



## Wystąpienie młodzieńczej padaczki mioklonicznej w okresie remisji łagodnej mioklonicznej padaczki niemowląt. Opis przypadku

### Benign Myoclonic Epilepsy of Infancy followed by Juvenile Myoclonic Epilepsy. Case report

Elżbieta Szczepanik, Dorota Hoffman-Zacharska, Iwona Terczyńska, Dorota Antczak-Marach

Clinic of Neurology, Epileptology and Sleep Disorders in Children and Adolescents

Chief: dr med. Elżbieta Szczepanik

Institute of Mother and Child

Director: prof. dr hab. med. W. Woźniak

#### Streszczenie

Słowa kluczowe: idiopatyczne padaczki uogólnione, łagodna miokloniczna padaczka niemowląt, młodzieńcza padaczka miokloniczna, współistnienie dwóch zespołów padaczkowych, genetyka padaczki

#### Abstract

Key words: idiopathic generalized epilepsy (IGE), benign myoclonic epilepsy of infancy (BMEI), juvenile myoclonic epilepsy (JME), coexistence of two IGE syndromes, epilepsy genetic

**Wprowadzenie.** Możliwość współistnienia dwóch zespołów padaczkowych u tego samego chorego jest zjawiskiem znanym, choć rzadko spotykanym. **Opis przypadku.** Autorzy przedstawiają przypadek 15-letniej obecnie dziewczynki, u której w wieku 8 miesięcy życia wystąpiły napady padaczkowe o charakterze mioklonii, głównie w obrębie kończyn górnych. W badaniu EEG we śnie stwierdzano obecność uogólnionych wyładowań iglic i zespołów wieloiglica-fala. Obraz kliniczny i elektroencefalograficzny odpowiadał łagodnej mioklonicznej padaczce niemowląt (BMEI). Włączenie preparatów kwasu walproinowego (VPA) spowodowało ustąpienie napadów. Od wieku 3 lat 5 miesięcy stopniowo w ciągu 2 lat wycofano leczenie. Remisja napadów trwała do 11 roku życia, kiedy to pojawiły się mioklonie i napady nieświadomości. Badanie EEG ujawniło na tle prawidłowej czynności podstawowej w czasie HV i FS uogólnione wyładowania wieloiglic i zespołów iglica-fala. W czasie badania wideo-EEG we śnie wystąpił uogólniony napad toniczno-kloniczny. Rozpoznano JME. Leczenie VPA spowodowało ustąpienie napadów. **Wnioski.** Współistnienie dwóch idiopatycznych uogólnionych zespołów padaczkowych u tego samego chorego może przemawiać za ich wspólnym podłożem genetycznym. Odpowiedź na pytanie, czy BMEI i JME są klinicznym continuum tego samego zespołu padaczkowego, czy stanowią dwa odrębne zespoły padaczkowe, pozostaje nadal sprawą otwartą.

**Introduction.** Coexistence of two epileptic syndromes in the same person has been already reported, although uncommon. **Case.** A 15 year old girl who had suffered since the age of 8 months of life from daily myoclonic seizures involving mainly the upper limbs was described. At that time sleep EEG showed generalized spikes and polyspike-waves. Clinical and EEG features were typical for Benign Myoclonic Epilepsy of Infancy (BMEI). Seizure remission was observed within few days on valproate (VPA). The treatment had been tapered off since the age of 3 years and 5 months within two years. The patient had been seizure free till the age of 11 years of life when absence and myoclonic seizures occurred. EEG during HV and FS showed generalized polyspikes and spike-waves. During sleep video-EEG the generalized tonic-clonic seizure was recorded. Based on both clinical and EEG features Juvenile Myoclonic Epilepsy (JME) was diagnosed. Seizure remission on VPA was achieved. **Conclusions.** Coexistence of two idiopathic generalized epileptic syndromes in one patient strongly suggests a common genetic background of both syndromes. The question whether BMEI and JME constitute either the clinical continuum of the same epileptic syndrome or two distinct syndromes still remains open.

