53.8)	-	-
3	-	8 (61.5)	-
4	-	4 (30.8)	-
Cranial MRI, n (%)	-	-	0.283
Normal	19 (59.4)	4 (40.0)	-
Abnormal	13 (40.6)	6 (60.0)	-

*p<0.05

SD: Standard deviation, EEG: Electroencephalogram, MRI: Magnetic resonance imaging

reports, approximately twice as many generalized seizures were found in patients with CP in our series, although it did not reach statistically significant values. This result is not surprising, considering that our patient group consists of advanced and tetraplegic patients. Electroencephalography is a crucial diagnostic tool that facilitates the diagnosis, classification of seizures and epilepsy, and choice of antiepileptic drugs for treatment. EEG also provides vital data for the diagnosis of non-convulsive status epilepticus and subclinical seizures[24]. It has previously been reported that 70.5% of children with CP[20] had EEG abnormalities. Gururaj et al.[25] have reported that more than half of the children with CP had a generalized seizure, and 39.3% had secondary generalized focal epileptic abnormalities in their EEGs[20-22]. This observation shows that EEG helps in the diagnosis and drug selection in patients with CP and epilepsy. In our study, mild EEG abnormalities were found in 64.1% of CP and epilepsy cases. The generalized epileptic activity was approximately twice higher than those with focal abnormalities in the EEGs of patients with CP. It is known that the prognosis is poor in patients with epileptic encephalopathy, especially those with a "burst suppression" pattern or severe cerebral dysfunction on EEG[26,27]. In our series, severe cerebral dysfunction was determined in two patients and the burst suppression pattern in one patient. Some studies aimed to reveal the relationship between the frequency of epilepsy and cerebral imaging findings in patients with CP have reported that the frequency of epileptic seizures is associated with treatment difficulties[28]. In some studies, it has been reported that MRI findings cannot predict epilepsy's prognosis and seizure frequency[29,30]. However, in 21% of children with focal epilepsy, while MRI was not pathological initially, 50% of potential epileptogenic lesions were detected on repeated MRI[31]. It has also been suggested that the first MRI scan should be performed at 9-18 months of age, and if it is negative, it should be repeated after the age of 2[32]. In our study, there was no difference between patients with and without MRI abnormalities in terms of epilepsy type, drugs used, and accompanying EEG findings. However, due to the small sample size in our series, a relationship could not be demonstrated between epilepsy and MRI findings.

It has been reported that seizure management in PPC patients is quite challenging[33,34]. The most commonly used drug in our study was levetiracetam, and the majority of patients had used more than one antiepileptic drug, including that 23.0% receiving 3-4 drugs. As expected, patients with severe abnormalities on MRI and EEG had 3-4 antiepileptic drugs in our series. Additionally, it has been reported that the need for PPC in severely ill children was related to severe brain damage and the presence of drug-resistant epilepsy[34]. Our study revealed that children with a diagnosis of epilepsy stayed in the hospital significantly longer than the patients without epilepsy, and children with focal seizures stayed in the hospital longer than those with other seizure types.

Study Limitations

The main limitation of the study was its retrospective design. Moreover, due to the newly established PPC service, the study had a limited number of patients. Therefore, more extensive and multi-center studies are needed to identify and address the needs of patients with epilepsy implicitly.

Conclusion

Epilepsy is a common disorder determined in more than half of the patients admitted to PPC units. The presence of epilepsy in CP and congenital metabolic diseases may cause these patients to stay in the hospital for a longer time.

Ethics

Ethics Committee Approval: The approval was obtained from the Ethics Committee of University of Health Sciences Turkey, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital (2019/337, date: 05.12.2019).

Informed Consent: The principles of the Helsinki Declaration were adhered to, and patient consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: N.H., Ü.Y., T.Ç., Design: N.H., Ü.Y., Data Collection or Processing: N.H., T.Ç., Analysis or Interpretation: N.H., Ü.Y., Literature Search: N.H., T.Ç., Writing: N.H.

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