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ORIGINAL ARTICLE

Clinical and Electrophysiological Characteristics of Patients with Juvenile Absence Epilepsy in a Turkish Cohort

Bir Türk Hasta Kohortunda Jüvenil Absans Epilepsi Tanılı Hastaların Klinik ve Elektrofizyolojik Özellikleri

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ABSTRACT

Juvenile absence epilepsy is an epileptic syndrome that usually begins between the ages of 9-13 and is classified in the group of genetic generalized epilepsies, in which absence seizures are seen mainly but may also be accompanied by motor seizures in the follow-up. In our study, 33 patients who were followed up in our clinic with the diagnosis of juvenile absence epilepsy between 2010-2022 were evaluated retrospectively. Thirteen of them were excluded from the study due to insufficient clinical or electrophysiological knowledge, being diagnosed with another epileptic syndrome during follow-up. The mean age of the 20 patients included in the evaluation was 16.8 years; The mean age of seizure onset was 10.6 years. All patients had absence seizures, which were not seen more often than once a day, 40% had additional generalized tonic-clonic seizures, and 20% had focal electroencephalographic abnormalities in addition to generalized discharges on electroencephalography. Seizures recurred in 3 of 5 patients whose treatment was terminated. It was found that currently 85% of the patients continued treatment with valproic acid and monotherapy was sufficient. While there are generalized discharges at the time of diagnosis electrophysiologically, focal findings tend to occur in the follow-up; This was also important in the evaluation of seizure recurrence and treatment options in patients with long-term follow-up.

Keywords: Juvenile absence epilepsy, electroencephalography, valproic acid

ÖZ

Juvenil absans epilepsisi, genellikle 9-13 yaşları arasında başlayan ve ağırlıklı olarak absans nöbetlerin görüldüğü ancak takipte motor nöbetlerin de eşlik edebileceği genetik jeneralize epilepsiler grubunda yer alan bir epileptik sendromdur. Çalışmamızda 2010-2022 yılları arasında juvenil absans epilepsi tanısı ile kliniğimizde takip edilen 33 hasta retrospektif olarak değerlendirildi. 13'ü klinik veya elektrofizyolojik bilgilerinin yetersiz olması, izlem sırasında başka bir epileptik sendrom tanısı alması nedeniyle çalışma dışı bırakıldı. Değerlendirmeye alınan 20 hastanın yaş ortalaması 16.8 idi; Ortalama nöbet başlangıç yaşı 10.6 yıldı. Tüm hastalarda günde bir defadan fazla görülmeyen absans nöbetleri, %40'ında ek jeneralize tonik-klonik nöbetler ve %20'sinde elektroensefalografide jeneralize deşarjlara ek olarak fokal elektroensefalografik anormallikler vardı. Tedavisi sonlandırılan 5 hastanın 3'ünde nöbetler tekrarladı. Halihazırda hastaların %85'inin valproik asit ile tedaviye devam ettiği ve monoterapinin yeterli olduğu bulundu. Elektrofizyolojik olarak tanı anında jeneralize deşarjlar varken, takipte fokal bulgular ortaya çıkma eğilimindedir; Bunun da uzun dönem takipli hastalarda nöbet nüksünün ve tedavi seçeneklerinin değerlendirilmesinde önemli olduğu bulundu.

Anahtar Kelimeler: Jüvenil absans epilepsi, elektroensefalografi, valproik asit

Introduction

Juvenile absence epilepsy (JAE) is an epileptic syndrome in the class of genetic generalized epilepsies, which mainly progresses with absence seizures, seen in an adolescent or adult without any significant health problems other than epileptic seizures, according to the 2017 classification of International League Against Epilepsy (ILAE) (1,2). Although the age of onset peaks between the ages of 9-13, it can occur between the ages of 8-20 (3).

In addition to typical absence seizures in JAE, more than 90% of the cases are accompanied by generalized tonic-clonic seizures and 20% of them are accompanied by myoclonic seizures. The differential diagnosis of juvenile myoclonic epilepsy (JME) and childhood absence epilepsy (CAE) is important. While myoclonic seizures occur in the morning in JME, they usually occur in the afternoon and evening in JAE. It can be distinguished from CAE by the fact that absence seizures are less frequent but longer in duration during the day and that generalized tonic-clonic seizures are frequently accompanied (4).