## Introduction

According to the International Classification of Epilepsies and Epileptic Syndromes (1989) and its revised Proposal (2001) benign myoclonic epilepsy of infancy and juvenile myoclonic epilepsy are both included into the group of idiopathic generalized epilepsies (IGEs, OMIM\_#600669) [1–4].

BMEI was described for the first time by Charlotte Dravet and Michelle Bureau in 1981. According to these authors 103 cases of BMEI had been published till 2002 (89 corresponding to the classical description and 14 reported as "reflex BMEI") [5]. It is a rare syndrome among IGEs, which accounts for up to 2% in the population of infants with epilepsy of onset in the first 3 years of life [5, 6]. The onset of the disease is between the ages of 6 months (or earlier) and 3 years of life. The history of febrile convulsions and/or epilepsy in patients' family is often positive. The myoclonic jerks involving mainly the upper limbs and the head are the only seizure type, despite the fact that Lin et al. (1998) reported a group of patients with afebrile convulsions occurring either before the onset of myoclonic seizures or during the clinical course [7]. Simple febrile convulsions occur in about 20% cases. The interictal EEG may be normal [5]. The ictal EEG shows generalized polyspikes or spike-waves synchronous with myoclonic fits [5, 6]. The seizures respond well to valproate treatment [6]. During adolescence of the BMEI patients' tonic-clonic seizures may occur [6]. Long-term developmental outcome is usually favourable, although some children show mental retardation [7].

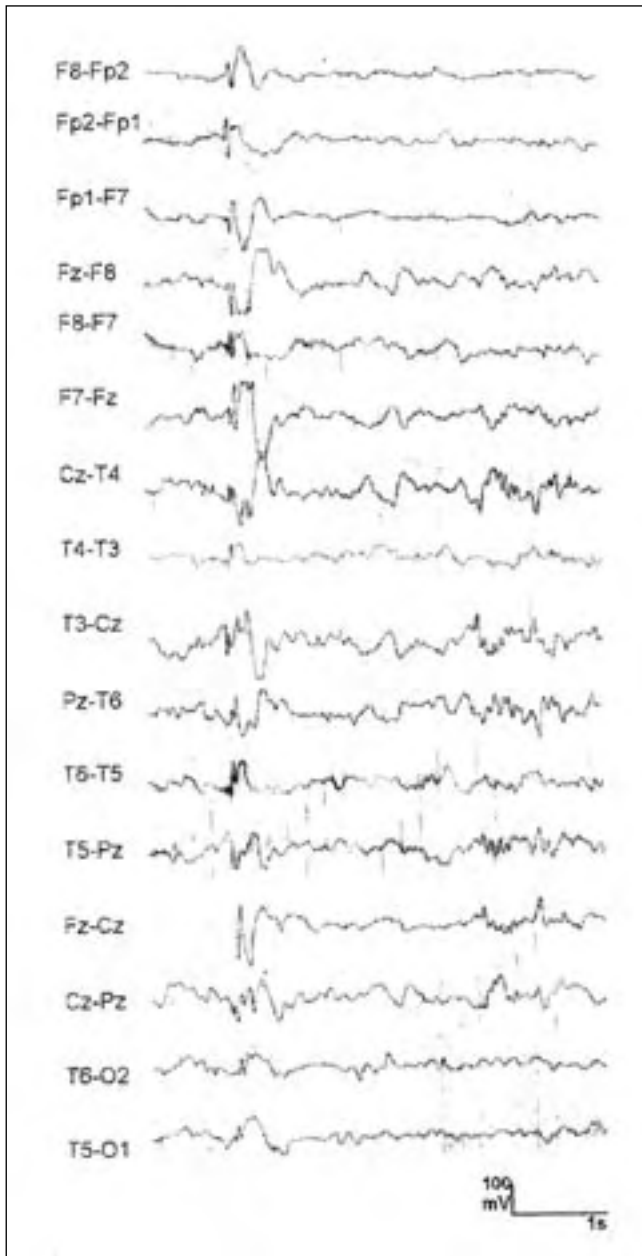
In contrast to BMEI, juvenile myoclonic epilepsy (JME, OMIM #609404) is much more common syndrome. It affects 4–11% of all patients with epilepsy, and is the most common syndrome of generalized grand mal epilepsy [8, 9]. The onset of disease is usually in early adolescence, mainly between 8–26 years of life. The family history of epilepsies is often positive [8–10]. The main symptoms of JME are myoclonic seizures, occurring preferentially on awakening. In 80–90% patients they are associated with generalized tonic-clonic seizures (GTCS) and in about 30% cases with typical absences [8]. The sleep deprivation, the sudden awakening, tiredness and photic stimulation are the common seizure precipitating factors. The seizures respond well to pharmacotherapy (valproate, lamotrigine, clonazepam). Nevertheless the JME tends to be a life-long disorder.

