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Outcomes of low-dose valproic acid treatment in patients with juvenile myoclonic epilepsy

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ABSTRACT

Purpose: There are conflicting data regarding the drug dose that is sufficient to achieve seizure control as well as the parameters of seizure remission in juvenile myoclonic epilepsy (JME). The present study aimed to identify factors that contribute to seizure control in JME and to evaluate factors associated with JME remission and the efficacy of low-dose valproic acid (VPA) therapy.

Methods: This retrospective, cross-sectional study included a total of 215 patients (121 female and 94 male; mean age: 28.03 ± 8.43 [14–59] years) diagnosed with JME. The patients were divided into remission and refractory groups. Remission was defined as a seizure-free (myoclonic, absence, and/or generalized tonic–clonic) period of at least 2 years. Patients in whom remission was achieved with VPA monotherapy were further divided into two groups according to the use of low-dose VPA therapy (VPA ≤ 750 mg/day and > 750 mg/day). Potential contributing factors were evaluated in terms of the relationship between the dose and the remission parameters.

Results: Remission was achieved with VPA monotherapy in 116 patients (87.9%) in the remission group; the VPA dose was ≤750 mg in 77.6% of the patients. The dose of VPA was higher in patients with absence seizure who achieved remission ($p = 0.026$). Remission was achieved with a lower dose of VPA in females than in males ($p = 0.004$).

Conclusions: Low-dose VPA can be used to achieve remission in JME. However, identification at follow-up visits of the factors that may affect remission may change the planned effective dose of VPA.

1. Introduction

Juvenile myoclonic epilepsy (JME) is characterized by the presence of bilateral myoclonic, generalized myoclonic, tonic–clonic, and (less often) absence seizures. Its prevalence comprises 5–10% of all epilepsies and 18% of genetic (idiopathic) generalized epilepsies [1]. Clinical symptoms occur between 6 and 22 years of age, most frequently during adolescence: age at onset is 13–16 years in half of affected patients [2]. Myoclonic seizures primarily occur between 12 and 18 years of age; these consist of generalized tonic–clonic (GTC) seizures in 80–97% of patients [3]. Previous studies have reported a female preponderance [4]. Notably, seizures are often provoked by sleep deprivation, fatigue, alcohol consumption, and stress [5]; avoidance of triggers and provision of lifestyle advice are integral aspects of seizure treatment [6].

Controversy remains regarding current parameters of clinical remission in JME, and patients require antiepileptic drugs (AEDs) throughout their lives [7–9]. However, AED resistance has been reported at a rate of 15% [10]. Valproate (VPA) monotherapy has been shown to achieve seizure control in 82–97% of patients [11]. In the present study, we aimed to evaluate the potential effects of low-dose VPA monotherapy on seizure control and teratogenicity in JME based on clinical and electrophysiological findings.

2. Material and method

This retrospective, cross-sectional study reviewed the outpatient clinical records of 290 patients among 5760 patients who underwent follow-up in the Epilepsy Outpatient Clinics of the Department of Neurology at Istanbul University Cerrahpaşa, School of Medicine who were diagnosed with and regularly followed for JME. The inclusion criteria were as follows: 1. Unequivocal clinical (historical) evidence of

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Table 1
Comparisons between clinical characteristics of patients with juvenile myoclonic epilepsy in refractoriness versus remission group.

Mean ± SD (min-max), n (%)	Total (n:215)	Refractoriness (n:83)	Remission (n:132)	P
Sex				
Female	121 (56,3%)	42 (50,6%)	79 (59,8%)	0,183
Male	94 (43,7%)	41 (49,4%)	53 (40,2%)	
Age	28,03 ± 8,433 (14–59)	27,57 ± 7,403	28,32 ± 9,035	0,526
Age at seizure onset	14,93 ± 3,20 (5–23)	14,65 ± 3,042	15,10 ± 3,484	0,337
Time from seizure onset until diagnosis	3,26 ± 2,532 (1–10)	3,04 ± 2,269	3,42 ± 2,728	0,545
GTCS Age	15,80 ± 3,895 (5–40)	15,46 ± 4,220	16,02 ± 3,665	0,320
Disease duration	12,35 ± 8,517 (2–41)	11,89 ± 7,940	12,64 ± 8,878	0,534
Follow up duration	9,98 ± 5,45 (2–25)	10,62 ± 5,72	9,59 ± 5,26	0,179

GTCS, generalized tonic-clonic seizure; SD,standard deviation.

myoclonic jerking, predominantly on awakening, with GTC seizures and/or the absence of seizures; 2. No evidence of a neurological or intellectual deficit; 3. A normal EEG, or a single abnormal EEG featuring generalized spike-wave or polyspike-wave discharges;4. Follow-up by a single neurologist for at least 2 years. Patients with brain stem injuries due to trauma or infections were excluded, as were those who had significant structural pathology on imaging studies (e.g., computed tomography (CT) or magnetic resonance imaging (MRI)). Finally, the study included 215 patients who met the study inclusion criteria. Written informed consent was obtained from each patient. The study protocol was approved by the institutional Ethics Committee, and the study was conducted in accordance with the principles of the Declaration of Helsinki.

