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Seizure outcome in 175 patients with juvenile myoclonic epilepsy — A long-term observational study

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Summary
Introduction: Juvenile myoclonic epilepsy (JME) is a genetic generalized epilepsy syndrome. Under appropriate antiepileptic drugs (AED) up to 85% of patients become seizure-free, but many may have a relapse after AED withdrawal.
Methods: We retrospectively studied 242 patients with JME at the Department of Neurology, Medical University Innsbruck, Austria (1975—2006). We analyzed age at seizure onset, age at last follow up, seizure types, photosensitivity, seizure outcome and neuroimaging findings; inclusion criterion was a medical treatment period of >2 years; exclusion criteria were traumatic or infectious brain injury before the onset of JME and/or gross structural pathology on neuroimaging.
Results: We identified 175 patients (111 women) with a median age at seizure onset of 15 years, (range 3—46) and a median age at follow-up (FU) of 38 years (range 14—87; median FU 8 years, range 2—38). Fourteen percent showed (24/175) photosensitivity on routine EEG. Seizure outcome: 62% (109/175) were seizure-free of myoclonic seizures (MS), generalized tonic clonic seizures (GTCS) and absence seizures (AS) for >1 year, and 53% (94/175) for >2 years, including 16 patients (9%) without AEDs. Thirty-one percent (54/175) were seizure-free between 2and 5 years, 15% (26/175) between 6 and 10, and 8% (14/175) >10 years; 38% (66/175) were not seizure-free. Not seizure-free patients had more often MS, AS and GTCS within the first year of epilepsy than those who were seizure-free at last FU (11% vs. 3%, $Chi^2 = 4.679$, df = 1, $p = 0.043$).

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Seizure-free patients had more often MS and GTCS as last seizure types in the year before becoming seizure-free (37% vs. 15%, $p = 0.003$), whereas in not seizure-free group MS only and GTCS only persisted.

Conclusions: JME does not always need lifelong treatment, as a substantial minority of patients remain seizure-free without AEDs. AS, MS and GTCS at onset of the disease are indicators of poor long-term seizure control.

Introduction

Juvenile myoclonic epilepsy (JME) is a common age related genetic generalized epilepsy syndrome and accounts for up to 10% of all epilepsies (Janz and Christian, 1957; Janz, 1969; Janz, 1985). Seizures typically manifest in adolescence, between 13 and 19 years. The syndrome is characterized by myoclonic seizures (MS), generalized tonic clonic seizures (GTCS) and absence seizures (AS) (Janz and Christian, 1957) Interictal EEG abnormalities comprise generalized polyspike — waves at 4—6 Hz with photosensitivity in about 30% of cases (Janz, 1985) and up to 90% after prolonged photic stimulation (Appleton et al., 2000). Under appropriate antiepileptic drug (AED) treatment the majority of patients will enter remission (Janz and Christian, 1957; Panayiotopoulos et al., 1994; Gelisse et al., 2001; Martinez-Juarez et al., 2006; Baykan et al., 2008; Camfield and Camfield, 2009; Geithner et al., 2012; Senf et al., 2013). However, after AED withdrawal, the relapse rate may be as high as 91% (Janz, 1985; Shinnar et al., 1994; Delgado-Escueta et al., 1997; Kleveland and Engelsen, 1998; Chakravarty et al., 2007). Only few studies focused on long-term seizure outcome of this syndrome (Martinez-Juarez et al., 2006; Baykan et al., 2008; Camfield and Camfield, 2009; Geithner et al., 2012; Senf et al., 2013). The decision about when to start tapering off medication or eventually withdraw AEDs is discussed controversially in the literature. Many authors recommend lifelong treatment (Dreifuss, 1989; Delgado-Escueta and Enrile-Bacsal, 1984; Panayiotopoulos et al., 1994; Penry et al., 1989; Grünewald and Panayiotopoulos, 1993; Kleveland and Engelsen, 1998; Martinez-Juarez et al., 2006; Meador, 2008). In view of chronic AED toxicity, which may be a special problem with valproic acid (VPA) (Genton et al., 2001; Luef et al., 2002; Luef et al., 2004; Rinnerthaler et al., 2005; Teich et al., 2004; Isojärvi et al., 1993; Hirsch et al., 2003), which is still regarded as the most effective drug in this syndrome, a lifelong treatment has to be carefully weighted against the risks of seizure recurrence.

The aim of our study was to analyse the long-term seizure outcome of patients with JME in a large hospital based cohort of a single center.

Methods

Study design and setting: Retrospective hospital based observational study with a cross sectional design performed in a large outpatient clinic of a university hospital as the only neurology service serving a population of more than 1 million.

