University of Belgrade
Faculty of Medicine
Department of Child and Adolescent Neurology and Psychiatry

Original study
Originalni naučni rad
UDK 616.853-036.1-085
DOI: 10.2298/MPNS1412372J

TERMINAL REMISSION IS POSSIBLE IN SOME PATIENTS WITH JUVENILE MYOCLONIC EPILEPSY WITHOUT THERAPY

TERMINALNA REMISIJA BEZ TERAPIJE MOGUĆA JE KOD BOLESNIKA SA JUVENILNOM MIOKLONIČNOM EPILEPSIJOM

Nebojša J. JOVIĆ, Ana KOSAĆ and Miloš D. BABIĆ

Summary

Introduction. Juvenile myoclonic epilepsy is considered to be a chronic disease requiring lifelong antiepileptic treatment. The aim of this study was both to identify factors predicting the kind of seizure control and to investigate the outcome in patients after therapy withdrawal. **Material and Methods.** The study included 87 patients (49 female, 38 male), aged from 17.5 to 43.5 years, referred to our Department between 1987 and 2008, with the seizure onset at the age of 14.3±2.9, and followed up for 13.3±5.8 years on average (from 5 to 23 years). **Results.** Sixty seven (77.0%) patients were fully controlled; whereas 13.8% had persistent seizures and 9.2% showed pseudoresistance. The combination of three seizure types and focal electroencephalogram features were independent factors of poor seizure control. Therapy was discontinued in 34 patients either by the treating physician (in 21 patients) or by the patients themselves (in 13 cases). In 18 subjects, all seizure types relapsed after 1.1 year on average (from 7 days to 4 years) and therapy was resumed in them. All patients but three (10/13), who stopped the treatment themselves, experienced recurrences. Seizure freedom off drugs was recorded in 10.3% patients. Nonintrusive myoclonic seizures recurred in 0.5-3 years as their only seizure type in four patients, but without reintroducing medication in three patients. **Conclusion** Combination of seizure types and focal electroencephalogram features are significant factors of pharmacoresistancy. Continuous pharmacotherapy is required in majority of patients, although about 10% of them appear to have permanent remission without therapy in adolescence.

Key words: Myoclonic Epilepsy, Juvenile; Treatment Outcome; Anticonvulsants; Seizures; Drug Therapy; Recurrence; Drug Resistance; Risk Factors; Electroencephalography

Sažetak

Uvod. Juvenilna miokloničnа epilepsija smatra se hroničnim stanjem koje zahteva doživotnu primenu antiepileptičkih lekova. Cilj ovog istraživanja bio je da utvrdi činioce predikcije vrste kontrole napada i da istraži ishod posle obustave terapije kod ovih bolesnika. **Materijal i metode.** Sačinjena je grupa od 87 bolesnika (49 ženskog, 38 muškog pola), upućenih na našu Kliniku u periodu 1987–2008. godine, starosti 17,5–43,5 godina, sa prosečnim početkom napada u životnom dobu od 14,3±2,9 godina i praćenih u proseku 13,3±5,8 godina (u rasponu 5–23 godine). **Rezultati.** Potpuna kontrola napada postignuta je kod 77% bolesnika, dok su se kod 13,8% napadi i dalje javljali a kod 9,2% postojala je pseudorezistencija. Pojava tri tipa napada i žarišne elektroencefalografske promene su nezavisni prediktivni faktori loše kontrole napada. Terapija je obustavljena kod 34 bolesnika: na predlog terapeuta kod 21 i po sopstvenoj odluci 13 bolesnika je samo obustavilo terapiju. Kod 18 ispitanika došlo je do recidiva svih tipova napada posle prosečnog perioda od 1,1 godine (raspon 7 dana do 4 godine) pa je terapija ponovo uvedena. Većina (10/13) je imala recidiv napada posle samoinicijativne obustave terapije. Potpuna remisija napada bez terapije zabeležena je kod 10,3% bolesnika. Blagi miokloničnі napadi javili su posle 0,5–3 godina kao jedini tip napada kod 4 osobe, bez ponovnog uvođenja leka. **Zaključak.** Više tipova napada i žarišne elektroencefalografske promene značajni su činioci farmakorezistencije. Stalna primena lekova neophodna je kod većine bolesnika sa juvenilnom miokloničnom epilepsijom, iako oko 10% postiže u adolescenciji dugotrajnu remisiju bez hronične terapije.