Interviews with patients were conducted either face-to-face (in outpatient clinics) or via telephone. Cranial imaging studies (MRI and/or CT), laboratory tests, and electroencephalogram (EEG) recordings in the patients' charts were evaluated. Twenty-one-channel EEG recordings were collected using the international 10–20 electrode placement system. Sleep-deprived EEG (4 h of sleep during the preceding 24 h) featuring 3 min of hyperventilation and photic stimulation (1–30 flashes/s) was performed for most patients. EEG asymmetries were defined as focal slowing, focal epileptiform discharges, asymmetric generalized spike/polyspike/wave discharges (exhibiting amplitude asymmetry greater than 50%), or lateralized sharp waves with spike/polyspike/slow wave complexes evident on more than one recording.

The final clinical examination was performed during face-to-face interviews. A follow-up form was prepared to record clinical and demographic characteristics. Sex and current age, age at the time of the first seizure, disease duration, and duration of follow up were recorded for each patient. Disease duration was defined as the time between the age at the first seizure (as recorded on the patients' charts) and the date of the last seizure. The duration of follow up was defined as the time between the initial admission and the date of the last visit. The type of seizure onset (i.e., absence, generalized tonic–clonic, or myoclonic), type of persistent seizure, and GTC seizure status as revealed by EEG findings and seizure diaries. The status of status epilepticus (SE), presence of clinical photosensitivity, photoparoxysmal response (PPR) on routine EEG recordings performed throughout the follow-up period, history of febrile convulsions and family history of epilepsy, and consanguinity between parents were examined. Furthermore, factors that may aggravate seizures were evaluated and recorded; these included substance or alcohol abuse, sleep deprivation, stress, menstrual period, fatigue, awakening in the morning, light exposure and fasting, computer usage or television viewing, and pregnancy. The first AED, add-on AEDs, total number of AEDs, onset of VPA therapy, remission and maintenance doses, presence of remission and refractoriness, and drug-related side effects were recorded. Patients were also evaluated to determine the presence of psychiatric illnesses and other comorbid conditions.

All patients were divided into two groups on the basis of remission and refractoriness during clinical follow up. Remission was defined as a seizure-free (i.e., myoclonic, absence, and/or GTC) period of at least 2 years. Factors that may have caused termination of the remission period were evaluated; these included irregular drug use, drug side effects, and drug change or discontinuation for any reason. Patients in whom the 2-year seizure-free period could not be achieved were included in the refractory group. Potential factors that may have caused refractoriness in this group were characterized; these included irregular drug use, inappropriate lifestyle (e.g., substance or alcohol abuse and shift work), presence of a psychiatric disorder, and other comorbid conditions. The dose of therapy during remission and the duration of the remission period were recorded for VPA and other AEDs in patients who achieved remission. Analysis relied on drug doses rather than serum concentrations. Patients who achieved remission with VPA monotherapy were further divided into two groups according to the dose of therapy during remission: those receiving VPA ≤ 750 mg/day and those receiving > 750 mg/day. Variables were compared between groups according to the dose of VPA therapy.

2.1. Statistical analysis

Statistical analysis was performed using SPSS software, version 22.0 (IBM Corp., Armonk, NY, USA). Data are expressed as mean ± standard deviation (SD), median (min–max), number, and frequency. The *t*-test was used to compare parametric values between groups; the chi-squared test was used to compare categorical variables. A p value of < 0.05 was considered statistically significant.

3. Results

In total, 215 patients with JME were included in this study; there were 132 patients (61.4%) in the remission group and 83 patients (38.6%) in the refractory group. There were no statistically significant differences between groups in terms of sex, age, age at the time of the first seizure, time from the first seizure to diagnosis, age at first GTC seizure, duration of epilepsy, or duration of follow up (Table 1). The rate of absence seizures during the course of the disease was significantly higher in the refractory group than in the remission group ($p = 0.001$). SE was observed during the follow-up period in eight patients (9.6%) in the refractory group; this rate was significantly higher than that in the remission group ($p = 0.008$). Family history of epilepsy was remarkable in 112 patients (52.1%), whereas 35 patients (16.3%) had history of febrile seizures and 46 patients (21.4%) had consanguineous parents; these proportions did not significantly differ between groups. Eighteen patients (8.4%) had comorbid conditions. In the remission group, three patients (2.3%) had hypothyroidism, and one patient (0.7%) had valvular heart disease. In the refractory group, six patients (7.2%) had hypothyroidism, one patient (1.2%) had valvular heart disease, one patient (1.2%) had hepatitis B infection, one patient (1.2%) had autism, and one patient (1.2%) had tic disorder. The rate of comorbid conditions was significantly higher ($p = 0.001$) in the refractory group, as was the rate of psychiatric disorders ($p = 0.008$)

Table 2
Clinical and demographic differences between groups.

