Clinical insights into juvenile myoclonic epilepsy: Our experience

Juvenil miyoklonik epilepsi üzerine klinik deneyimimiz

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Abstract

Aim: Juvenile Myoclonic Epilepsy (JME) is predominantly observed during adolescence, characterized by myoclonic jerks exacerbated by sleep deprivation. Generalized tonic-clonic (GTC) and absence seizures are also common in JME. Patients are often photosensitive and usually require long-term treatment. This study aims to retrospectively evaluate the clinical, demographic, and electroencephalography (EEG) findings of patients diagnosed with JME at our Pediatric Neurology Clinic.

Methods: Patients who were followed up at the Department of Pediatric Neurology between 2017-2022, diagnosed with JME based on clinical and EEG findings, and had at least one year of follow-up were included in this study. The clinical characteristics of the patients, as well as their diagnostic and follow-up EEG results, were retrospectively reviewed.

Results: Of the patients, 12 (55%) were female and 10 (45%) were male. The mean age of the patients was 17±1 (range 14-18) years, and the average age at first seizure was 13±2 (range 12-16) years. When examining the types of seizures in our cases; 12 (55%) had myoclonic and GTC seizures, 4 (18%) had a combination of myoclonic-GTC-absence, and 6 (27%) had isolated myoclonic seizures. EEG results showed that 6 (27%) of the patients had spike and multiple spike waves at 3-5.5 Hz during sleep, while the remaining 16 (73%) had these during wakefulness. Fourteen (64%) of the patients responded to photic stimulation. Six (27%) of the patients had a first-degree relative with a history of epilepsy. A significant association was found between the presence of photosensitivity and family history of epilepsy (p=0.03).

Conclusion: Juvenile myoclonic epilepsy is a type of epilepsy observed in the adolescent period, characterized by myoclonic jerks and photosensitivity. In patients with JME who have a family history of epilepsy, photosensitivity is more commonly observed

Keywords: Adolescent; myoclonic epilepsy; photosensitivity,

Öz

Amaç: Juvenil Miyoklonik Epilepsi (JME) daha çok ergenlik döneminde ortaya çıkan, uykusuzlukla tetiklenen miyoklonik jerklerin hakim olduğu kliniktir. JME'de jeneralize tonik-klonik (JTK) ve absans nöbetler görülebilmektedir. Hastalar çoğunlukla fotosensitiftir ve genelde uzun süreli tedavi gereklidir. Bu çalışmada Çocuk Nöroloji kliniğimizde JME tanısıyla takipli hastalarımızın klinik, demografik ve elektroensefalografi (EEG) bulgularının retrospektif olarak değerlendirilmesi amaçlanmıştır.

Yöntemler: Çocuk Nöroloji Kliniği'nde 2017-2022 yılları arasında takip edilen, klinik ve EEG bulgularıyla JME tanısı alan ve en az 1 yıl takibi olan olgular çalışmaya dahil edilmiştir. Hastaların klinik özellikleri, tanı ve takipteki EEG sonuçları geriye dönük olarak incelenmiştir.

Bulgular: Hastaların 12'si (% 55) kız, 10'u (% 45) erkek idi. Hastaların ortalama yaşı 17±1 (14-18) yıl, ilk nöbet geçirme yaşı 13±2(12-16) yıl idi. Olgularımızın nöbet tipleri incelendiğinde; 12 (%55) hastada miyoklonik ve JTK nöbet, 4 (%18) hastada miyoklonik-JTK-absans birlikteliği ve 6 (%27) hastada ise izole miyoklonik nöbetler olduğu tespit edildi. Hastaların EEG sonuçları incelendiğinde; 6 (%27) hastanın uyku, diğer 16 (%73) hastanın uyanıklık EEG sonucunda 3-5,5 Hz diken ve çoklu diken dalgalar mevcuttu. Hastaların 14 (%64) tanesinde fotik stimülasyona cevap vardı. Hastalarımızın 6 (% 27) tanesinin birinci derece akrabalarında epilepsi öyküsü mevcuttu. Fotosensitivite ile ailede epilepsi varlığı arasında anlamlı bir ilişki olduğu saptandı (p=0.03).

Sonuç: Juvenil miyoklonik epilepsi adölesan dönemde görülen, miyoklonilerin ve fotosensitivitenin ön planda olduğu bir epilepsi türüdür. Fotosensitive, ailede epilepsi öyküsü olan JME hastalarında daha sık görülmektedir.