Ključne reči: Juvenilna miokloničnа epilepsija; Ishod lečenja; Antiepileptici; Epileptični napadi; Terapija; Rekurenca; Rezistencija lekova; Faktori rizika; Elektroencefalografija

Introduction

Juvenile myoclonic epilepsy (JME) is a common idiopathic generalized epilepsy syndrome with the prevalence of 6 to 12% among all patients with epilepsy based on hospital and clinical records [1, 2]. As a specific electroclinical syndrome, it is characterized by a genetic predisposition, no evidence of neurological or intellectual deficit and by mandatory or typical myoclonic seizures alone (irregular jerks of the shoulders and arms) or combined with generalized tonic–clonic seizures (GTCS) in 80% or the absence seizures in 15–30%. Bilateral myoclonic seizures and GTCS are provoked by sleep deprivation and predominantly occur after awakening [1, 3, 4]. The seizures may also be precipitated by fatigue, alcohol intake, and stress [4]. Series of myoclonic seizures often precede GTCS

Corresponding Author: Prof. dr Nebojša Jović, Klinika za neurologiju i psihijatriju za decu i omladinu, 11000 Beograd, Dr Subotića 6, E-mail: nj268j@gmail.com

Abbreviations

JME – juvenile myoclonic epilepsy
GTCS – generalized tonic–clonic seizures
EEG – electroencephalography
CAE – childhood absence epilepsy
AEDs – antiepileptic drugs
MRI – magnetic resonance imaging
VPA – valproate
TPM – topiramate
LTG – lamotrigine
LEV – levetiracetam
PPR – photoparoxysmal response

[5]. JME with isolated jerks usually developed in patients between 12 and 18 years of age with the female predominance. Interictal electroencephalography (EEG) in JME shows interictal epileptiform discharges such as generalized spikes, polyspikes, bilateral-synchronous 4–6/s spike-wave complexes, or combinations of these [6, 7]. Myoclonic jerks appear to be time-locked to generalized 3–5 Hz spike-and wave complexes [8]. Photoparoxysmal response was seen in 40% of patients. Some authors consider cases of childhood absence epilepsy (CAE) developing to JME to be subtypes of JME with a different outcome [2]. Despite the well-defined clinical and EEG features, JME is very often underdiagnosed and errors and considerable delays in diagnosis have been attributed to many factors. Focal features may contribute to misdiagnosis of JME as focal epilepsy [9].

Many large case series suggest the efficacy of valproate for the therapy of JME but the relative value of other, newer antiepileptic drugs (AEDs) have been suggested [10]. Valproate is very effective and leads to total control of seizures in about 80% of patients.

Although JME is recognized as a common form of epilepsy, its long-term follow-up has rarely been performed. Earlier studies reported JME to be a chronic disease that required lifelong AED treatment with virtual certainty of relapse if medication was discontinued [2, 3]. Only a limited decrease (or with no decrease at all) in seizure propensity was stressed [3]. Withdrawal of medication even in well controlled patients may precipitate seizures [11, 12]. In many case series, a small percent of patients with clear-cut JME can discontinue AEDs and enter a very long (if not permanent) remission. It is usually assumed that continuous pharmacotherapy is required, although about 10% of them appear to have permanent remission in adolescence [13]. Discontinuing AED treatment in JME is very important for the long-term social outcome and quality of life of the patients and requires an individual risk assessment [9, 14].

The aim of this study was both to identify factors that are predictive for seizure remission/drug resistance and to investigate the long-term seizure outcome in patients with JME after the AED withdrawal. Patients were followed up for at least 5 years since the onset of seizure. While the majority of people with JME have a chronic disorder, there are some adolescents with a long-term remission without AEDs according to our experience.

Material and Methods

This retrospective study included the records of JME patients who had been referred to our Department for the first time between 1987 and 2008. An epilepsy syndrome diagnosis was made for each patient, based on the clinical and EEG features according to the International Classification of Epilepsies [6] and on classic treatment [1, 4]. The study sample consisted of 87 patients (49 female, 38 male) aged from 17.5 to 43.5 years (the mean age being 27.6), who had had their first seizure at 14.3±2.9 years of age (their age ranging from 8.3 to 20.5) and were followed up for 13.3±5.8 years on average (from 5 to 23 years). Our Epilepsy Ward is a part of a University Department and a well-established tertiary referral center for children and adolescents with epilepsy in Serbia. Having given their consent, these patients were followed up periodically.

