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# Determination of the factors that cause valproic acid resistance in the pediatric juvenile myoclonic epilepsy cohort

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**Abstract**
Juvenile myoclonic epilepsy (JME) has an approximate prevalence of 18%–20% among idiopathic generalized epilepsy types. Valproic acid (VPA) is the first line treatment of JME; however, resistance to VPA was detected as the most important prognostic entity for refractory seizures. The present study aims to determine the factors that induce VPA resistance in pediatric patients with JME. Patients between the ages of 10 and 18 who were diagnosed with JME were examined retrospectively. The groups with VPA resistant and non-resistant group were statistically analyzed. Total of 62 patients diagnosed with JME, 41 (66.1%) of them were female. The average age was 15.48±2.11 years. VPA resistance was detected in 21(33.8%) of our patients. Seizure onset age of patients younger than 15 years, presence of febrile seizure (FS), photosensitivity, seizure type, seizures occurring both at day and night, and epileptic discharge longer than 3 seconds during EEG were found to be statistically significant risk factors for the development of VPA resistance. Close monitoring of individuals with these risk factors is recommended for VPA resistance.

**Keywords:** Juvenile myoclonic epilepsy, EEG, Valproic acid resistance, treatment

## Introduction

Juvenile myoclonic epilepsy (JME) is an epileptic syndrome with a prevalence of approximately 18% among the JME idiopathic generalized epilepsy types [1]. The age of onset of seizures changes between 10 and 25 years, and it frequently peaks during teenage [2]. JME is characterized by myoclonic jerks predominantly on waking, generalized tonic-clonic seizures (GTC), and absence seizures (AS) seen in about 1/3rd of patients [2]. Myoklonic jerks are fast and irregular clonic movements mainly affecting upper extremities [3]. AS are subtle impairment of consciousness, which is different from absence seizures of childhood absence epilepsy or juvenile absence epilepsy (JAE) [4]. GTC seizures are seen in nearly all patients with JME and mostly appear after a series of myoclonic jerks on awaking [2]. Photosensitivity accompanies JME at a rate of 30%. Further, 15% of febrile seizures (FS) were reported in the history of patients with JME [5]. The classical EEG finding of JME is 3–6 hz generalized poly-spike wave discharge [6]. Valproic acid (VPA) is the first line treatment of JME. However, 15%–20% of VPA resistance was reported in literature [7]. Resistance to VPA was the most important factor for drug resistant epilepsy. Resistance to VPA had a specificity of 100% to identify patients with drug resistance and strongly related with low disease outcome [8]. However, the number of studies in literature investigating VPA resistance in pediatric JME cases is very limited

Therefore, our aim in this study is to identify the factors that induce VPA resistance in our pediatric patient group being followed up for JME.

## Materials and Methods

This is a single-center retrospective study approved by the Ethics Committee of Kartal Dr. Lutfi Kirdar City Hospital with the number of 2021/514/202/25. The study was conducted in accordance with the principles of the Declaration of Helsinki. The informed parental consent was not obtained due to retrospective of study and we had only used patients' electronic data without ID information.

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### Patient's

Data were collected at pediatric neurology outpatient clinic of hospital between the years 2020 and 2021. Inclusion criterias were as follows: 1) 10-18 age, 2) Diagnosis of JME on the basis of International League against Epilepsy (ILAE) with normal neurological examination 3) Patients, who started VPA as the first drug for treatment; Exclusion criterias were as follows: 1) Being over 18 years old, 2) Presence of classical focal epilepsies 3) Abnormal brain imaging of computed tomography or magnetic resonance imaging, neuro-degenerative or metabolic diseases, and patients with mental retardations syndromes or dysmorphic features. We defined "valproic acid adequate doses" in accordance with the World Health Organization daily doses provided that the plasma concentration was within normal therapeutic profile. Truly resistant patients were defined as those with ongoing seizures (myoclonic jerks and/or absence seizures and/or GTC seizures) despite recomended lifestyle and treatment with sufficient doses of VPA. A total of 62 pediatric patients who met these criteria were included in the study.