Anahtar Sözcükler: Adölesan; fotosensitivite; miyoklonik epilepsi

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INTRODUCTION

The term Juvenile Myoclonic Epilepsy (JME) was first mentioned by Herpin in 1867 (1). The disease was comprehensively defined 90 years later, in 1957 by Janz and Christian, using the term "impulsive petit mal" (2). It took time for JME to gain an international definition. It was eventually included in the International League Against Epilepsy's (ILAE) first international classification proposal for epilepsies and epileptic syndromes in 1985 (3). JME predominantly emerges during adolescence, the onset age is mostly between 12-18 years. The disease is characterized by bilateral, single or repetitive, irregular arrhythmic myoclonic jerks, usually in the arms. Seizures usually occur shortly after waking and are often triggered by sleep deprivation (3). The most significant clinical finding is myoclonic jerks that appear in the early morning hours. It has been noted that the excitability measured by transcranial magnetic stimulation increases in the early morning in patients with JME, which is associated with increased seizures at this time of day (4).

Often, the myoclonus, causing objects to drop from the patients' hands, is perceived as clumsiness by families. While myoclonus does not involve loss of consciousness, it can occasionally cause sudden falls. Myoclonic seizures are indispensable for diagnosis. Other types of seizures include absence seizures, seen in approximately 35-40% of patients, and generalized tonic-clonic (GTC) seizures seen in approximately 85-90% of patients (5). These three different seizure types in JME have distinct clinical implications. For instance, while GTC seizures are a relatively nonspecific type seen in many epilepsy types, studies have suggested that absence of seizures in JME might indicate a form of endophenotyping (6). Although absence seizures alone may not carry significant meaning, the progression from childhood absence epilepsy to JME has been indicated as an adverse prognostic marker (7). Patient groups exhibiting all three types of seizures are associated with a high risk of antiseizure medication resistance (8). For a diagnosis of JME, the presence of myoclonic seizures along with 3-5.5 Hz generalized spike or polyspike waves in ictal or interictal electroencephalography (EEG) is a prerequisite (9). The spike-wave discharges in JME are thought to originate from abnormal neuronal discharges in cortico-subcortical networks and dysfunction in thalamofrontal circuits (10).

JME is the epilepsy syndrome most characterized by reflex epileptic traits. These include photosensitivity, eye-closure sensitivity, orofacial reflex myoclonus, and praxis induction (3). Photosensitivity is the most commonly encountered type of reflex epilepsy. It is described as the elicitation of spike-wave discharges following intermittent photic stimulation, typically originating and being dominant in the occipital region. The association between this condition and JME was first described by Wolf and Gooses in 1986. The prevalence of photosensitivity in patients is reported to be between 50-90% (11). Intermittent light stimulation brings out photosensitivity either in the form of seizures or as a 'photoparoxysmal response' visible in EEG as spike and wave discharges.

Eye-closure sensitivity is defined as the appearance of spike and wave discharges within 2 seconds after closing the eyes. While it is pathognomonic for Jeavons syndrome, it also occurs in about 20% of JME cases (3). Orofacial reflex myoclonus consists of small myoclonic jerks in the tongue, throat, jaw, and perioral muscles. While primarily seen in reading epilepsy, it is also found in approximately 30% of patients with JME (8). Praxis induction is the emergence of epileptic seizures and epileptiform EEG discharges with complex cognitive behaviors involving visual-motor coordination and decision-making. In other words, it is the appearance of myoclonic jerks with cognitive effort. This clinic is observed in approximately 30-50% of JME patients (12). A survey conducted among JME patients identified that those with praxis induction clinic have a more severe course than the other reflex epileptic features (13).

Considering the reflex epileptic features of JME, it is thought to arise from disturbances in the functional anatomical networks of the brain. Disruption of thalamo-cortical network functions can lead to impairments in higher-level frontal lobe lesions such as working memory, planning, and risk-taking, resulting in poor socioeconomic outcomes and unemployment in this patient group (14). Patients with JME exhibit impaired working memory functions. Behavioral traits among patients with JME can include indiscipline, insensitivity and instability, which may affect their ad-

Table 1. Gender comparison in photosensitivity patients

	Male	Female	*Total*
Photosensitivity present	7	7	14
Photosensitivity absent	3	5	8
	10	12	**p=0.45**

Table 2. Relationship between photosensitivity and iron deficiency

	Ferritin <10 ng/ml	Ferritin > 10 ng/ml	*Total*
Photosensitivity present	4	10	14
Photosensitivity absent	2	6	8
	6	16	**p=0.6**

Table 3. Photosensitivity and epilepsy relationship in the family

	Family history of epilepsy	Alt sütun yukarıdakilerle hizalansın	*Total*
Photosensitivity present	6	8	14
Photosensitivity absent	0	8	8
	6	16	**p=0.03**

herence to treatment. Furthermore, studies have found higher pharmacoresistance in patients with psychiatric comorbidities (15).

