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Original Article

Epilepsy and drug-resistant epilepsy in neurocutaneous syndromes

Nörokutanöz sendromlarda epilepsi ve dirençli epilepsi

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ABSTRACT

Aim: Epilepsy frequently accompanies neurocutaneous syndromes. Due to the comorbid conditions that epileptic seizures may cause, their frequency, type, and duration also affect the prognosis of neurocutaneous diseases. The purpose of this study was to examine the frequency of epilepsy and drug-resistant epilepsy in neurocutaneous syndromes, and factors affecting the development of drug-resistant epilepsy.
Material and Methods: In our clinic, nine of the 24 patients who were under follow-up due to neurocutaneous syndromes were diagnosed with Tuberous Sclerosis Complex (TSC), six with Sturge-Weber syndrome, and nine with Neurofibromatosis type 1. We examined the age at diagnosis, findings at the time of the diagnosis, the presence of accompanying epilepsy, age at onset of seizures, seizure type and frequency, antiepileptic drugs used, responses to antiepileptic drugs, electroencephalography and brain magnetic resonance imaging findings, neurological-neuro-ophthalmological and physical examination results, and systemic findings.
Results: Age at onset of seizures ranged between four months and four years. A pre-diagnosis history of seizure was present in all the patients with TSC, and the first seizure in 55% of the patients was epileptic spasm type. Hemiparesis and port wine stain were present at the time of diagnosis in Sturge-Weber syndrome, while accompanying seizures were observed later.
Conclusion: The frequency of accompanying epilepsy and drug-resistant epilepsy is higher in the TSC.

Keywords: Drug-resistant epilepsy, epilepsy, neurocutaneous syndromes

ÖZ

Amaç: Epilepsi sıklıkla nörokutanöz sendromlara eşlik eder. Epileptik nöbetlerin neden olabileceği komorbid durumlar nedeniyle nöbet sıklığı, tipi ve nöbetin süresi de nörokutanöz hastalıkların prognozunu etkiler. Bu çalışmanın amacı, nörokutanöz sendromlarda epilepsi ve ilaca dirençli epilepsi görülme sıklığını ve ilaca dirençli epilepsi gelişimini etkileyen faktörleri incelemektir.
Gereç ve Yöntemler: Kliniğimizde nörokutanöz sendromlar nedeniyle takip edilen 24 hastanın 9'u Tüberoz Skleroz Kompleksi (TSK), 6'sı Sturge-Weber sendromu ve 9'u Nörofibromatozis tip 1 tanısı aldı. Tanı yaşı, tanı anındaki bulgular, eşlik eden epilepsi olup olmadığı, nöbet başlangıç yaşı, nöbet tipi ve sıklığı, kullanılan antiepileptik ilaçlar, antiepileptik ilaçlara yanıt, elektroensefalografi ve beyin manyetik rezonans görüntüleme bulguları, nörolojik-nöro-oftalmolojik ve fizik muayene ve sistemik bulgularını inceledik.
Bulgular: Nöbetlerin başlama yaşı 4 ay-4 yıl arasında değişmekteydi. TSK'lı hastaların tümünde tanı anında nöbet öyküsü vardı ve hastaların %55'inde ilk nöbet epileptik spazm şeklindeydi. Sturge-Weber sendromunda tanı anında hemiparezi ve porto şarabı lekesi bulunurken, daha sonra eşlik eden nöbetler gözlendi.
Sonuç: TSK'da eşlik eden epilepsi ve ilaca dirençli epilepsi sıklığının oldukça yüksek olduğu söylenebilir.

Anahtar kelimeler: Dirençli epilepsi, epilepsi, nörokutanöz sendromlar

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INTRODUCTION

Neurocutaneous syndromes are a group of disorders with a risk of presenting with epilepsy and are associated with central nervous system anomalies with characteristic skin lesions (1). Epilepsy is both a cause and one of the clinical features of several neurocutaneous syndromes. The diagnosis of specific neurocutaneous syndromes and treatment of epilepsy, if present, is of considerable importance in terms of neurodevelopment (1,2).