	Total	Refractoriness	Remission	p
Type of seizure onset, n (%)				
Absence	27 (12,6)	19 (22,9)	8 (6,1)	0,001*
GTCS	141 (65,9)	59 (71,1)	82 (62,1)	0,178
Myoclonic	81 (37,7)	29 (34,9)	52 (39,4)	0,512
Type of persisting seizure, n (%)				
Absence	61 (28,4)	44 (53,0)	17 (12,9)	0,001*
GTCS	198 (92,1)	79 (95,2)	119 (90,2)	0,183
Myoclonic	211 (98,1)	81 (97,6)	130 (98,5)	0,641
Status Epilepticus, n (%)	10 (4,7)	8 (9,6)	2 (1,5)	0,008*
Photosensitivity, n (%)	31 (14,4)	11 (13,3)	20 (15,2)	0,700
Aura, n (%)	32 (14,9)	17 (20,5)	15 (11,4)	0,067
History of CAE, n (%)	9 (4,2)	6 (7,2)	3 (2,3)	0,080
Febril seizures, n (%)	35 (16,3)	17 (20,5)	18 (13,6)	0,129
Family history of epilepsy, n (%)	112 (52,1)	45 (40,2)	67 (59,8)	0,675
Consanguinity, n (%)	46 (21,4)	20 (24,1)	26 (19,7)	0,444
Comorbid conditions, n (%)	18 (8,4)	14 (16,9)	4 (3,0)	0,001*
Pyschiatric disorders, n (%)	34 (15,8)	20 (24,1)	14 (10,6)	0,008*

GTCS, generalized tonic clonic seizure; CAE, childhood absence epilepsy.
* Statistically significant at $p < 0.05$.

(Table 2).

Sleep deprivation was the most common factor triggering seizures in 169 patients (78.6%). Stress (n = 114, 53%), fatigue (n = 66, 30.7%), menstruation (n = 41, 19.1%), light exposure (n = 26, 12.1%), fasting (n = 17, 7.9%), computer usage/television viewing (n = 16, 7.4%), alcohol use (n = 11, 5.1%), and puerperium (n = 11, 5.1%) were among the triggering factors reported by patients in this study. There were no significant differences in seizure-triggering factors.

The study groups were evaluated with respect to first-line treatment options; there was no significant relationship between drug options and gender (Table 3). Additionally, VPA was the most commonly preferred first-line pharmacological agent in 125 patients (n = 40 in the refractory group and n = 85 in the remission group). The rate of refractoriness was significantly higher among patients who received medications other than VPA as first-line treatment, whereas the rate of remission was higher in patients who received VPA as first-line treatment (p = 0.019). The mean VPA doses at the start of therapy did not significantly differ between groups (p = 0.058) (Table 3).

The dose of VPA was ≤750 mg in 77.6% of patients who achieved remission. Remission was more likely to occur with VPA therapy in the second and third decades of life, and the rate of remission declined in later decades (p = 0.001). The mean VPA dose during remission was significantly lower in females (p = 0.004). Furthermore, the mean VPA dose during remission was significantly higher in patients with absence seizures (p = 0.026) (Table 4).

The 132 patients in the remission group were divided into three subgroups based on their treatment approaches. Remission was achieved with VPA alone in 116 patients (87.9%), with VPA and an add-on AED in 7 patients (5.3%), and with medications other than VPA in 9 patients (6.8%). Thirteen patients who were in remission during the follow-up period chose to discontinue treatment; two of these patients had recurrent seizures. Eleven patients achieved sustained remission. The mean duration of remission in these 11 patients was 8.9 ± 5.76 (4–24) years; the mean age at achieving remission was 25.10 ± 7.18 (14–38) years, and the mean age of the patients during the study was 34 ± 7.23 (22–46) years. The mean duration of remission was 4 years in the two patients who experienced relapse. One patient who achieved remission with other agents did not experience relapse after drug discontinuation.

The factors contributing to relapse were irregular drug use (mean duration of remission: 5.80 ± 3.57 years) in 15 patients (11.4%), drug change due to side effect (mean duration of remission: 3.60 ± 1.40 years) in five patients (3.8%), and drug discontinuation after 4 years of remission in two patients (1.5%). The reason for refractoriness was irregular lifestyle in 16 patients (19.2%), presence of a comorbid psychiatric disorder in 7 patients (8.4%), and irregular drug use in 17 patients (20.4%); notably, no obvious reason could be identified in 43 patients (51.8%).

Abnormal EEG findings were detected in 191 patients (88.8%). EEG recordings after sleep deprivation were obtained for most patients. EEG asymmetries were evident in 42 (21.9%) and usually featured asymmetric waves (rarely, lateralized sharp waves) with spike/polyspike/slow wave complexes or discharges exhibiting voltage asymmetries of over 50%. Focal epileptiform discharges were noted in five cases. When the groups were compared in terms of EEG findings, asymmetric changes were more common in the refractory group, whereas generalized epileptiform discharges were more common in the remission group (p = 0.001). Asymmetric changes were significantly more common in males (p = 0.021) (Table 5).