Valproic acid and lamotrigine are the first choice drugs in the treatment. Ethosuximide, which can be used for absence seizures, is not a suitable option as it is ineffective in generalized tonic-clonic seizures. Although the response to treatment is generally good in JAE, the relapse rates are very high in patients who are discontinued, and treatment should be continued for life most of the time (5,6).

In this study, we tried to determine the clinical, electrophysiological and prognostic features of our patients who were followed up with the diagnosis of JAE in our clinic. Thus, we can potentially provide better

follow-up and treatment in the long-term follow-up of patients with JAE.

Material and Methods

In the study, 33 cases who were followed up in Kocaeli University Faculty of Medicine Pediatric Neurology Clinic between 2010-2022 and met the diagnostic criteria of JAE according to the ILAE 2017 criteria were included in the preliminary evaluation. Seven of the thirteen cases were excluded from the study because of insufficient patient data, 3 of whom were diagnosed with other epileptic syndromes during follow-up, and 3 of whom could not be reached during follow-up. The remaining 20 patients were included in the study.

Age, gender, date of birth, neurological examination, age of seizure onset, seizure types before the start of treatment, seizure frequency, history of status epilepticus, additional seizure types (generalized tonic-clonic seizure, myoclonic seizure), family history of epilepsy, antiepileptic drugs taken, responses to these drugs and duration of use, seizure-free time if antiepileptic treatment was discontinued, relapse time if any, reason if antiepileptic treatment was changed, name of the new drug started, and the patient's response to the new treatment were recorded. In addition, laboratory, electroencephalogram (EEG) findings (spike-wave frequency, background activity abnormalities, focal epileptic discharges) and neuroimaging (brain computed tomography (CT), brain magnetic resonance imaging (MRI)] examinations, if any, of all patients were retrospectively re-evaluated. Patients who had not been seen in our hospital in the last 6 months were called again and their information was renewed, and all patient data were processed into information cards created for patients. Seizure-free state was defined as the absence of seizures for 2 years or more, with or without antiepileptic therapy.

Approval was obtained from the local ethics committee for this study.

Results

Twenty patients were included in the study. The cohort consisted of 13 (65%) female and 7 (35%) male patients. Currently, the mean age of patients is 16.8 years (10-23 years); the mean age of onset of absence seizures was 10.6 years (standard deviation: ±2.1 years; minimum-maximum age: 8-14 years).

Neurological examination of all patients were normal. None of the patients had intellectual disability. 3 patients had poor academic achievement, but mental capacity was normal in their psychiatric evaluations and no special education was required. Three patients had additional health problems at the time of diagnosis: uveitis (1 patient), asthma (1 patient), and hypothyroidism (1 patient). These patients were being treated in the relevant units and their diseases were under control. 8/20 (40%) patients had a family history of epilepsy (siblings of 4 patients; uncle, aunt, aunt and cousin of 4 patients).

All patients had absence epilepsy, but there was no one with a seizure frequency of more than 1 per day at the time of diagnosis. While generalized tonic-clonic seizures were observed in 8/20 (40%) patients, myoclonic seizures were not detected in any of the cases.

Generalized spikes and slow waves at frequencies ranging from 2.5 to 3.5 Hz were observed on EEG in all patients. In 4/20 (20%) patients, focal epileptiform anomalies were also observed in addition to generalized discharges. Triggering was detected by hyperventilation in 12/20 (60%) patients and by transition to sleep in 1 patient.

Brain MRI was performed on 11/20 (55%) patients. Brain MRI was performed in our clinic on 4 patients with focal discharges on EEG and 3 patients with poor performance at school. In the remaining 4 patients, brain MRI was performed in other centers based on the diagnosis of epilepsy upon the request of the family. Only 2 patients had arachnoid cysts that did not cause compression and/or deterioration in CSF circulation, the others were considered normal.