### Data collection

The demographic characteristics of the patients, age of seizure onset, history of FS, presence of epilepsy in family members, presence of photosensitivity, EEG findings, and data on the seizures' resistance to VPA were retrospectively obtained from the hospital automation system and recorded in an Excel file. The data obtained were statistically analyzed.

### Statistical Analyses

NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) program was used for the purposes of statistical analysis. Descriptive statistical methods (mean, standard deviation, frequency, and percentage) were used while evaluating the study data. Shapiro-Wilk test and graphical analysis was used to confirm the suitability of quantitative data to normal distribution. Independent groups t test was used to compare normally distributed quantitative variables between the two groups. Pearson's Chi-square test and Fisher's exact test were used to compare qualitative data. A multivariable logistic regression analysis was performed to determine the risk factors affecting the state of being resistant. Statistical significance was accepted as $p<0.05$.

### Results

In this retrospective study, we had a total of 62 patients diagnosed with JME, 41 (66.1%) of whom were female. The average age was 15.48±2.11 years. The age of onset of seizures in 40 patients (64.5%) was less than 15 years, and the age of onset of seizures in 22 patients (35.4%) was over 15 years old. Twelve (19.3%) patients had a history of FS. Eighteen patients (29.02%) had an individual diagnosed with epilepsy in their families. Photosensitivity was detected in 22 patients (35.4%). Focal epileptiform discharges accompanied the EEGs of nine patients (14.5%). VPA resistance was detected in 21 of our patients (33.8%).

There was no statistically significant difference in age between patients with and without VPA ($p>0.05$). No statistically significant difference was found in sex, family history of epilepsy, discharge frequency, and EEG in terms of the percentage of resistance compared to focal finding ($p>0.05$).

It was found that the percentage of cases with VPA resistance in patients aged between 10 and 15 years was significantly higher than in patients aged >15 years ($p=0.013$). Also VPA resistance was significantly higher in patients with FS than in patients without FS ($p=0.002$).

Patients with Absence seizure (AS) + Myoclonic seizure (MYC) + Generalized tonic-clonic seizure (GTC) compared to patients with MYC or MYC + GTC were found as a risk factor for the development of VPA resistance ($p<0.001$).

Additionally, resistant cases was higher in patients with state of seizure occurring at sleep + awaking than those with only awakening ($p<0.001$). Photosensitivity was found significantly higher in VPA resistant cases ($p<0.001$). Moreover, It was found that the percentage of resistant cases was higher in patients with epileptiform runs of ≥3 s($p<0.001$) (Table 1).

**Table 1**. Predictive factors for VPA resistance

| | Total | No resistance | Resistant | p |
|---|---|---|---|---|
| **Number (%)** | 62 (100.0) | 41 (66.1) | 21 (33.9) | [a]0.247 |
| **Age** | 15.48±2.11 | 15.71 ± 2.12 | 15.05 ± 2.06 | |
| **Gender** | | | | |
| **Female** | 41 | 28 (68.3) | 13 (31.7) | [b]0.615 |
| **Male** | 21 | 13 (61.9) | 8 (38.1) | |
| **Age at onset** | | | | |
| **10–15 years** | 40 | 22 (55.0) | 18 (45.0) | [b]0.013* |
| **>15 years** | 22 | 19 (86.4) | 3 (13.6) | |
| **FS** | | | | |
| **No** | 50 | 38 (76.0) | 12 (24.0) | [c]0.002* |
| **Yes** | 12 | 3 (25.0) | 9 (75.0) | |
| **Family history of epilepsy** | | | | |
| **No** | 44 | 31 (70.5) | 13 (29.5) | [b]0.261 |
| **Yes** | 18 | 10 (55.6) | 8 (44.4) | |
| **Seizure type** | | | | |
| **MYC+(MC+GTC)** | 40 | 34 (85.0) | 6 (15.0) | [b]<0.001* |
| **AS + MYC + GTC** | 22 | 7 (31.8) | 15 (68.2) | |
| **State of seizure** | | | | |
| **Awakening** | 40 | 35 (87.5) | 5 (12.5) | [b]<0.001* |
| **Sleep + Both** | 22 | 6 (27.3) | 16 (72.7) | |
| **Discharge frequency** | | | | |
| **>4 hz** | 19 | 13 (68.4) | 6 (31.6) | [b]0.800 |
| **<4 hz** | 43 | 28 (65.1) | 15 (34.9) | |
| **Photosensitivity** | | | | |
| **No** | 40 | 35 (87.5) | 5 (12.5) | [c]<0.001* |
| **Yes** | 22 | 6 (27.3) | 16 (72.7) | |
| **Epileptiform runs ≥3 s** | | | | |
| **No** | 40 | 33 (82.5) | 7 (17.5) | [c]<0.001* |
| **Yes** | 22 | 8 (36.4) | 14 (63.6) | |
| **Focal finding on EEG** | | | | |
| **No** | | 37 (69.8) | 16 (30.2) | [c]0.251 |
| **Yes** | | 4 (44.4) | 5 (55.6) | |