Despite traditional teachings that do not expect morphological abnormalities in JME, micro-architectural level magnetic resonance (MR) studies in JME have revealed reductions in functional and structural connectivity within the motor cortex, anterior supplementary motor area and frontoparietal cognitive networks (16). Furthermore, a meta-analysis found increased grey matter volume in the bilateral medial frontal gyrus and anterior cingulate, along with decreased volume in the bilateral thalamic region (17). MR spectroscopy reports on patients have observed that in those with photosensitivity, frontal cortical and thalamic dysfunction extends to the occipital region (18). Some of the genes associated with JME include CACNB4, GABRA1, GABRD, CASR, and EFHC1 (19). In addition, abnormal functional MR frontal lobe working memory activation has been observed in the healthy siblings of JME patients (20). The treatment objective of this disease involves lifestyle changes and medication adherence. Generally, the response to appropriate antiseizure medication is favorable.

In this present study, we aimed to evaluate the clinical findings of JME patients along with the frequently observed photosensitivity and share with the literature.

MATERIAL AND METHODS

This study was approved by Necmettin Erbakan University Ethics Committee (date: 07.07.2023, desicion no: 2023/4405). The diagnosis of JME was made referencing the International League Against Epilepsy's (ILAE) guidelines published in 2022 (21).

Clinical, demographic, and EEG findings of 22 patients diagnosed with JME and followed at Necmettin Erbakan University, Meram Faculty of Medicine, Department of Pediatric Neurology, between 2017-2022 were retrospectively evaluated. Patients who had been followed for at least one year were included in the study. Patients with external center diagnoses, follow-ups, and additional diseases were excluded from the study.

Patients' demographic data (age, gender, family history, etc.), clinical data (presence of seizures, antiseizure medication used, age at seizure onset, duration of follow-up, etc.), electroencephalography (EEG), laboratory results (complete blood count, biochemistry, hormones), and brain magnetic resonance (MR) imaging findings were retrospectively scanned from our hospital's e-medical record system.

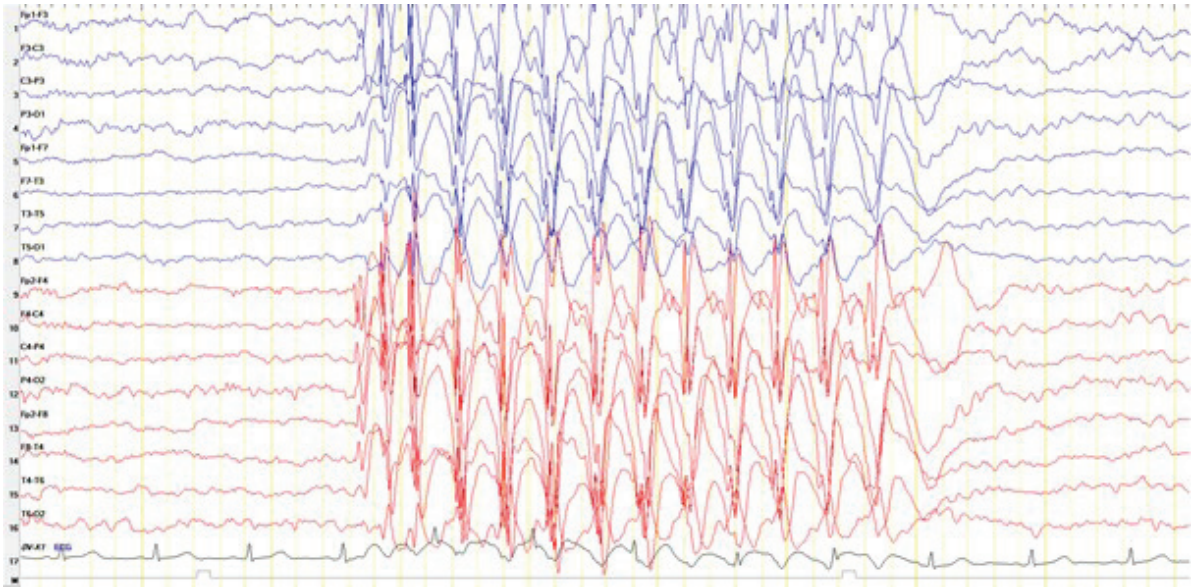

Figure 1. Generalized high-amplitude 3-5 Hz multi-spike slow wave paroxysms, maximal in the frontal region