TSC is one of the most common neurocutaneous syndromes, with an incidence of 4.9/100,000. Diagnostic features can be indistinct under the age of two years. A prevalence of 70-90% has been reported for epilepsy in TSC and the majority of seizures begin before the age of 12 months. Adverse effects on cognitive functions and more significant learning difficulties have been reported in patients undergoing intensive seizures under the age of 12 months (1).

Studies have shown that early control of epilepsy improves neurodevelopmental outcomes (3-5). Predicting epilepsy development and drug-resistant epilepsy development, early treatment, observation, and interventions are therefore very important in terms of the consequences of neurocutaneous diseases (6,7).

Characteristics involved in the development of seizures among patients followed-up with diagnosis of tuberous sclerosis include central nervous system lesions, white matter abnormalities, male gender, and the tuberous sclerosis phenotype. Pathogenic TSC2 variants are associated with an increased risk of infantile spasms and a more severe phenotype (8-10).

Interictal epileptiform discharges in electroencephalography (EEG) are useful in predicting approaching epilepsy but are not early risk predictors (11).

Sturge-Weber syndrome is associated with leptomeningeal angioma, trigeminal port wine stain, epilepsy, and glaucoma. Both seizures and headaches are observed in many patients with the syndrome (12).

The purpose of this study was to examine the frequency of epilepsy accompanying neurocutaneous syndromes and factors affecting the development of epilepsy and drug-resistant epilepsy.

MATERIAL AND METHODS

Twenty-four patients aged 0-18 years presented to the Abant İzzet Baysal University pediatric neurology clinic, Turkey, in 2020-2022 and followed-up with diagnoses of neurocutaneous syndromes (nine with Tuberous sclerosis, six with Sturge-Weber syndrome, and nine with Neurofibromatosis type 1) were included in the study. Patients' ages, sex, type of neurocutaneous syndrome, age at diagnosis, findings at the time of diagnosis, presence of accompanying epilepsy, age at onset of seizures, type and frequency of seizures, antiseizure medication use, responses to antiseizure drugs, EEG and brain magnetic resonance imaging (MRI) findings, neurological-neuro-ophthalmological, physical examination findings, and systemic findings were investigated retrospectively from the case files. The sociodemographic characteristics, neurological examination findings, systemic involvement, and EEG/MRI characteristics of patients with accompanying epilepsy and drug-resistant epilepsy were also examined. Diagnosis of TSC was based on International Tuberous Sclerosis Complex Consensus Group criteria updated in 2012 (13).

RESULTS

Two (22.2%) of the nine patients diagnosed with TSC were girls and seven (77.7%) were boys. The patients' mean age was 8.55±4.85 years, the mean age at the time of the diagnosis was

9.55±5.17 months, and the mean age at the first seizure was 14.33±13.57 months. Six patients were diagnosed before the age of 12 months. Cutaneous involvement and seizure were present in all the patients at the time of the diagnosis. Cardiac rhabdomyoma was determined in three patients at the time of the diagnosis, and renal angiomyolipoma in two. Accompanying seizures were present in all cases, with West syndrome present at the time of the diagnosis in five patients, generalized tonic seizure in one, and focal motor seizure in three. Three patients were followed-up with the diagnosis of drug-resistant epilepsy (incidence of 33%). The most common antiseizure drug was Vigabatrin. Mechanistic targets of rapamycin inhibitors were used in two cases. Other frequently administered antiseizure drugs include carbamazepine, levetiracetam, clobazam, and valproate. Cortical and subcortical tubers were observed in the brain MRI of all the patients (Tables 1-3).

Table 1. The demographic, clinical, and radiological findings of the children with tuberous sclerosis complex.