In this paper we report a girl with BMEI who later in her adolescence, after about 10 years seizure-free period, developed JME. As far as we know, according to published data no patient with these two successively appearing syndromes has been described, even though one unpublished case was suggested [5].

## Case report

A 15 year-old girl of the Caucasian race was born after unremarkable pregnancy as a third child to the healthy unrelated parents. There was no obvious family history of epilepsy, febrile convulsion and other neurological diseases. Proband's father complained of sensitivity to flashing lights occasionally resulting in headaches, his brother was diagnosed with epilepsy in the age of 40, but in this case it could be connected with alcoholic problem. Development was normal and she remained asymptomatic until the age of 8 months when she experienced her first seizures with forward head dropping, sometimes accompanied by shoulder and upper limbs elevation. The seizures were not provoked. Consciousness assessment during seizures was difficult to obtain; nevertheless the child activity was not obviously interrupted. There were numerous daily seizures lasting up to few seconds. Head trauma appeared several times during seizures. At the age of 9 month she was given clonazepam (CLN) and phenobarbital (PB) – about 50% seizure reduction was observed. During admission to our clinic at the age of 18 months (March 1991) physical examination and child development were normal, except for some forehead bruises (due to seizure traumas). The EEG performed during spontaneous sleep displayed normal background activity modified by low amplitude postpharmacological fast beta activity and discharge of generalized spikes and polyspike-waves with amplitude up to 100  $\mu$ V lasting 2 seconds without concomitant clinical events. Photic stimulation was not performed (that EEG record is not available now). Taking into account myoclonic feature of seizures, no other seizures accompanied, normal girl development, BMEI was considered. Sodium valproate (VPA) was introduced while CLN and PB were withdrawn. Seizure remission was observed within a few days. Follow-up valproate dose reached 600 mg/d being within the therapeutical range (around 100  $\mu$ g/ml). The EEG performed during a spontaneous sleep two months after valproate introduction showed normal background activity. There were few bursts of theta and sharp waves. The next EEG recorded during the treatment at the age of 3 years of life was similar. No seizures were observed, so valproate was tapered off within two years since the age of 3 years and 5 months (March 1993).