Sixty-two pregnancies occurred in 42 women, 50 of which were intended; four of these 62 pregnancies ended in abortion. During the pregnancy period, 34 patients (54.8%) used VPA, 15 patients (24.2%) used medications other than VPA (three used carbamazepine, two used diphenylhydantoin, five used lamotrigine, and five used levetiracetam), one patient (1.6%) used VPA and lamotrigine, and 12 patients (19.3%) did not use any medications. The dose of VPA during pregnancy was ≤500 mg in 28 patients, 500–1000 mg in four patients, and ≥1000 mg in three patients. One of three patients who used VPA at a dose of ≥1000 mg also had thyroid disease; one of the remaining two patients

Table 3
First-line treatment options and outcome.

	Refractoriness			Remission			Total			p
	Male	Female	Total	Male	Female	Total	Male	Female	Total	
VPA, n	16	24	40	36	49	85	52	73	125	0,803
Carbamazepine, n	7	8	15	10	14	24	17	22	39	0,759
Diphenylhydantoin, n	4	1	5	3	2	5	7	3	10	0,490
Oxcarbazepine, n	6	3	9	3	4	7	9	7	16	0,341
Phenobarbital, n	1	1	2	1	1	2	2	2	4	0,833
Lamotrigin, n	1	3	4	–	2	2	1	5	6	0,667
Levetiracetam, n	5	2	7	–	2	2	5	4	9	0,073
Topiramat, n	1	–	1	–	5	5	1	5	6	0,014*
Total, n			83			132			215	0,183
VPA, n (%)	40 (48,2%)			85 (64,4%)			125			0,019*
Other, n (%)	43 (51,8%)			47 (35,6%)			90			
VPA dose, Mean ± SD	735,90 ± 335,60			632,56 ± 251,44			664,75 ± 284,20			0,058

VPA, valproic acid.
* Statistically significant at $p < 0.05$.

Table 4
Remission VPA dose.

		VPA dose Mean ± SD (n; %)	p
Sex	Male (n:52)	769,23 ± 327,82	0,004*
	Female (n:71)	612,68 ± 238,25	
Absence seizure	Present (n:17)	823,5 ± 286,79	0,026*
	Absent (n:103)	655,34 ± 276,20	
Age	Total	21,73 ± 7,60 (n:123)	
	1.decad	9,00 ± 1,41 (2; 1,5%)	0,001*
	2.decad	16,21 ± 2,31 (6; 46,2%)	
	3.decad	25,11 ± 2,75 (46; 34,8%)	
	4.decad	34,00 ± 2,69 (12; 9,09%)	
	5.decad	48,00 ± 0,00 (1; 0,7%)	
	6.decad	55,00 ± 0,00 (1; 0,7%)	
Classification according to VPA dose	≤750 mg/day	93; 75,6%	0,001*
	> 750 mg/day	30; 24,4%	

SD, standard deviation.
* Statistically significant at $p < 0.05$.

was in the refractory group.

Among all pregnancies, congenital anomaly was observed in nine infants (14.5%). Four infants had major malformations (6.4%), whereas five infants (8%) had minor congenital malformation and dysmorphic findings. In the major malformation group, two infants (3.2%) had atrial septal defect and two infants (3.2%) had skeletal anomaly. The mean VPA dose was 500 ± 279.50 mg/day among all patients who had infants with malformations. The mean VPA dose was significantly higher in the major malformation group than in the minor malformation group (p = 0.004) (Table 6). When the infants were evaluated for the presence of other diseases, one infant (1.7%) had congenital hypothyroidism (VPA: 750 mg/day), one infant (1.7%) had phenylalaninemia (VPA: 500 mg/day), one infant (1.7%) had autism (VPA: 750 mg/day), and one infant (1.7%) had dyslexia, hyperactivity, and attention deficit disorder (VPA: 750 mg/day).

Table 6
Malformations.

	Patient		VPA dose (mg/day)		p
Major anomalies	1	Skeletal anomaly	750,00	750 ± 204,12	0.004*
	2	Skeletal anomaly	500,00		
	3	ASD	1000,00		
	4	ASD	750,00		
Minor anomalies and dysmorphic findings	1	phimosis	500,00	300 ± 111,80	
	2	frenulum	250,00		
	3	frenulum	250,00		
	4	cafeu-lait-spot	250,00		
	5	cafeu-lait-spot	250,00		
Total, n; mean ± SD	9			500 ± 279.50	

ASD, atrial septal defect.
* Statistically significant at $p < 0.05$.