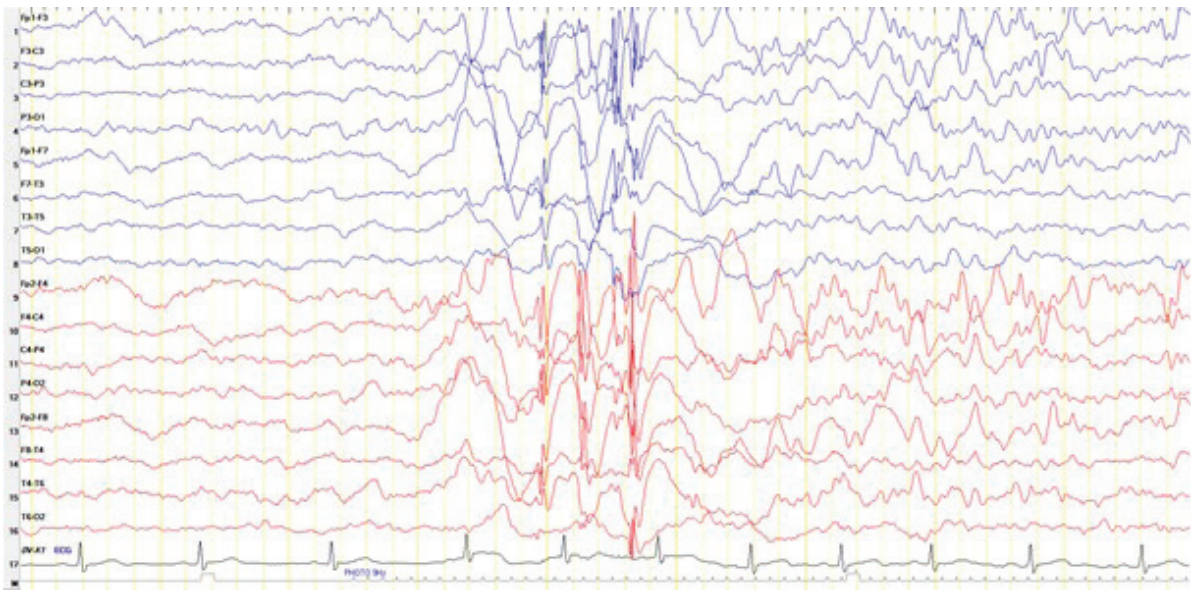

Figure 2. Generalized high-amplitude 4-5 Hz multiple spikes and sharp slow wave paroxysms lasting about 1-2 seconds, maximal in bilateral frontal regions.

Photosensitivity was considered an abnormal clinical response developed with light effect along with findings in the electroencephalography. Patients with anemia in the complete blood count and a ferritin value of <10 ng/ml were considered to have severe iron deficiency anemia. Severe iron deficiency anemia, family history of epilepsy, and gender were analyzed for their association with photosensitivity.

Statistical Analysis

The data of the present study were analyzed statistically using SPSS version 22 software (Statistical Package for the Social Sciences, Chicago, IL, USA). In the descriptive analysis of the data, continuous variables were presented as median and interquartile range (IQR), minimum and maximum values, and categorical variables as frequency (n) and percentage (%). The

association of the presence of photosensitivity with iron deficiency anemia, family history of epilepsy, and gender were analyzed via Pearson Chi-square test. A value of $p<0.05$ was considered statistically significant throughout the study.

RESULTS

Of the patients, 12 (55%) were female and 10 (45%) were male. The average current age of the patients was 17±1 (range 14-18) years, and the average age at first seizure was 13±2 (range 12-16) years.

The types of seizures in our cases were as follows: 12 (55%) had myoclonic and GTC seizures, 4 (18%) had a combination of myoclonic-gtc-absence seizures, and 6 (27%) had isolated myoclonic seizures.

Looking at the EEG results of our cases; 6 patients (27%) exhibited 3-5.5 Hz spikes and multiple spike waves during sleep, while the remaining 16 patients (73%) had these during wakefulness (Figures 1 and 2). Additionally, photic stimulation was found to be effective in 14 patients (64%). Photosensitivity was present in 7 (% 32) of the girls and 7 (% 32) of the boys. A gender comparison among photosensitive patients revealed no significant difference between the two genders in terms of photosensitivity ($p=0.45$) (Table 1).