All patients were independently evaluated by at least two of the experienced epileptologists during the long-term follow-up.

The analysis of the seizure type distribtion revealed myoclonic seizures in all patients, GTCS in 82.8% of them, and absences in 21.8%. Myoclonic jerks only were present in 10 patients. All types of seizures (myoclonic, GTC and absence) were observed in 14 patients, whereas the combination of myoclonic and GTC seizures in 58 and the combination of myoclonic seizure and the absence of seizures were found in five patients. Epilepsy remission at follow-up was defined as a terminal seizure-free period lasting for at least 5 years. Relapse was defined as a recurrence of seizures after being seizure-free for at least 5 years. The patients were divided into three groups: I- fully controlled patients, II- truly resistant patients defined as persisting seizures despite adequate lifestyle and treatment that included adequate doses of AED, III pseudo-resistant patients due to inadequate lifestyle, low compliance, or inadequate choice of drugs.

EEG studies at the time of diagnosis and during the course were performed in all patients using the international 10–20 system of electrode placement. Focal EEG features were defined as regional or lateralized EEG epileptiform patterns. Photoparoxysmal response (PPR) is defined as the occurrence of spikes, spike waves, poly-spike waves, or repetitive spikes in response to intermittent photic stimulation, which was observed in 30 patients (34.5%), while focal EEG abnormalities were recorded in 25 of our patients (28.7%). EEG when asleep, after the whole-night sleep deprivation, was recorded in 47/87 patients with bilateral par-

oxysms of spike-waves activated in 36 of 47 (76.5%) sleep deprived subjects.

Brain imaging was not usually required. Magnetic resonance imaging (MRI) of the brain was obtained in 57/87 patients. Neuroimaging was normal in 46 and abnormal in 11 patients.

It was found that AED treatment was discontinued in 34/87 patients (39.1%) which was not proposed to all seizure-free patients. Discontinuation of AED treatment in 21 seizure-free patients was attempted on physician's proposal and only if desired by the patient (group A). In addition, 13 patients who discontinued therapy by their own choice and without agreement of the treating physician (group B) were separately considered. In a non-standardized interview during the regular visit after >3 years since the seizure onset, the patients commented on lifelong therapy irrespective of seizure remission. In addition, they were asked regularly about AEDs side effects (e.g. weight gain and/or teratogenicity).

Data were stored and analyzed in Statistical Package for the Social Sciences (SPSS)17.0 (SPSS Inc., Chicago, U.S.A.), which was used for statistical processing of the data. The statistical methods were descriptive statistics with frequency analysis and cross-tab analysis, as well as mean and standard deviation calculation in parametric data. Statistical significance was assessed using Fisher's exact test to compare categorical variables and χ^2 test, with the significance defined as a p-value of <0.05. Fisher exact tests were selected in order to be comparable with similar investigations [15, 16].

Results

At the end of the follow-up, 67 patients (77.0%) were found to be fully controlled (I), whereas 12 patients (13.8%) had persistent seizures (II). Long-term remission was achieved by valproate (VPA) in 55 of 67 our JME patients with complete seizure control (82.1%), while in 12 patients (17.9%) other AEDs were used, such as topiramate (TPM), lamotrigine (LTG), levetiracetam (LEV) in 2, 6 and 4 patients, respectively. The most common reasons for breakthrough seizures reported by the patients were sleep deprivation, stress, alcohol, non-compliance and menses. Other reported triggers for seizures were fatigue, hyperventilation, photosensitivity and physical exertion. A pseudoresistance was noted in 8 patients (9.2%) (III). Ten patients were initially misdiagnosed as having focal epilepsy. After a change of treatment, all patients who had shown aggravation on carbamazepine (8/10) got obviously better either on VPA monotherapy or on bitherapy combining VPA with LTG, phenobarbital, or a benzodiazepine.