4. Discussion

Overall, VPA monotherapy in the present study achieved a remission rate of 64.4%. In the remission group, the rate increased to 75.6% for patients using low-dose VPA (≤ 750 mg/day) therapy. Previous studies reported seizure control in 19–80% of patients receiving VPA monotherapy [9,11–13]. In a large series involving 201 patients with JME, Jayalakshmi et al. reported a seizure-free period of at least 2 years in 19% of patients who were receiving VPA therapy; this number likely differs from those reported in previous studies because of the high number of patients (33%) with comorbid psychiatric disorders [13]. Gelisse et al. reported pseudoresistance and truly resistant epilepsy in 9.7% and 15.5% of 155 patients with JME, respectively. They found that resistance to drug therapy increased in patients with psychiatric disorders and a combination of three seizure types. They also found that seizure control was poor with VPA mono- or polytherapy in patients with a prolonged duration of epilepsy, a combination of three seizure types, and epileptiform discharges in EEG [10]. However, Geithner et al. found no significant relationship between JME-specific seizure types and long-term outcomes [9]. In 1997, Jain et al. reported good long-term prognosis only in a subgroup of patients with JME who had benign myoclonic seizures [14]. Baykan et al. reported a true resistance rate of 16.7% in patients with JME and suggested that this may be related to comorbid thyroid diseases or the presence of psychiatric disorders [15]. In the present study, remission was achieved in 64.4% of patients who began VPA monotherapy as first-line treatment (p = 0,019, Table 4). Comorbid conditions and psychiatric disorders were significantly more common in the refractory group (Table 2). In the literature, it has been reported that thyroid diseases may cause fluctuations in seizure control by increasing AED resistance in patients with JME [16,17]. In our series, hypothyroidism was the most common comorbid condition in the refractory group, although no significant relationship was found between the presence of thyroid disease and refractoriness. Consistent with the literature, the present study found no

Table 5
EEG Findings.

	Total	Refractoriness	Remission	p	Female	Male	
EEG features, n (%)	215	83 (38,6)	132 (61,4)		121 (56,2)	94 (43,7)	
Normal EEG, n (%)	24 (11,2)	11 (13,3)	13 (9,8)	0,803	16 (13,2)	8 (8,5)	0,118
Abnormal EEG, n (%)	191 (88,8)	72 (86,7)	119 (90,2)	0,602	105 (86,7)	86 (92,5)	0,217
GED	149 (78,1)	40 (55,6)	109 (91,5)		88 (72,7)	61 (64,9)	0,021*
Asymmetric abnormalities	42 (21,9)	32 (44,4)	10 (8,4)	0,001*	17 (14,0)	25 (26,6)	
Positive PPR, n (%)	30 (13,9)	23 (76,6)	7 (23,3)	0,001*			

GED, generalized epileptiform discharges; PPR, Photoparoxysmal response at EEG.
* Statistically significant at $p < 0.05$.

relationships between remission and the following factors: duration of epilepsy, age at disease onset, sex, family history of epilepsy, or time to diagnosis on remission [11]. Medical history of febrile seizures has been more commonly reported in patients with JME than in the normal population (4.4–10%) [18]. This rate was 16.3% in the present study, which was higher than that reported in the literature. This difference can likely be explained by ethnic and genetic differences, as well as by the increased rate of consanguineous marriage in the Turkish population.

Various EEG profiles have been reported in patients with JME. The photoparoxysmal response is common (8–90% of patients) [19], and Appleton et al. reported that 90% of JME patients developed a PPR upon intense and prolonged stimulation [20]. The PPR prevalence varies by age, sex, ethnicity, medication, and methodology. EEG timing (sensibility is higher in the morning) [21] and sleep deprivation [22] increase the incidence of PPR. Medication (especially VPA) is effective in patients with PPR [14]. We found that clinical photosensitivity noted in charts was more prevalent in the remission group and PPR more prevalent in the refractory group, perhaps reflecting both the VPA medication status and methodology employed. We suggest that the refractory group responded poorly to VPA, increasing the PPR rate. EEG timing may also be in play. Unfortunately, not all EEGs were performed early in the morning, and some patients were not sleep-deprived.

Several studies have shown that focal EEG findings are associated with increasing drug resistance [11,23]; however, other studies have suggested no prognostic relationship [24–26]. The rates of SE, asymmetric changes in EEG were higher in our refractory group. Possible mechanisms include imbalance between cerebral hemispheres, presence of a focal cortical pathology (e.g., micro-dysgenesis), and hyperexcitability of cortical structures at a lower threshold due to genetic and environmental factors [27]. These data indicate that the chance of achieving remission may be lower with low doses in patients with SE and asymmetric changes on EEG. Furthermore, asymmetric changes on EEG occurred significantly more commonly in male patients. Such associations have not been previously shown in the literature. Moreover, the increased rate of remission with low-dose VPA monotherapy in female patients may be a result of the lower rate of asymmetric changes on EEG in female patients.

Auras (especially visual auras) have been described in JME patients, often overlapping with idiopathic photosensitivity of the occipital lobe and/or temporal lobe epilepsy [24,28,29]. The latter conditions render both diagnosis and treatment difficult. Taylor et al. considered that shared genetic determinants explain the overlap in clinical features [28]. Atypical seizure characteristics including aura and post-ictal confusion were associated previously with drug resistance in JME patients [11], but we found no such association. Further work is needed.