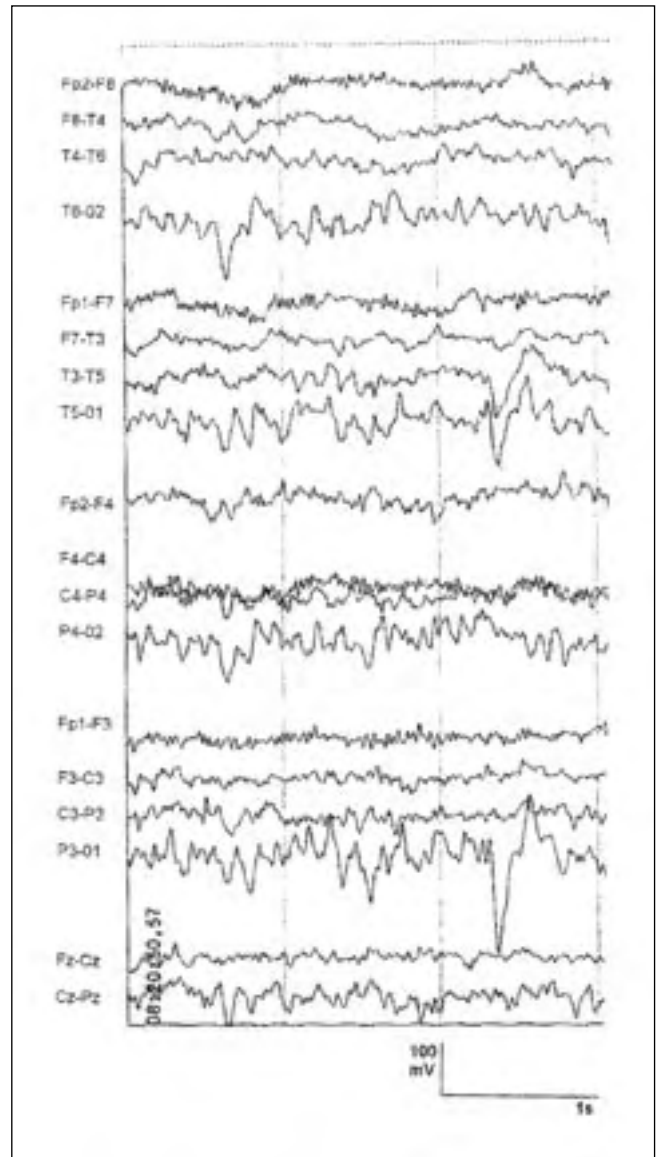
The EEG performed during sleep at the age of 3 years and 11 months (August 1993) showed normal background activity and paroxysmal group of spike-slow waves (Fig. 1). The next EEG performed during wakefulness at age of 5 years (September 1994) showed mild localised theta and sharp waves with amplitude up to 130  $\mu$ V. There were very few generalized group of theta waves and spikes with amplitude to 180



**Fig. 1.** The electroencephalogram performed during sleep at the age 3 years 11 months (August 1993) – paroxysmal group of spike-slow wave complexes

$\mu\text{V}$  (Fig. 2). EEG done at the age of 5 years 6 months (March 1995) was similar. Mental child development was good.

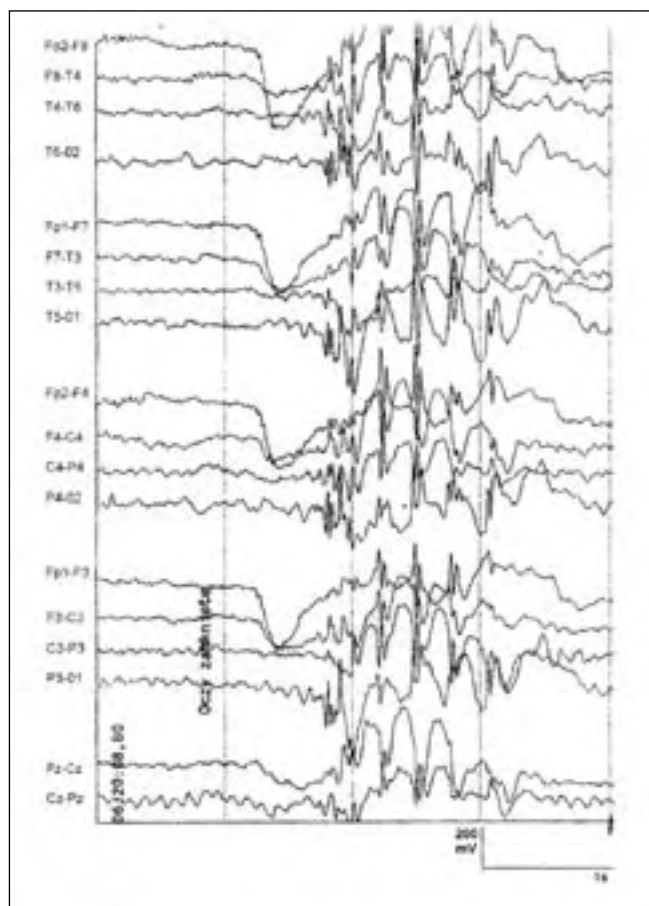
Next EEG was recorded at the age of 6 years 3 months (December 1995) during wakefulness, when she was without treatment (Fig. 3). The background activity was normal. There were quite numerous generalized polyspikes, spike-waves and slow waves 3–4 Hz, 500  $\mu\text{V}$  in amplitude and 0,5 to 2 seconds in duration. In response to oral HV generalized spike-waves 3 Hz and polyspikes of amplitude to 600  $\mu\text{V}$  lasting to 3 seconds appeared. No accompanied clinical events were observed. Next EEG performed two months later during wakefulness was similar. In that time, during photic stimulation (between 10 and 20 Hz) bursts of generali-