Antiepileptic drug treatments applied to the patients are given in Table 1. It was seen that valproic acid was started in 14/20 (70%) patients and the treatment continued by providing seizure control with this monotherapy. Ethosuximide was started in one patient who had only absence seizures at the beginning. When generalized tonic-clonic seizures emerged during the follow-up, valproic acid treatment started and seizure control was achieved. In two patients, complete seizure control was achieved after valproic acid treatment, and the drug was gradually discontinued after the treatment continued for 5 years. Upon the development of seizure recurrence in the follow-up of the patients, levetiracetam treatment was started considering the focal findings in the EEG and the possible teratogenic effects of valproic acid in girls of childbearing age, and the treatment was continued by providing seizure-freeness. Obesity and hirsutism developed in 1 patient who was started on valproic acid treatment, and lamotrigine was started as a drug-related side effect. It was determined that skin rashes appeared in one of the 2 patients in whom lamotrigine was started as the first treatment option and the other did not respond to the treatment, so valproic acid was switched to and seizure control was achieved. It was observed that 17/20 (85%) patients were currently treated with valproic acid, 2/20 (10%) patients with levetiracetam, and 1/20 (5%) patients with lamotrigine.

Recurrence was observed in 3/5 (60%) of 5/20 (25%) patients whose treatment was gradually discontinued after 5 years of seizure-freeness. The mean time between complete discontinuation of treatment and relapse was found as 10 months (7-12 months). Generalized tonic-clonic seizures and a family history

of epilepsy were remarkable in three of the 3/5 relapsed patients. It was noteworthy that generalized tonic-clonic seizures were not seen in 2/5 patients without recurrence. One of these 2 patients had a family history of epilepsy.

Table 1: Medications given to patients we followed up with the diagnosis of JAE, reasons for medication changes, and last seizure control status

Number of patients	First choice drug	Second choice drug	Reason for medication change	Last seizure control status
14	Valproic acid	-		9 patients were seizure free, 3 patients had seizures in the last 2 years. The drug was discontinued in 2 patients and no recurrence was observed afterwards.
1	Ethosuximide	Valproic acid	Generalized tonic-clonic seizures	Seizure free
2	Valproic acid	Levetiracetam	Seizure recurrence after treatment discontinuation and focal findings on EEG	Seizure free
1	Valproic acid	Lamotrigine	Obesity and hirsutism development as a drug side effect in the patient	Had a seizure 13 months ago
2	Lamotrigine	Valproic acid	Significant skin rash developed in one patient, seizures persisted in the other patient	Seizure free

Discussion:

In this study, 20 patients who were followed up with the diagnosis of JAE according to the ILAE 2017 diagnostic criteria in Kocaeli University Faculty of Medicine Pediatric Neurology Clinic were retrospectively evaluated and the clinical, electrophysiological and prognostic characteristics of the patients were tried to be determined.

Tovia E. et al. (7) published the data of 17 patients diagnosed with JAE. In this publication, it is seen that there are 7/17 male patients and 10/17 (58.8%) female patients. In the same study, the mean age at diagnosis was 12.2 years (9.8-18 years) and the familial rate of epilepsy was 5/17 (29.4%). In our study, it was determined that the mean age at diagnosis decreased to 10.6 years (8-14 years) and a family history of epilepsy was 8/20 (40%). According to the aforementioned study, the mean age at diagnosis and the lower limit of age at diagnosis decreased by about 2 years. This shows that more attention should be paid to the classification of epileptic syndrome, especially in absence epilepsies starting before the age of 10. In addition, in our study, female predominance was noted at similar rates with the literature. It is clear that larger case series are needed to reach a judgment on family history.

Boesen MS et al. (8) in the analysis of 92 Danish children with JAE, found that the need for special education increased by 2 times compared to the normal population and the rate of higher education was 15% lower. In our study, it was observed that 3 patients had poor course success, but none of them needed special education. It was reported that these 3 patients were followed up in terms of attention deficit hyperactivity disorder in their subsequent psychiatric evaluations, but pharmacological treatment had not been started yet and a decision would be made according to the follow-up.

In the background examination of the patients, it was found that 3 patients had an additional disease at the time of diagnosis (asthma, uveitis and hypothyroidism). However, a direct cause-effect relationship between juvenile absence epilepsy and these diseases could not be determined in the literature review.