Clinical features associated with poor seizure control despite adequate treatment (group II) were assessed in comparison with the patients with good control (group I). Family history of epilepsy among the first and second degree relatives (23.8% in group I *vs.* 33.3% in group II), age at onset of seizures (mean 14.7±2.9 in subjects with seizure freedom vs. 13.8±2.3 years in those with poor seizure control) and sex (females 60% of patients in group I *vs.* 41.6% of patients in group II) were not significantly associated with drug resistance. In addition to the clinical parameters, the presence of photoparoxysmal response (38.8% in group I vs.-16.7% in group II), and delay of diagnosis since seizure onset (mean 8.0 years, SD 7.5 in group I *vs.* 8.5 years, SD 6.7 in group II) had no significant influence. However, focal EEG abnormalities were significantly more often recorded in the patients with incomplete seizure control than in those with seizure freedom (66.7% of patients vs. 27.4%, Fisher's exact test, p=0.016). Psychiatric disorders were found in 41.6% of AED-resistant patients and in 22.2% of well-controlled patients (Fisher's exact test, p=0.156, p>0.05), which was nearly significant for resistant course. Non-specific abnormal neuroimaging findings were found in eleven of 57 patients (11.7% of patients in group I v*s.* 25% of patients in group II), including a common arachnoid cyst (two), a mild ventricular enlargement (two), a mild diffuse cerebral atrophy and ventricular enlargement (five), intracranial calcifications (one), and pituitary hyperplasia (one). All of these patients but three were fully controlled and the course of the disease was benign. Thus, the abnormal neuroimaging findings seemed to be non-relevant for the clinical expression and evolution of JME.

The influence of the combination of seizure types to the therapeutic response was not statistically significant (χ^2 test, p=0.067). More precisely, the coexistence of all three types of seizures was associated with drug resistance, and was found in 41.7% of resistant cases *vs.* 11.8% in non-resistant cases (Fisher's exact test, p=0.022). Only one of the resistant patients had myoclonic jerks as the only seizure type vs. 10.4% in group I, and none had a combination of absence seizures and myoclonic jerks vs. 7.3% patients with seizure freedom.

Presence of the combination of three seizure types and focal EEG features are independent factors of poor seizure control despite adequate treatment, compared with patients with seizure freedom, achieved with AEDs.

Termination of AED treatment was not proposed to all seizure-free patients. Analysis of medical records from the follow-up visits about 5 years after the seizure onset disclosed that more than half of well-controlled patients (37; 55.2%) stated that assertion on lifelong therapy was hardly acceptable after years of remission. In addition, a number of them (21; 31.4%) at that time reported their concern about VPA effects (weight gain and / or teratogenicity).

Therapy was discontinued in 34 patients. In 21 patients (group A), the discontinuation of therapy

Table 1. Clinical outcome in 34 patients with discontinued therapy
Tabela 1. *Klinički tok kod 34 bolesnika posle obustave terapije*

Characteristic/*Karakteristika*	Number/*Broj*	% and range/*% i raspon*
Therapy discontinued/*Obustavljena terapija*	34/87	39.1%
Group/*Grupa* A – Decided by the physician/*po odluci lekara*	21	24.1% (61.8%)
Group/*Grupa* B – Patients themselves decided/*samoinicijativno*	13	14.9% (38.2%)
Seizure relapses/*Recidivi napada*	22/34	64.7%
Relapses in group A/*Recidivi u grupi A*	12/21	(57.1%)
Relapses in group B/*Recidivi u grupi B*	10/13	(76.9%)
Relapses of GTCS/A/MS/*recidivi GTKN/AN/MN*	18	52.9%
Relapses of myoclonic seizures only/*Recidivi miokloničkih napada samo*	4	11.8%
No relapses/*Bez recidiva napada*	12/34	35.3%
AED restarted/*Ponovo uveden AEL*	20/34	58.8%
after seizure relapses/*posle recidiva napada*	18	52.9%
after EEG aggravation/*posle EEG pogoršanja*	2	5.9%
AED (and Seizure) freedom/*Bez AEL (i bez napada)*	12/87	13.8%
Seizure and AED freedom/*Bez napada i bez AEL*	9	10.3%
AED freedom (MS only)/*Bez AEL (MN samo)*	3	3.4%