FS: febrile seizure, MYC: myoclonic seizure, AS: absence seizure, GTC: generalized tonic clonic seizure. [a]Independent groups t test [b]Pearson chi-square test [c]Fisher's exact test*$p < 0.05$

Multivariable logistic regression analysis was performed to determine the risk factors affecting resistance. Age at onset, FS, seizure type, and photosensitivity, which were observed to have significant effects in univariable evaluations, were included in the analysis as independent variables. The model obtained as a result of the analysis was statistically significant ($\chi2=42.385, p<0.001$). While age at onset became insignificant in the model, it was observed that FS, seizure type, and photosensitivity variables were significant; thus, were included in the analysis (FS, p=0.044; seizure type, p=0.018; photosensitivity, p=0.001) (Table 2).

**Table 2**. Determining risk factors affecting VPA Resistance

| | Beta | OR (95% CI) | p |
|---|---|---|---|
| **Age at onset (10–15)** | 1.244 | 3.470 (0.459. 26.210) | 0.228 |
| **FS (present)** | 2.292 | 9.894(1.060. 92.338) | 0.044* |
| **Seizuretype (AS+MC+GTC)** | 2.259 | 9.577 (1.469. 62.441) | 0.018* |
| **Photosensitivity** | 3.440 | 31.200 (4.426. 219.951) | 0.001* |

FS: febrile seizure, MYC: myoclonic seizure, AS: absence seizure, GTC: generalized tonic clonic seizure.
OR: Odds Ratio, CI: Confidence Interval
*p < 0.05

## Discussion

JME constitutes 5%-10% of childhood epilepsies [9]. VPA is considered the most effective drug in JME. Gesche et al. (2017) proposed that resistance to VPA is a new clinical indicator for drug-resistant genetic generalized epilepsy and suggested that "drug-resistant Genetic generalized epilepsy" should not be stated unless patients have been sufficiently treated with VPA [8]. Psychosocial and intellectual outcome is low in patients with drug-resistant JME [10]. In that regard, it is important to determine the factors affecting VPA resistance. In addition, there are only a limited number publications in literature investigating VPA resistance in JME. Our total number of patients were 63 and 41 of them were female. There is a marked female predominance in our cohort as reported in literature [1]. However, no significant relationship was found between sex and VPA resistance. As reported by Gelisse et al (2001) and Chen et al. (2020), drug resistance is more common in early-onset seizures [7,11]. In our study, we found that VPA resistance was higher in patients, that first seizure started before the age of 15. In the Chen et al. (2020) study, higher levels of neurocognitive disorders were found in early-onset JME cases [11]. With an aim to investigate the reason of this Lin et al. (2014), compared new-onset pediatric JME cases with healthy controls for cortical volume, thickness, and found that the said rate was significantly low. As a result, children with JME have abnormal structural brain development and altered cognition early in the course of their disease [12]. It was suggested that the earlier the onset time of epilepsy is the more pronounced this remodeling would be. This might account for the association between the lower age of onset of epilepsy and VPA resistance.