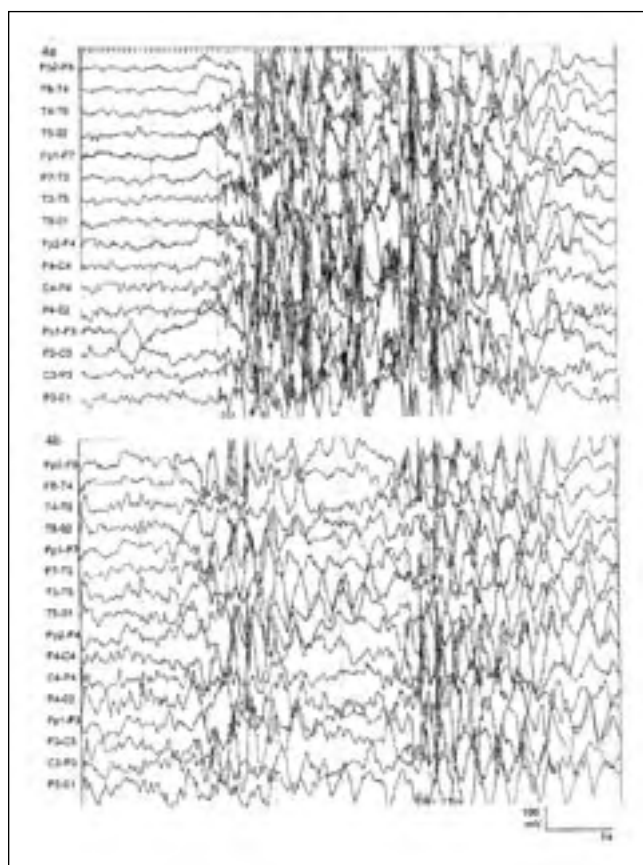
**Fig. 2.** The electroencephalogram performed during awakening at the age 5 years (September 1994) – sporadic theta and sharp waves in posterior temporal and occipital areas (with left predominance)

zed polyspikes, spike-waves and slow waves 3 Hz with amplitude to 350  $\mu\text{V}$  were precipitated. The patient and her parents denied any seizures. At that time video-EEG recording was not available. Since then the girl disappeared from our observation.