Legend: GTCS – generalized tonic-clonic seizures, A-absences, MS-myoclonic seizures, *GTKN – generalizovani toničko-klonički napadi, AN − apsansni, MN − miokloničk napadi*

followed the protocol of AED withdrawal. Majority were treated by VPA-16, while four patients used LTG and one patient received TPM. The drug withdrawal process was managed by the treating physician after 8.5±5.2 years of seizure freedom. However, 13 patients (group B) themselves attempted the drug discontinuation after 5.3±2.4 years of complete seizure remission (**Table 1.**). Majority in group B were also treated by VPA-9, while two patients used LTG or LEV each. In 18 subjects, all seizure types relapsed after 1.1 year on average (from 7 days to 4 years) and AED was restarted in them. In two patients, AED (VPA and LTG) was reintroduced because of EEG aggravation without overt seizure relapse. No seizure occurred in them after such therapeutic decision during the period of 2.5 and 1.5 years, respectively. Nonintrusive myoclonic seizures recurred in 0.5-3 years as their only seizure type in 4 patients, but without restarted medication in 3 patients. No GTCS occurred during the follow-up in the period from 2 to 4.5 years in them. One patient was lost for the follow-up. No relapses were observed in 12 of 34 patients. Seizure freedom off drugs lasting for 4.1 years on average (from 2.8 to 9 years) was observed in 10.3% patients.

No specific AED was associated with the type of therapy termination ($p>0.05$). Neither the type of therapy discontinuation (group A and group B) nor the prescribed AED was significantly associated with the recurrence rate. Statistical significance was not reached despite the fact that all patients but three (10/13), who themselves stopped the treatment, experienced recurrences ($p=0.21$). The reason for AED withdrawal (either decided and advised by the physician or by the patients themselves) was not significantly associated with a) the duration of remission with AED (8.5±5.2 years in group A, 5.3±2.4 in group B) (M W=90.0, $p=0.256$) nor b) the duration of remission after AED withdrawal till the recurrence (A-1.8±1.2 years, B-0.5±0.4 years; T=1.840, DF=32, $p=0.579$). Age at chronic AED withdrawal was not significantly different in patients with various types of therapy discontinuation (21.4 years in group A, 19.4 years in group B; MW-85.0, $p=0.180$).

Discussion

When Delgado-Escueta and Enrile-Bacsal [3] described their experience with 43 patients in 1984, they said that 86% of them had seizure remission with valproic acid but 12 of 13 who discontinued medication had their seizures return. It has been generally accepted that JME is lifelong and that it is unwise to discontinue treatment once seizure control has been established [1, 4, 13].

Generally speaking, JME is not considered a severe condition. The diagnosis of JME is often delayed. Complete, long-term seizure control was achieved in 77% of our patients, whereas 13.8% of them had persistent seizures. Additional 9.2% had pseudoresistant seizures. These findings are in accordance with the experience reported by others, who found that 66-88.3% of patients were controlled on valproate monotherapy [3, 11, 13, 16, 17]. True resistance to adequate drugs is not uncommon, and it was found in 11.7-16.7% of patients [8, 15–17). Pseudoresistance was found in 9.7-16.7% of patients [15, 16]. The course of disease may vary and some patients with a benign form can have a transient period of aggravation, whereas others who are more difficult to treat may experience spontaneous improvement later.

Despite the favorable seizure outcome in most of the cases, 3/4 of patients with JME have at least one major unfavorable social outcome [18]. Clinical features associated with drug resistance in our study

were the presence of the combination of seizure types and focal EEG features. The presence of three types of seizures was found in 41.7% of resistant cases *vs.* 11.8% of well-controlled cases. Only one of the resistant patients had myoclonic jerks as the only seizure type vs. 10.4% of those in group I, and none had a combination of absence seizures and myoclonic jerks vs. 7.3% of those seizure-free. Similar results were found in a number of studies [15–17]. Family history of epilepsy, age at onset of seizures, sex, presence of PPR, results of conventional magnetic resonance imaging (cMRI) and delayed diagnosis were not significantly associated with drug resistance as reported in some previous studies [15, 16]. Contrary to our results, the true-resistant course was significantly associated with psychiatric disorders [14–16] and the presence of thyroid diseases [16]. Myoclonic jerks alone, without GTCS or absence seizures have been reported to occur in 7-17% of JME probands [1]. Patients with myoclonic jerks alone may represent a benign subgroup of JME that may be genetically distinct from classic JME and the jerks may even spontaneously remit in a few cases [5]. The possible sub-syndromes of JME, its genetic background, and its pathophysiological and neuroimaging correlations should be further investigated [18].