Patient	Age	Gender	Findings at the time of diagnosis	Diagnosis age	Epilepsy	Age at first seizure	Seizure frequency	Anti-seizure medication
1	4y	M	ICR, WS, CNSI	7m	+	7m	4-5/day	VGB
2	4y	M	ICR, WS, CI, CNSI	6m	+	4m	5-6/day	VGB, CBZ, Everolimus
3	8y	M	CI and CNSI	18m	+	18m	2-3/day	OXC, LEV, VPA
4	17y	M	CI, CNSI, renal angiomyolipom	18m	+	18m	5-6/year	KBZ
5	12y	F	CI, CNSI	4m	+	4m	1-2/day	KBZ, LEV, VGB
6	12y	M	CNSI, CI, renal angiomyolipom	1m	+	1m	2-3/week	LEV, VGB
7	7y	F	WS, CNSI, CI	7m	+	7m	7-8/day	VGB, VPA, ACTH, CLB
8	2y	M	WS, CNSI, CI	7m	+	7m	3-4/day	VGB
9	11y	M	WS, CNSI, CI	8m	+	8m	9-10/day	VPA, CLB, VNS, mTOR inhibitor

WS: West syndrome, ICR: Intracardiac rhabdomyoma, CI: cutaneous involvement, CNSI: Central Nervous System Involvement, m: month, y: year, M: male, F: female, OXC: Oxcarbazepine, LEV: Levetiracetam, VPA: Valproic asit, VGB: Vigabatrin, ACTH: Adrenocorticotropic hormone, CLB: Clobazam.

Table 2. The demographic, clinical, and radiological findings of the children with Sturge Weber syndrome.

Patient	Age	Gender	Age at diagnosis of SWS	Findings at the time of diagnosis	Epilepsy	Seizure frequency	Anti-seizure medication	MRI/CT findings
1	16y	F	2m	CI (PWS), CNSI	+	4-5/d	VPA, TPM, PHB, LTG, PHT	Cortical calcification
2	6y	M	1m	CI (PWS), CNSI	+	3-4/w	PHT, OXC, PHB	Leptomeningeal angiomatosis and calcification
3	14y	M	3m	CI (PWS), CNSI, glaucoma	+	1-2/w	LEV, VPA, CBZ	Leptomeningeal angiomatosis and calcification
4	9y	M	2m	CI (PWS)	+	No seizure	OXC, VPA	Leptomeningeal angiomatosis and calcification
5	10y	F	3m	CI (PWS), CNSI	+	No seizure	LEV, TPM	Leptomeningeal angiomatosis, calcification and atrophy
6	2.5y	M	1m	CI (PWS), CNSI, glaucoma	+	No seizure	PHB, LEV	Leptomeningeal angiomatosis

CI: cutaneous involvement, PWS: Port wine stain, CNSI: Central Nervous System Involvement, m: month, y: year, M: male, F: female, OXC: Oxcarbazepine, LEV: Levetiracetam, VPA: Valproic asit, PHB: phenobarbital, LTG: lamotrigine, PHT: phenytoin, TPM: Topiramate.

Table 3. The clinical and electrophysiologic findings of the children with neurocutaneous syndromes.

Patient	Type of neurocutaneous syndrome	The age of first seizure	Seizures	EEG findings
1	TSC	7m	Epileptic spasm	Hypsarrhythmia
2	TSC	4m	Epileptic spasm	Hypsarrhythmia
3	TSC	18m	Focal motor seizures	R hemisphere centrotemporal high-amplitude, epileptiform abnormalities
4	TSC	8m	Focal motor seizures	L hemisphere temporal epileptiform abnormalities
5	TSC	3y	GTCA	Centrotemporal biphasic epileptiform abnormalities
6	TSC	1y	GTCA	Frontoparietal biphasic epileptiform abnormalities
7	TSC	7m	Epileptic spasm, focal motor seizures	Hypsarrhythmia
8	TSC	7m	Epileptic spasm	Hypsarrhythmia
9	TSC	8m	Epileptic spasm	Hypsarrhythmia
10	SWS	9m	Focal motor seizures	L temporo-occipital epileptiform abnormalities
11	SWS	6m	Focal motor seizures	R PO epileptiform abnormalities
12	SWS	3m	GTCA	Jeneralize
13	SWS	3m	Focal motor seizures	R PO epileptiform abnormalities
14	SWS	6m	Focal motor seizures	L PO epileptiform abnormalities
15	SWS	3m	Focal motor seizures	L CP epileptiform abnormalities

SWS: Sturge Weber syndrome, TSC: Tuberous Sclerosis Complex, y: year, m: month, GTCA: Generalized tonic-clonic seizures, R: right, L: left, PO: Parieto-occipital, CP: Centro-parietal.