There has been a limited number of studies regarding the recommended therapeutic dose of VPA therapy. Although the daily recommended dose is 1000–2000 mg [30], Panayiotopolus et al. were the first to report successful treatment with low-dose VPA therapy (400 mg/day) [12]. Karlovassitou-Koniari et al. treated 14 patients with JME using a single daily dose of VPA 500 mg for a mean duration of 35.6 months; they reported successful control of GTC seizures and absence seizures in all patients [31]. However, those authors also used clonazepam in the low-dose group; among the 14 patients included in that study, high-dose VPA was administered to six patients for 1–2 years and to three patients for < 1 year. De Toffol and Auret reported the successful treatment of six patients who were treated with a single dose of VPA 500 mg and then maintained on this dose [32]. Miro et al. prospectively evaluated the efficacy of low-dose VPA (< 1000 mg/day) in 54 patients with idiopathic generalized epilepsy (IGE). The initial treatment (23 with JME, 17 with juvenile absence epilepsy, and 14 with GTC epilepsy) involved high-dose VPA in 45 patients (> 1000 mg/day), polytherapy in 8 patients, and low-dose VPA in 9 patients. They reported seizure control by reducing the dose of VPA to < 600 mg/day at the end of the 2-year follow-up period in 13 patients (92.9%) with GTC and 18 patients (78.3%) with JME; in contrast, the rate of seizure control was only 29.4% in patients with juvenile absence epilepsy, suggesting that absence seizures may be the cause of resistance [33]. In that study, the authors indicated that the type of epilepsy was the most important contributor to the efficacy of low-dose therapy; however, their study involved a small number of patients and a short follow-up duration. In the present study, which involved a larger number of patients who were followed for a longer duration, there were higher rates of the onset and persistence of absence seizures in the refractory group. In the remission group, the VPA dose was significantly higher in patients with absence seizures compared with patients with other types of seizures. This finding indicates the importance of regular long-term clinical follow up for detecting changes in seizure type and JME subgroup as well as for monitoring disease course and planning treatment. We speculate that the use of VPA as first-line therapy may increase the chance of remission.

Although CBZ is considered inappropriate for treatment of JME, seizures were controlled by CBZ in 24 patients of our remission group who had earlier exhibited persistent, generalized, tonic-clonic seizures. CBZ was given because of inadequate responses to first-line treatments. Also, if the seizures had been controlled with CBZ prior to referral to us, we did not change the drug. In addition, if the seizures recurred after CBZ withdrawal, we recommenced the drug. Kenyon et al. also described a group of refractory IGE patients whose seizures were controlled with CBZ [34]. It was suggested that IGE syndromes are genetically heterogeneous, and some patients are responsive to CBZ. CBZ was effective in IGE patients who failed to respond to first-line AEDs, especially in those with primary, generalized, tonic-clonic seizures [34]. The mechanism of action of CBZ in such JME patients requires further exploration, but CBZ must be used with caution because it may exacerbate or increase absence seizure frequency and/or myoclonic seizure frequency.

The increased incidence of JME among adolescents and in female patients increases the importance of drug selection and the achievement of efficacy at low doses [35]. Some studies have reported an increased risk of congenital malformations with the use of AEDs [36]. Moreover, there is an increased risk of teratogenicity with VPA compared to other AEDs; this risk increases in a dose-dependent manner [37,38]. Some data are suggestive of associations between prenatal VPA exposure and postnatal cognitive developmental failure, as well as between prenatal VPA exposure and the development of autism spectrum disorders [39]. The 2018 data of the International Registry of Antiepileptic Drugs and Pregnancy showed that VPA increases the risk of malformations in a dose-dependent manner [40]. The prevalence of major congenital events in association with the use of VPA at doses of 100–3000 mg/day was reported to be 10.3% (8.8–12%). Notably, the risk of major congenital events persists even with low doses; the prevalence rate was 6.3% (4.5–8.6%) among patients using doses of ≤650 mg/day. The results of the present study are consistent with these data. The VPA dose was significantly higher in the major malformation group than in the minor malformation group ($p = 0.004$). The rate of consanguineous marriage in the general Turkish population, as well as that among the parents of the current study population, may be important factors that may have further increased the risk of malformations. The finding that lower doses of VPA therapy achieved seizure-free periods among females in the remission group supports the use of low-dose VPA in women of reproductive age. However, in accordance with the recent regulations of the European Medicines Agency, VPA can be used only in women who fail to respond to alternative therapies and after strict pregnancy control measures have been implemented. However, for patients who respond only to VPA, low-dose VPA monotherapy could be appropriate (ideally ≤500 mg daily) [41].

In conclusion, although many studies have investigated the clinical characteristics of JME, few have evaluated treatment selection and therapeutic dose. The inadequacy of long-term follow up and the

inability to clearly identify clinical differences are regarded as the two factors that may have the greatest impact on treatment selection. The large number of patients and wide age range in the present study enabled us to monitor clinical differences that may occur during long-term follow up. Based on our study results, we suggest that a high rate of remission can be achieved by use of low-dose VPA therapy. VPA is effective for treatment of idiopathic generalized epilepsy; however, current guidelines caution against the use of VPA during pregnancy. According to recent regulations, drug dose selection is as important as the selection of the drug itself. For women with generalized epilepsies that cannot be controlled with other AEDs, VPA may be prescribed; however, the dose should remain as low as possible. Thus, based on the close clinical follow up, our results may have important implications for demonstrating that low-dose VPA maintains seizure control for women with JME.