A normal EEG while the patient is receiving daily AED treatment is a good sign for the prognosis [10]. Focal clinical and/or EEG features in patients with JME are common. Focal EEG abnormalities, consisting of transients of localized spikes, slow and sharp waves have been found in 16.5–36.7% of JME patients depending on the methodology applied [8, 12, 13]. They were recorded in our patients with poor seizure control significantly more often than in seizure-free patients (66.7% vs. 27.4%). According to recent results, focal findings indicate poor response to treatment of JME [19]. A few EEG and neuroimaging studies indicate that the cortex precedes the thalamus at the onset of generalized spike-wave discharges [9]. PPR is obtained in 27-33% of JME patients [12, 13, 20]. Unexpectedly, the PPR in our patients (38.8% in group I vs 16.7% in group II) was nearly significant for favorable course, contrary to the study conducted by Baykan at al.[16, 18]. The PPR could be a final expression of pathogenic phenomena occurring in the striato-thalamocortical system, possibly a core feature of system epilepsy JME. Abnormal response to photic stimulation in JME in an EEG-functional magnetic resonance imaging (fMRI) study disclosed prominent involvement of basal ganglia circuitry [21].

Janz stated that JME could be controlled very well by valproate and/or primidone. A complete cure, nevertheless, does not seem to be possible [1]. Long-term remission was achieved by VPA in 82.1% of our JME patients with complete seizure control, while other AEDs were used in 17.9% of them. No randomized trials specifically address the treatment of JME [10]. It has been suggested that VPA is more effective than other medications; however, consideration of weight gain, concern of teratogenicity in unplanned pregnancy, and the disorder of polycystic ovaries may lead to an attempt of treatment with LTG, TPM, LEV or clonazepam [13, 20]. However, management of JME should also include interventions in lifestyle, with strict avoidance of sleep deprivation and management of co-pathologies, including the cognitive and psychiatric problems that are often encountered [22]. Detailed results on both initial and maintenance AED therapy in our patients will be soon separately reported.

International workshops on JME were conducted in Avignon, France (2011) and in the Hague, the Netherlands (2012) and included a group of experts on JME, together with one of the founding fathers of the syndrome of JME (*Janz syndrome*), Prof. Dr. Dieter Janz from Berlin. Most clinicians are still reluctant to withdraw medication. Only if the patient is seizure-free for at least 5 years, has a normal EEG, and has a low risk of recurrence of GTCSs the AED(s), the withdrawal could be considered. For women with JME, who are planning to get pregnant, most clinicians attempt to withdraw or reduce VPA dosage as much as possible before the planned conception [23].

After the AED discontinuation in 34/87 patients, 22 patients relapsed. In 18 subjects, all seizure types relapsed and continuous AED was restarted in them. Seizure freedom of drugs was observed in 10.3% patients. Termination of AED treatment was not proposed to all seizure-free patients, so there was selection bias from the physician's side.

Wolf et al. hypothesized that in many patients with epilepsy who are seizure-free under treatment, a gradual decrease in seizure propensity occurs that allows AED dose reduction and, in some patients, discontinuation of AED. Relapses were not increased in their patients with JME (10/21; 47.6%) [24]. A relatively low relapse rate of these patients with JME could not be explained by a slower in-study reduction rate. The more rapid reduction used in some other studies seemed to cause more relapses. Oller-Daurella et al., who also used a very slow rate of reduction after 5 seizure-free years, observed no relapses in 16 cases of JME [25]. In a Norwegian clinic study, 7% of 43 patients with definite or probable JME had a terminal remission without AEDs and an additional 10 patients were seizure-free for >5 years with AEDs [26]. As in the case of absence epilepsy, the enduring propensity of the system to generate seizures needs to be demonstrated. Brain maturation seems to influence cerebral hyperexcitability, which could explain why JME and related conditions appear/abate at a certain age [27].

Pannaiyotopoulos et al. reported that VPA dosage was successfully reduced in 15 patients who were seizure-free for >2 years and had infrequent

seizures before treatment, but 9 of 11 patients relapsed after VPA discontinuation [13]. Long-term follow-up of different clinical JME subtypes (classic JME; childhood absence epilepsy evolving to JME, JME with adolescent absence and JME with astatic seizures) conducted by Martinez-Juarey et al. indicates that all sub-syndromes are chronic and perhaps lifelong [2]. Only 8 of 161 (5%) patients with classic JME were in remission from all seizures without treatment. Epilepsy was clearly chronic as shown by recurrence of seizures upon discontinuation of medications. In addition, only 3 of 35 patients with CAE evolving into JME achieved complete freedom from seizures [2]. In 5/12 our patients with poor seizure control, absences occurred, comparing with 14/75 with complete seizure freedom. In a study conducted by Pavlovic et al., all 17 studied patients with JME, who had discontinued AED, relapsed after the AED withdrawal [12]. In their study, Canevini et al. reported relapses in 8 out of 60 JME patients who had attempted to discontinue AED. They relapsed during the follow-up period lasting from 6 months and 1 year [15]. In a study of Nicolson et al. [20], the relapse rate following AED withdrawal was 93.6%.