Six of the patients (four boys and two girls) were diagnosed with Sturge-Weber syndrome. Their mean age was 9.6±4.84 years, the mean age at the first diagnosis was 2.1±0.75 months, and the age at first seizure was 4.6±2.5 years. Port wine stain and hemiparesis were present in all the patients at the time of presentation. Glaucoma developed during follow-up in five patients, and epileptic seizures were observed in all the patients. All the patients were using multiple antiseizure drugs and seizures refractory to medication were present in three (Tables 2 and 3).

The mean age of the nine patients followed-up with diagnoses of Neurofibromatosis type 1 was 7.8±3.5 years, and their mean age at the time of diagnosis was 5.6±4.1 years. Family histories were present in seven patients. No epileptic seizures occurred during the follow-up.

DISCUSSION

In this study, diagnoses of epilepsy were present in all the patients with TSC and Sturge-Weber syndrome, and drug-resistant epilepsy was observed in almost half of the participants, despite multidrug use. None of the patients followed-up by us due to Neurofibromatosis type 1 (NF1) was also diagnosed with epilepsy. This suggests a lower incidence of development of epilepsy in childhood in patients with NF 1, and that if seizures do occur, these are more likely to be added to the clinical presentation in adulthood. The estimated prevalence of epilepsy in patients with NF1 is 4-13% (14,15). Observational studies have shown that epileptic seizures in individuals with NF1 may generally be associated with intracranial tumors or structural abnormalities (14). No intracranial mass or structural abnormality was present in any of our patients with NF-1 at the time of diagnosis or during short-term follow-up.

In a previous study of 23 patients with neurocutaneous syndromes, epilepsy was diagnosed in 39.13% of cases with neurocutaneous disorders preceding clinical diagnosis. Age at onset of seizures ranged between four months and five years. The most common seizure type is reported to be focal seizures, in which awareness is impaired. Intellectual impairment has been reported in 21.73% of patients. The effectiveness of antiseizure drugs has been reported to vary depending on the type of seizure and the type of neurocutaneous syndrome (2). In our case series,

age at onset of seizures ranged between four months and four years. A history of seizure prior to diagnosis was present in all the patients with TSC, and the first seizures of 55% of the patients were epileptic spasm type. Hemiparesis and port wine stain were present at the time of diagnosis in SWS, and seizures accompanied the condition subsequently. The incidence of drug-resistant epilepsy was also high in both syndromes. Seizure was the most common and the most important cause of presentation among neurocutaneous syndrome patients.

In another study involving 29 patients, TSC was present in 10 individuals (35.5%). Antiseizure medication was discontinued in one of the patients followed-up with TSC, one patient received monotherapy, and eight received polytherapy. However, seizures were reported to persist in nine patients despite receipt of antiseizure drugs (16). All the patients with TSC in the present study were receiving polytherapy, although their seizures persisted. Seizure control was achieved with monotherapy in 50% of our patients with Sturge-Weber syndrome. In the present study, the incidence of seizure and multidrug-resistant seizure was highest in the patients with TSC.

The limited number of patients in this sentence may have resulted in a higher incidence of epilepsy in neurocutaneous syndromes presenting due to seizure and severe symptoms in patients diagnosed with and followed-up due to such syndromes. Due to the low rate of asymptomatic patients with cutaneous findings and mild symptoms, our knowledge about the spectrum of patients with TSC and had no accompanying seizures is very limited .

Pediatric patients diagnosed with neurocutaneous syndromes may contribute to the literature in terms of the age of admission to clinics, symptoms, frequency of seizures, frequency of drug-resistant seizures, and treatment of seizures. Furthermore, we believe that this can also be useful in terms of follow-up in childhood.

In conclusion, the incidence of epilepsy and drug-resistant epilepsy accompanying neurocutaneous syndromes are relatively high. It can be concluded that the frequency of epilepsy and refractory epilepsy is higher in TSC, one of the neurocutaneous-type syndromes.

Ethics Committee Approval: The study protocol was approved by the Bolu Abant İzzet Baysal University Clinical Researches Ethics Committee (04.01.2022 / 2021/307).

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