Ethical publication statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. Ethical approval the study was approved by Istanbul Cerrahpaşa University Ethics Committee.

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Contributions

Reyhan G. M.D.: Database development, study design, data collection, statistical analysis, manuscript preparation. Şenay A, M.D. and Çiğdem Ö, PhD.: Database development, study design, statistical analysis, manuscript preparation.

References

[1] Jallon P, Latour P. Epidemiology of idiopathic generalized epilepsies. Epilepsia 2005;46(9):10–4.
[2] Arzimanoglou A, Guerrini R, Aicardi J. Epilepsies with predominantly myoclonic seizures. Aicardi's epilepsy in children. Philadelphia: Lippincott Williams & Wilkins; 2004. p. 58–80.
[3] Genton P, Gelisse P, Thomas P. Juvenile myoclonic epilepsy today: current definitions and limits. In: Schmitz B, Sander T, editors. Juvenile myoclonic epilepsy: the Janz syndrome. Petersfield: Wrighton Biomedical Publishing; 2000. p. 11–32.
[4] Gelisse P, Malafosse A, Genton P, Thomas P, Moulard B, BaldyMoulinier M. Aspects génétiques de l'épilepsie myoclonique juvénile (genetic aspects of Juvenile myoclonic epilepsy). Epilepsies 2001;13:97–102.
[5] Pedersen SB, Petersen KA. Juvenile myoclonic epilepsy: clinical and EEG features. Acta Neurol Scan 1998;30:389–99.
[6] Kasteleijn-Nolst Trenité DG, Schmitz B, Janz D, Delgado-Escueta AV, Thomas P, Hirsch E, et al. Consensus on diagnosis and management of JME: from founder's observations to current trends. Epilepsy Behav 2013;28(1):87–90.
[7] Delgado-Escueta AV, Enrile-Bascal F. Juvenile myoclonic epilepsy of Janz. Neurology 1984;34:285–94.
[8] Martínez-Juárez IE, Alonso ME, Medina MT, Durón RM, Bailey JN, López-Ruiz M, et al. Juvenile myoclonic epilepsy subsyndromes: family studies and long term follow up. Brain 2006;129(5):1269–80.
[9] Geithner J, Schneider F, Wang Z, Berneiser J, Herzer R, Kessler C, et al. Predictors for long term seizure outcome in juvenile myoclonic epilepsy:25-63 years of follow-up. Epilepsia 2012;53(8):1379–86.
[10] Gelisse P, Genton P, Thomas P, Rey M, Samuelian JC, Dravet C. Clinical factors of drug resistance in juvenile myoclonic epilepsy. J Neurol Neurosurg Phychiatry 2001;70(2):240–3.
[11] Fernando-Dongas MC, Radtke RA, Van Landingham KE, Husain AM. Characteristics of valproic acid resistant juvenile myoclonic epilepsy. Seizure 2000;9(6):385–8.
[12] Panayiotopoulos CP, Obeid T, Tahan AR. Juvenile myoclonic epilepsy: a 5-year prospective study. Epilepsia 1994;35(2):285–96.
[13] Jayalakshmi S, Vooturi S, Bana AK, Sailaja S, Somayajula S, Mohandas S. Factors associated with lack of response to valproic acid monotheraphy in juvenile myoclonic epilepsy. Seizure 2014;23(7):527–32.
[14] Jain S, Padma MV, Maheshwari MC. Occurrence of only myoclonic jerks in juvenile myoclonic epilepsy. Acta Neurol Scand 1997;95:263–7.
[15] Baykan-Kurt B, Gökyiğit A, Çalışkan A. Juvenile myoclonic epilepsy. Arch Neuropsychiatry 1991;28(1):41–8.
[16] Su YH, Izumi T, Kitsu M, Fukuyama Y. Seizure threshold in juvenile myoclonic epilepsy with Graves disease. Epilepsia 1993;34:488–92.
[17] Obeid T, Awada A, al Rajeh S, Chaballout A. Thyroxine exacerbates absence seizures in juvenile myoclonic epilepsy. Neurology 1996;47:605–6.
[18] Genton P, Salas Puig X, Tunon A, Lahoz C, Del Socorro Gonzales Sanchez M. JME and related syndromes: clinical and neurophysiologic aspects. In: Malafosse A, Genton P, Hirsch E, Marescaux C, BroglinBemasconi R, editors. Idiopathic generalized epilepsies. London: R. John Libbey; 1994. p. 253–65.
[19] Canevini MP, Mai R, Di Marco C, Bertin C, Minotti L, Pontrelli V, et al. Juvenile myoclonic epilepsy of Janz: clinical observations in 60 patients. Seizure 1992;1:291–8.
[20] Appleton R, Beirne M, Acomb B. Photosensitivity in juvenile myoclonic epilepsy. Seizure 2000;9:108–11.