Camfield and Camfield [28] conducted a population-based study of 24 JME patients after 25-year long follow-up. All seizure types in JME resolved in 4 (17%) and for 3 (13%) only myoclonus persisted after stopping AEDs. Therefore, troublesome seizures vanish in one-third of people with JME and AED treatment is no longer needed. A Turkish clinical study showed that although a great majority of the patients with JME had continuing seizures after a follow-up of 20 years, almost all had either 5-year remission or a substantial alleviation of the myoclonic seizures in the fourth decade. In 54.2% of the patients, myoclonia were in remission for a mean duration of 8.4 ±7.7 years [16]. The majority of patients with JME have continuing seizures after a follow-up of two decades. However, 17% are able to discontinue medication and remain seizure-free thereafter [18]. Nonintrusive myoclonic seizures recurred in 2.4-4 years as the only seizure type in 4 of our subjects, and without restarted medication. No GTCS occurred during the follow-up in them. It is possible that relatively optimistic rate of remission is related to the age of patients at the end of follow-up: seizure-provoking factors such as binge drinking and sleep deprivation are likely to decrease with age [28]. The tendency of myoclonic seizures in JME toward remitting with age could be unrelated to the AED treatment or to the lifestyle changes. We could not comment on this issue, because our series included a small number of patients having myoclonus only.

Pavlovic et al. stated that EEG worsening during and/or after the AED withdrawal was an independent prognostic variable associated with the higher risk of seizure relapse in generalized epilepsy [9, 12, 21]. In two of our patients, the AED was reintroduced because of EEG aggravation without overt seizure relapse. Although no seizure occurred in them during the period of 2.5 and 1.5 years, there is no strong evidence to justify such therapeutic decision.

Conclusions

The presence of the combination of seizure types and focal electroencephalogram features are independent factors of poor seizure control despite adequate treatment. With 64.7% of patients having seizure recurrences upon antiepileptic drug discontinuation after >5-year stable seizure freedom, and the necessity to restart therapy in them, there is little doubt that the majority of people with juvenile myoclonic epilepsy have a lifelong disorder. Our experience indicates that there are some (10.3%) patients with a relatively short active phase followed by a long-term remission without antiepileptic drugs. Recurrence of myoclonic seizures only may not lead to the reintroduction of chronic therapy. Identifying juvenile myoclonic epilepsy patients prospectively who will have remission of their epilepsy and be able to discontinue antiepileptic drug treatment should be an issue of further research.

References

1. Janz D. Epilepsy with impulsive petit ma1 (juvenile myoclonic epilepsy). Acta Neurol Scand. 1985;72:449-59.

2. Martınez-Juarez IE, Alonso ME, Medina MT, et al. Juvenile myoclonic epilepsy subsyndromes: family studies and long-term follow-up. Brain. 2006;129:1269-80.

3. Delgado-Escueta AV, Enrile-Bacsal F. Juvenile myoclonic epilepsy of Janz. Neurology. 1984;34:285-94.

4. Janz D, Durner M. Juvenile myoclonic epilepsy. In: Engel JR, Pedley TA, editors. Epilepsy: a comprehensive textbook. Philadelphia: Lippincott-Raven; 1997. p. 2389-400.

5. Jain S, Padma MV, Maheshwari MC. Occurrence of only myoclonic jerks in juvenile myoclonic epilepsy. Acta Neurol Scand. 1997:95:263-7.

6. Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. Epilepsia. 1989;30:389-99.

7. Usui N, Kotagal P, Matsumoto R, Kellinghaus C, Luders HO. Focal semiologic and electroencephalographic features in patients with juvenile myoclonic epilepsy. Epilepsia. 2005;46(10):1668-76.

8. Oguni H. Symptomatic Epilepsies Imitating Idiopathic Generalized Epilepsies. Epilepsia. 2005;46(9 Suppl):84S-90.

9. Seneviratne U, Cook M, D'Souza W. Focal abnormalities in idiopathic generalized epilepsy: a critical review of the literature. Epilepsia. 2014;55(8):1157-69. DOI: 10.1111/epi.12688. Epub 2014 Jun 17.