It is known that a complex/polygenic inheritance model is valid in JAE (9). In our study, 8/20 (40%) of the patients had a family history of epilepsy, but genetic studies were not performed on any of them. However, it is planned to be done with easier access to genetic studies in the next follow-up period.

Macau MA et al. (10), in a study to determine the long-term prognosis of JAE patients, reported that 86% of 21 patients had generalized tonic-clonic seizures and 14% had trace myoclonies. Danhofer et al. (11) in a 46-patient study on the long-term prognosis of JAE stated that 65% of the patients initially had absence seizures, and 32% of them started with generalized tonic-clonic seizures. However, in long-term follow-up, 93% of these patients have generalized tonic-clonic seizures. It was emphasized that only one of 46 patients had absence status epilepticus. In our patients, it was observed that all patients started with absence seizures and were diagnosed. During the follow-up period, generalized tonic-clonic seizures occurred in 8/20 (40%) patients, and status epilepticus was never observed. We still believe that these findings are valuable in our study, which is more limited in terms of patient numbers and follow-up time compared to the case series in the literature. Namely; when we look at the literature, there is an opinion that the natural course of the disease is the onset of absences first, followed by generalized tonic-clonic seizures, and myoclonic seizures are the last and most rare. It is thought that the risk of both other seizure types and status epilepticus will be significantly reduced if the disease is diagnosed and treated and closely observed while the disease is still in the absence phase, thanks to the close follow-up and attention of parents, educators and health personnels.

Typical EEG findings of genetic generalized epilepsies are bilateral, synchronized generalized spike wave or multiple spike wave discharge (12) However, focal abnormalities and asymmetries are also possible in juvenile absence epilepsy (13). Japaridze G. et al. (14), in a JAE series of 58 patients, reported that focal

epileptic discharges were observed in 56% of the patients and focal slowing was observed in 51% of the patients. In our patient series, focal epileptiform anomaly was observed in 4/20 (20%) patients on EEGs at the time of initial diagnosis. In the last EEG of the patients, 12/20 (60%) focal epileptic discharges were present. This finding makes us think that while generalized discharges are at the forefront at the time of diagnosis in JAE, generalized discharges are suppressed and focal discharges come to the forefront in the follow-up with the natural course of the disease or the effect of the drugs used. This is our opinion, and Tezer et al. (15) also agree with the findings and results obtained in their study.

Brain MRI routine visual evaluations are normal in genetic generalized epilepsies (16). Therefore, routine cranial imaging is not recommended in absence epilepsy if there is no focal finding in neurological or electrophysiological evaluations. In our patient series, brain MRI was performed in 11/20 (55%) patients and it was reported as normal except for simple arachnoid cysts in only 2 of them. In the literature, it is seen that morphometric analysis with advanced MRI examinations are mostly performed in genetic generalized epilepsies. In these studies, an increase or decrease in cortical volume is prominent with the decrease in thalamic volüme (17).

Seventeen (85%) of 20 patients in our study are currently continuing their treatment with valproic acid. Consistent with the literature, valproic acid stands out as the most effective treatment in our series (11). However, considering that most of the time the treatment in JAE is life-long, and even if valproic acid treatment is started, the possible side effects (hirsutismus, obesity, etc.) and the risk of teratogenicity for girls who come to the reproductive age should be kept in mind. Although the most effective drug in alternative treatment is lamotrigine for now, the increasing frequency of levetiracetam use is also striking (18-20).

Conclusion:

We retrospectively evaluated 20 patients diagnosed with JAE followed in our clinic. Consistent with the literature, it was found that valproic acid was the most effective treatment, alternatively lamotrigine and especially levetiracetam were suitable alternatives in those with focal findings, and the risk of recurrence was still high after 5 years of seizure-freeness. We believe that the low rate of focal findings during the diagnosis we found in our study and that this rate tends to increase during the follow-up and treatment process is a valuable information that will contribute to the literature. We think that if this information is confirmed with larger series, JAE treatment will also be reconsidered, especially in case of long-term follow-up or recurrence.

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