[21] Labate A, Ambrosio R, Gambardella A, Sturniolo M, Pucci F, Quattrone A. Usefulness of a morning routine EEG recording in patients with juvenile myoclonic epilepsy. Epilepsy Res 2007;77:17–21.
[22] Scollo-Lavizzari G, Scollo-Lavizzari GR. Sleep and sleep deprivation, photosensitivity and epilepsy. Eur Neurol 1974;11:1–21.
[23] Matsuoka H. The seizure prognosis of juvenile myoclonic epilepsy. Jpn J Psychiatry Neurol 1992;46(2):293–6.
[24] Baykan B, Altındag EA, Bebek N, Ozturk AY, Aslantas B, Gurses C. Myoclonic seizures subside in the fourth decade in juvenile myoclonic epilepsy. Neurology 2008;70(22):2123–9.
[25] Guaranha MS, Filho GM, Lin K, Guilhoto LM, Caboclo LO, Yacubian EM. Prognosis of juvenile myoclonic epilepsy is related to endophenotypes. Seizure 2011;20(1):42–8.
[26] Letourneau K, Cieuta-Walti C, Deacon C. Epileptiform asymmetries and treatment response in juvenile myoclonic epilepsy. Can J Neurol Sci 2010;37(6):826–30.
[27] Lancman ME, Asconape JJ, Penry JK. Clinical and EEG asymmetries in juvenile myoclonic epilepsy. Epilepsia 1994;35:302–6.
[28] Taylor I, marini C, Johnson MR, Tuner S, Berkovic SF, Scheffer IE. Juvenile myoclonic epilepsy and idiopathic photosensitive occipital lobe epilepsy: is there overlap? Brain 2004;127(8):1878–86.
[29] Koutroumanidis M, hennessy MJ, Elwes RD, Binnie CD. Coexistence of temporal lobe and idiopathic generalized epilepsies. Neurology 1999;53(3):490–5.
[30] Davis R, Peters DH, McTavisch D. Valproic acid: a reappraisal of its pharmacological properties and clinical efficacy in epilepsy. Drugs 1994;47:332–7.
[31] Karlovassitou-Koniari A, Alexiou D, Angelopoulos P, Armentsoudis P, Dimitrakoudi E, Delithanasis I, et al. Low dose sodium valproate in the treatment of juvenile myoclonic epilepsy. J Neurol 2002;249(4):396–9.
[32] De Toffol B, Autret A. Tratiement de l'epilepsie myoclonique juvenile par des faibles doses de valproate de sodium. Rev Neurol (Paris) 1996;152:708–10.
[33] Miro J, Aiguabella M, Veciana M, Juvany R, Santurino M, Leiva E, et al. Low-dose sodium valproate in the treatment of idiopathic generalized epilepsies. Acta Neurol Scand 2014;129(5):e20–3. https://doi.org/10.1111/ane.12216.
[34] Kenyon K, Mintzer S, Nei M. Carbamazepine treatment of generalized tonic-clonic seizures in idiopathic generalized epilepsy. Seizure 2014;23:234–6.
[35] Veroniki AA, Cogo E, Rios P, Straus SE, Finkelstein Y, Kealey R, et al. Comparative safety of anti-epileptic drugs during pregnancy: a systematic review and network meta-analysis of congenital malformations and prenatal outcomes. BMC Med 2017;15(1):95.
[36] Vajda FJ, O'Brien TJ, Graham JE, Lander CM, Eadie MJ. Dose dependence of fetal malformations associated with valproate. Neurology 2013;81:999–1003.
[37] Hernández-Vanegas LE, Jara-Prado A, Ochoa A, Rodríguez Y Rodríguez N, Durón RM, Crail-Meléndez D, et al. High dose versus low-dose valproate for the treatment of juvenile myoclonic epilepsy: Going from low to high. Epilepsy Behav 2016;61:34–40. https://doi.org/10.1016/j.yebeh.2016.04.047. Epub 2016 June 11.
[38] Tomson T, Battino D, Bonizzoni E, Craig J, Lindhout D, Sabers A, et al. Dose- dependent risk of malformations with antiepileptic drugs: an analysis of data from the EURAP epilepsy and pregnancy registry. Lancet Neurol 2011;10:609–17.
[39] Christensen J, Gronborg TK, Sorensen MJ, Schendel D, Parner ET, Pedersen LH, et al. Prenatal valproate exposure and risk of autism spectrum disorders and childhood autism. JAMA 2013;309:1696–703.
[40] Tomson T, Battino D, Bonizzoni E, Craig J, Lindhout D, Perucca E, et al. Comparative risk of major congenital malformations with eight different antiepileptic drugs: a prospective cohort study of the EURAP registry. Lancet Neurol 2018;17(June):530–8.
[41] Serafini A, Gerard E, Genton P, Crespel A, Gelisse P. Treatment of juvenile myoclonic epilepsy in patients of child-bearing potential. CNS Drugs 2019;33(3):195–208. https://doi.org/10.1007/s40263-018-00602-2.