In addition, we found that the presence of FS caused the development of VPA resistance in JME. Chen et al. (2020) reported the presence of FS as a factor affecting drug resistance in JME. In that article, it was suggested that FS increased the risk of hippocampal sclerosis, and drug resistance might develop as a result of FS. However, hippocampal sclerosis was not observed in patients with FS in our cohort [11]. In recent studies, it was shown that genes such as SCN1A and GABRAB1, which cause genetic epilepsy with FS plus, were also in the etiology of JME [13,14]. These genes were reported to cause resistant epilepsies, depending on the mutation site. In this study, we suggest that the existence of FS inducing VPA resistance may be mostly associated with the underlying genetic etiology.

In this study, patients with MYC + GTC + AS seizure type had a higher rate of VPA resistance compared to the non AS group. JME is a heterogeneous syndrome that includes different subtypes. Senf et al. (2013) reported absence seizures at onset of JME as an independent risk factor for ongoing seizures [15]. Accordingly, this led to different clinical outcomes. In the study conducted by Gilesse et al. (2001), drug resistance was significantly higher in patients with GTCS + AS + MYC compared to the other group. However, in the same study, drug resistance was not seen in the AS + MYC group [7].

Photosensitivity has been identified by the presence of generalized spikes, spike and wave, or poly-spike and wave in response to intermittent light stimulation; it is reported to occur in approximately 40% of patients with JME [16]. Menini and Naquet et al. presented three types of photosensitivities. Type A is an inappropriate function of the GABAergic system. It is bilateral and synchronous, and develop in the fronto-rolandic cortex. Type B arise in the lower brainstem (ponto-bulbar reticular formation), and it is not epileptic. Type C is associated with spike-waves during slow wave-sleep. It originate from the lower brainstem and the cortex [17-19]. Although VPA was reported as a potent treatment in the treatment of photosensitivity, combinations of VPA and levetirecetam were effective in cases resistant to lamotrigine and benzodiazepines [20]. Additionally, it was suggested to avoid triggering factors. In our study, the presence of photosensitivity in JME cases was an independent risk factor for VPA resistance.

JME in particular bears an intimate relationship with the sleep-wake cycle. Most of patients show myoclonic jerks and GTC on waking up in the morning during the transitional phase from sleep to wakefulness. [21]. The mechanisms underlying the interaction between the sleep-wake cycle and different forms of epileptic seizures and syndromes are largely unknown. It could be that this is related to circadian fluctuations in cortical excitability [22]. In our study, nocturnal seizures were observed in addition to daytime seizures in 22 patients diagnosed with JME, which was determined as a risk factor for VPA resistance.

Japaridze et al. (2015) found focal epileptiform discharge in 70.2% of 168 patients diagnosed JAE and JME and investigated the effect of this on treatment [23]. It was demonstrated that focal epileptiform discharges did not affect the treatment process. Similarly, in our study, focal epileptiform discharge was detected in 14% of patients, and their presence had no effect on the development of VPA resistance.

In addition, we found that epileptiform runs of ≥3 s were risk factors for VPA resistance in patients. This factor was specified as a good prognostic factor in the 2020 study by Chen, and it is not consistent with our study [11]. The fact that none of our patients

had 24 hours of EEG monitoring is a limitation for our study.

This study has additional limitations. The major limitation is that it is a single-center retrospective study. Second, the sample size is relatively small; so that large series are needed to confirm our findings.

## Conclusion

In summary, photosensitivity, FS, and the presence of MYC + AS + GTC seizures in patients with JME were identified as independent risk factors for the development of VPA drug resistance. Early onset of seizures and presence of nocturnal seizures were found to be significantly higher in the group with VPA resistance. Close monitoring of individuals with these risk factors is recommended for drug resistance and other psychosocial complications of JME.

**Conflict of interests**
*The authors declare that they have no competing interests.*

**Financial Disclosure**
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**Ethical approval**
*This study was approved by the local ethics committee of Kartal Dr. Lutfi Kirdar City Hospital with the number of 2021/514/202/25.*

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