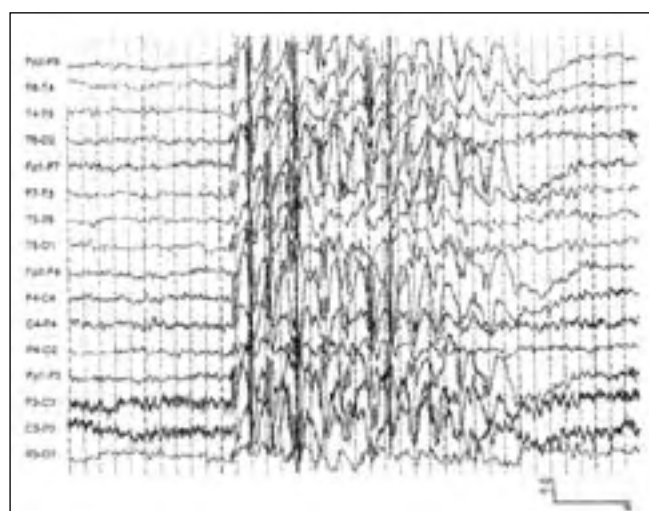
She came back at the age of 11 years 7 months (April 2001) complaining of epileptic seizures, which had appeared 6 months earlier. There were absences with upward deviation of the eyes lasting 2–3 seconds and early morning myoclonic seizures involving the upper limbs. Her school performance was satisfactory despite of dyslexia. At that time the interictal EEG performed during wakefulness revealed normal background activity and bilateral (with right side preponderance) central-temporal-occipital slow waves and spikes. During HV and photic stimulation (between 12 and 20 Hz) burst of generalized polyspikes, spike-slow wave



**Fig. 3.** The electroencephalogram performed during awakening at the age 6 years 3 months (December 1995) – generalized paroxysmal discharges of polyspikes, spike and slow wave complexes and slow waves in both centrotemporal and occipital areas (theta, sharp and slower wave complexes); 4a: Photostimulation at 12–20 flashes/sec – activated generalized paroxysmal discharges of polyspikes, spike and slow wave complexes and slow waves with beginning in posterior regions (more right); 4b: HV activated generalized paroxysmal discharges of spike-slow wave complexes and polyspikes-slow wave complexes with fragmentation and accentuation in both frontal areas



**Fig. 4.** The electroencephalogram performed during awakening at the age 11 years 7 months (April 2001) – in rest record shows localized epileptiform abnormality in both centrotemporal and occipital areas (theta, sharp and slower wave complexes); 4a: Photostimulation at 12–20 flashes/sec – activated generalized paroxysmal discharges of polyspikes, spike and slow wave complexes and slow waves with beginning in posterior regions (more right); 4b: HV activated generalized paroxysmal discharges of spike-slow wave complexes and polyspikes-slow wave complexes with fragmentation and accentuation in both frontal areas



**Fig. 5.** The electroencephalogram performed during awakening at the age 13 years 10 months (July 2003) – generalized paroxysmal discharges of polyspikes-slow wave complexes, spike-slow wave complexes and sharp waves of amplitude up to 330uV and duration up to 4 seconds with predominance in both frontal areas

complexes of amplitude up to 500  $\mu$ V lasting up to 5 seconds were demonstrated (Fig. 4a, 4b). 10 days later a video-EEG recording during spontaneous sleep was obtained. Soon after awakening during photic stimulation GTCS occurred. JME was diagnosed. All types of seizures disappeared within 3 months after valproic acid therapy (600 mg/d) introduction. The EEG performed 4 months after treatment initiation showed lack of generalized bursts and photosensitivity.

At the age of 13 years 9 months (June 2003) absences reappeared. The dosage of valproic acid was 800mg per day at that time (the body weight was 50 kg). The awake EEG (July 2003) showed generalized paroxysmal discharges of polyspikes-slow waves complexes, spike-slow waves complexes and sharp waves of amplitude to 330  $\mu$ V lasting up to 4 seconds with

predominance in both frontal areas (Fig. 5). Brain magnetic resonance imaging (MRI) was normal. The dosage of VPA was increased up to 1000mg/d with good clinical result.

Because in BMEI and JME and the common genetic background could be expected, DNA sample of patients and family members was obtained and stored for the further analysis\*.

\* Approval of local ethic committee was obtained.

## Discussion

The differentiate diagnosis of BMEI includes: benign myoclonus of early infancy, reflex myoclonic epilepsy in infancy, West syndrome, myoclonic-astatic epilepsy or early onset of JME. JME may start in the early childhood – the earliest described onset of JME was a case of 2 years old girl presented by Gram et al. (1988) who experienced ultra short absences with head-drop and upward deviation of the eyes [10]. The EEG showed generalized bursts of polyspikes and slow waves. Myoclonic seizures started at the age of 3 years.