As shown in the table, photosensitivity was observed in 4 patients with iron deficiency, while photosensitivity was present in 10 patients without iron deficiency. Upon diagnosis, it was observed that there was no significant relationship between patients with photosensitivity in EEG and those with severe iron deficiency ($p=0.6$) (Table 2).

Six (27%) of our patients had a first-degree relative with a history of epilepsy. When comparing presence of photosensitivity with the presence of epilepsy in the family, a significant relationship was found ($p=0.03$) as shown in Table 3.

Eleven of our cases were taking valproic acid, nine were on levetiracetam, and two were receiving a combination treatment of valproic acid and lamotrigine. It was observed that two of the patients on levetiracetam had initially received valproic acid treatment but were switched to levetiracetam due to the development of tremors in the hands during follow-up. All of our cases brain MR imaging did not reveal any pathology and was reported as normal.

DISCUSSION AND CONCLUSION

Juvenile myoclonic epilepsy is seen in approximately 0.5-1% of the general population and represents about 5-15% of all epilepsies (22). While it was previously considered to affect both genders equally, recent studies have indicated a higher prevalence in females (23). In line of these results, in our patient group, the number of female patients was relatively higher.

The inheritance pattern of juvenile myoclonic epilepsy is not fully defined, but a family history is present in the majority of patients (25-65%) (24). Some genes most associated with JME inheritance include CACNB4, CASR, GABRA1, GABRD, and EFHC1 (19). In our cases, 27% had a family history, but no genetic panel testing was conducted for any patient. Personality and behavioral disorders observed in some patients have been associated with frontal lobe involvement, and brain MR imaging has indicated increased gray matter volume in the frontal and cingulate gyrus and decreased volume in the thalamus (17). Nevertheless, the normal interpretation of MR reports for our patients was related to the inability to perform functional MRI and the use of thicker slices. More research is needed on this topic.

In cases with JME, ictal and interictal EEGs show fast generalized, often irregular spike and polyspike waves, while the baseline rhythm is normal. However, there is no synchronization between myoclonic jerks and spike waves in EEG. When the EEGs of the 22 patients in our study were examined, all had a normal baseline rhythm, while 6 had 3-5.5 Hz spike and polyspike waves during sleep, and the remaining 16 were during wakefulness.

Photosensitivity is an abnormal sensitivity response of the brain to complex stimuli such as light flashes, intermittent light sources, visual patterns, and video games. It occurs in 5-10% of epilepsy patients and 40-50% of JME patients (11). It is more commonly seen in adolescents and females (25). In our patient group, 64% exhibited photosensitivity. The distribution of photosensitive patients was equal among both genders. It is often stated that photosensitivity is predominantly

inherited as an autosomal dominant trait. Our study also supports this finding that it is more common in those with a family history. Therefore, patients with a family history of epilepsy and clinical photosensitivity can be candidate for comprehensive genetic studies.

In treatment management, the proper use of antiseizure medication and avoiding situations such as stress, sleep deprivation, sudden lights, and anxiety are fundamental (26). In our study, 5 patients had been seizure-free for more than a year, and this was associated with their adherence to treatment and avoidance of triggers. While lifelong treatment was recommended in previous years due to the high risk of relapse, some recent studies do not support this (27). Studies suggest that valproic acid is the first choice in JME treatment, affecting all three types of seizures and achieving a clinical response rate of 85%. If there is drug interaction or adverse effects from valproic acid, lamotrigine, clobazam, levetiracetam, and topiramate is recommended (28). When polytherapy is needed, the combination of valproic acid and lamotrigine can be effective, but attention must be given to rashes and side effects.

The homogeneity of our patient group, with none having additional diseases and the majority exhibiting photosensitivity, is a strength of our study. However, limitations include the limited number of patients and the retrospective nature of the study method.

In conclusion, JME is a type of epilepsy observed in the adolescent period, characterized by prominent myoclonus and photosensitivity, and is heterogeneous due to various seizure types and responses. In patients with juvenile myoclonic epilepsy (JME) who have a family history of epilepsy, photosensitivity is more commonly observed

Conflict-of-interest and financial disclosure

The authors declare that they have no conflict of interest to disclose. The authors also declare that they did not receive any financial support for the study.

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