10. Camfield C, Camfield P. Management guidelines for children with idiopathic generalized epilepsy. Epilepsia. 2005; 46(9 Suppl):112S-6.

11. Grunewald RA, Chroni E, Panayiotopoulos CP. Delayed diagnosis of juvenile myoclonic epilepsy. J Neurol Neurosurg Psychiatry. 1992;55:497-9.

12. Pavlovic M, Jovic N, Pekmezovic T. Antiepileptic drugs withdrawal in patients with idiopathic generalized epilepsy. Seizure. 2011;20(6):520-5.

13. Panayiotopoulos CP, Obeid T, Tahan AR. Juvenile myoclonic epilepsy: a 5-year prospective study. Epilepsia. 1994;35:285-96.

14. Jovic NJ. Frontal lobe dysfunctions in patients with juvenile myoclonic epilepsy. J Pediatr Epilepsy. 2012;1(2):77-85.

15. Gelisse P, Genton P, Thomas P, Rey M, Samuelian JC, Dravet C. Clinical factors of drug resistance in juvenile myoclonic epilepsy. J Neurol Neurosurg Psychiatry. 2001;70:240-3.

16. Baykan B, Altindag EA, Bebek N, et al. Myoclonic seizures subside in the fourth decade in juvenile myoclonic epilepsy. Neurology. 2007;70:2123-9.

17. Canevini MP, Mai R, Di Marco C, et al. Juvenile myoclonic epilepsy of Janz: clinical observation in 60 patients. Seizure. 1992;1:291-8.

18. Baykan B, Martínez-Juárez IE, Altindag EA, Camfield CS, Camfield PR. Lifetime prognosis of juvenile myoclonic epilepsy. Epilepsy Behav. 2013;28(Suppl 1):S18-24.

19. Güveli BT, Baykan B, Dörtcan N, Bebek N, Gürses C, Gökyiğit A. Eye closure sensitivity in juvenile myoclonic epilepsy and its effect on prognosis. Seizure. 2013;22:867-71.

20. Nicolson A, Appleton RE, Chadwick DW, Smith DF. The relationship between treatment with valproate, lamotrigine and topiramate and the prognosis of the idiopathic generalized epilepsies. J Neurol Neurosurg Psychiatry. 2004;75(1):75-9.

21. Bartolini E, Pesaresi I, Fabbri S, et al. Abnormal response to photic stimulation in juvenile myoclonic epilepsy: an EEG-fMRI study. Epilepsia. 2014;55(7):1038-47. doi: 10.1111/epi. 12634

22. Crespel A, Gelisse P, Reed RC, et al. Management of juvenile myoclonic epilepsy. Epilepsy Behav. 2013;28(Suppl 1): S81-6.

23. Kasteleijn-Nolst Trenite DG, Schmitz B, Janz D, et al. Consensus on diagnosis and management of JME: from founder's observations to current trends. Epilepsy Behav. 2013;28(Suppl 1):S87-90.

24. Wolf P, Pastuchova T, Mataringa M. Decline in seizure propensity in seizure-free patients as reflected in the evolution of the therapeutic antiepileptic drug threshold. Epilepsy Behav. 2006;8:384-90.

25. Oller-Daurella L, Pamies R, Oller Ferrer Vidal L. Reduction or discontinuance of antiepileptic drugs in patients seizure free for more than 5 years. In: Janz D, editor. Epileptology. Stuttgart: Thieme; 1976. p. 218-27.

26. Kleveland G, Engelsen BA. Juvenile myoclonic epilepsy: clinical characteristics, treatment and prognosis in a Norwegian population of patients. Seizure. 1998;7:31-8.

27. Avanzini G, Manganotti P, Meletti S, et al. The system epilepsies: a pathophysiological hypothesis. Epilepsia. 2012;53: 771-8.

28. Camfield CS, Camfield PR. Juvenile myoclonic epilepsy 25 years after seizure onset: a population-based study. Neurology. 2009;73:1041-5.

Rad je primljen 3. II 2014.
Recenziran 26. IX 2014.
Prihvaćen za štampu 27. IX 2014.
BIBLID.0025-8105:(2014):LXVII:11-12:372-378.