At present, we can neither exclude nor confirm that episodes of dropping head of our patient would had not be accompanied by very-short absences. EEG finding (at age of 18 months) resembled the EEG record of a patient presented by Gram et al. [10]. So, could we have the case of extremely early onset of JME instead of BMEI? The anticonvulsant treatment was withdrawn up to 5 years of our patient's life. The EEG performed about 4 months later showed reappearance of generalized burst of polyspikes and spike-waves syndromes. About 5 years after valproate had been discontinued myoclonic seizures and absence appeared.

As Dravet and Bureau stated, BMEI may be the equivalent of JME in the youngest children [5]. It would mean that BMEI and JME constitute a type of clinical continuum of the same epileptic syndrome. Differences in clinical manifestation probably would depend on degree of the brain structures maturity. If so, and as JME is usually a long-life condition, the most of patients with BMEI should experience reappearing of the seizures after discontinuation of the treatment. But it may occur much later in patients' lifetime (for example during adulthood). The periods of follow-up of published till now cases of BMEI have not been long enough yet to get know if JME occurred later on in these patients. Rossi et al. (1997) reported 11 cases of BMEI and the mean follow-up was below 7 years [6]. Puig et al.

(1990) published a case with observation ended when patient was 3 years and 5 months old [12].

Coexistence of two epileptic syndromes in the same person has been already reported, although uncommon [13–16]. Two syndromes may occur in parallel or successively. There may be two idiopathic or mixed (idiopathic plus symptomatic) or two symptomatic syndromes. Moreover, there may be coexistence of two generalized epilepsies or generalized plus partial epilepsies or two partial epilepsies.

It may be possible that BMEI and JME are not a clinical continuum of one syndrome and they may constitute two distinct syndromes. However, occurrence of two IGE syndromes in one patient strongly suggests their common genetic background. So far no data are available on genetic factors contributing to such rare epileptic syndrome as BMEI. Zara et al. (2000) have mapped a gene for Familial Idiopathic Myoclonic Epilepsy of Infancy on chromosome 16p13 [17]. However, this syndrome inherited as an autosomal recessive trait doesn't seem to be much consistent with BMEI described by Dravet and Bureau because of quite different clinical picture. Data concerning genetic background of JME reported by different authors are conflicting but they show evidence of genetic heterogeneity within JME [9]. So far three genes involved in JME expression have been identified: *GABRA1* on chromosome 5q34-q35 (OMIM \*137160) [18], *CACNB4* on 2q22-q23 (OMIM \*601949) [19] and *CLCN2* on 3q26 (OMIM \*600570) [20]. Additionally by linkage analysis two JME loci have been mapped EJM1 on 6p21 (OMIM \*254770) [21, 22] and EJM2 on 15q14 (OMIM \*604827) [23]. Recently however Pal et al. (2003) showed that gene *BRD2 (RING3)* (OMIM \*601540) may be the most susceptibility gene for EJM1 locus [24].

It is generally accepted, that IGEs syndromes (except for neonatal syndromes) have a common genetic origin [9, 25] despite the results of Delgado-Escueta et al. (1990), Italian Genetic Collaborative Group (1993) and recently Winawer et al. (2003), who in their study, concerning affected family members of JME probands', didn't find any cases of BMEI [4, 26, 27]. The current data suggest, that the genes involved in pathogenesis of the idiopathic epilepsies might express themselves in different way, depending how they interfere with each other or with the different nongenetic factors [9, 19]. The results are being seen in variety epileptic phenotypes. So, the genetic relationship between BMEI and JME still remains a matter to be solved.

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Adres autora:

Klinika Neurologii, Epileptologii i Zaburzeń Snu u Dzieci i Młodzieży IMD  
00-211 Warszawa  
ul. Kasprzaka 17