All data of patients treated at the seizure outpatient clinic at the Department of Neurology, Medical University Innsbruck, Austria between 1975 and 2006 were entered prospectively into a database. We identified 242 patients with the diagnosis of JME in this database. Inclusion criteria were: (1) a diagnosis of JME, based on the criteria of the International League against Epilepsy (ILAE), (Commission on Classification and Terminology of ILAE, 1989); (2) a medical treatment period of more than 2 years in our outpatient clinic. Exclusion criteria were: (1) traumatic or infectious brain injury before the onset of JME and (2) gross structural pathology on neuroimaging (CT/MRI). Fifty-eight out of 242 patients had a treatment period of less than 2 years, seven patients died and charts of two patients were missing.

The national death registry records only the ICD coded condition judged by the reporter to be the primary cause, with no record of comorbidities/contributors. These were chronic kidney disease (two patients); mental and behavioral disorders due to use of alcohol (2), cardiomyopathy (1), poisoning by unspecified drug or medicinal substance (1) and grand mal status epilepticus (1). Thus, 175 patients remained for further analysis. We extracted clinical information including age at seizure onset, age at the last visit in the outpatient clinic, gender, first documented seizure type at onset (during the first year of disease), last documented seizure type (during the last year of active epilepsy) and photosensitivity (as assessed by routine EEG recordings at any time during the course of disease). In addition data on neuroimaging (MRI, CT), febrile convulsions (FC), family history of epilepsy, neurological examination, response to medical treatment with various AEDs and seizure outcome with or without AED therapy were extracted from the patients' charts.

The endpoint of our study was defined as the seizure outcome at the last visit in our outpatient clinic. Three categories were defined: (1) seizure-free for more than one and less than or equal to 2 years, (2) seizure-free for more than 2 years and (3) not seizure-free.

Statistical analysis

Data processing and analysis were performed with SPSS Version 12.0 for Windows. The statistical methods were descriptive statistic Chi^2 test for categorical variables for group comparisons and *t*-tests for continuous variables. Significance was defined as *p*-value of ≤ 0.05. Binary linear regression analysis was used to identify predictive factors for seizure outcome.

Non-parametric data (age at seizure onset, age at last visit, etc.) were analysed by Kruskal—Wallis and

Table 1 Demographic data.

Patients	*N* = 175 (111 women)
Median age at seizure onset	15 years (range 3—46)
Median age at follow up	38 years (range 14—87)
Median observation period	8 years (range 2—38)
Family history of epilepsy	41% (71/175)
Febrile seizures	4% (7/175)
Photosensitivity	14% (24/175)

Mann—Whitney tests for multiple and pair-wise comparisons, respectively (Tables 1—6).

Results

Patients

We analysed 175 patients (111 women), median age at seizure onset was 15 years (range 3—46) and median age at the last follow up was 38 years (range 14—87) with a median observation period of 8 years (range 2—38). Mean epilepsy-duration was 24 years (SD ± 14.2), median 23 years (range 3—73). Seventy-one (41%) patients had a positive family history of epilepsy; seven (4%) had a history of febrile convulsions.

Twenty-four patients (14%) showed photosensitivity on routine EEG recordings (Table 1).

Overall seizure outcome

Sixty-two percent (109/175) of patients were completely seizure-free more than one year under AED treatment, 53% (94/175) were seizure-free for more than 2 years, including 16 patients (9%) without taking any AED.

Thirty-one percent (54/175) of patients were seizure-free between 2 and 5 years, 15% (26/175) between 6 and 10 years and 8% (14/175) more than 10 years.

Thirty-eight percent (66/175) were not seizure-free despite appropriate AED treatment (Table 2).

Table 2 Duration of seizure-freedom at the last follow-up in patients with JME (Total number of patients = 175; total number of more than one year seizure-free patients = 109).

Time of FU	1—2 years *n* (%)	2—5 years *n* (%)	6—10 years *n* (%)	≥10 years *n* (%)	Total ≥2 years *n* (%)	Total ≥2 years with AED *n* (%)	Total ≥2 years without AED *n* (%)
N = (%)	15/109 (14)	54/109 (49)	26/109 (24)	14/109 (13)	94/175 (54)	78/175 (45)	16/175 (9)
Seizure-free pts with photosensitivity *N* = (%)	—	6/109 (6)	7/109 (6)	4/109 (4)	17/175 (10)	11/175 (6)	6/175 (3)

Abbreviations: FU = Follow up; JME = Patients with juvenile myoclonic epilepsy; f = Female; m = Male; AED = Antiepileptic drug; pts = Patients.

Table 3 Outcome and documented seizure types at first year of epilepsy.

	Seizure-free ≥1year *n* (%) *N* = 109 (62%)	Not seizure-free ≥1year *n* (%) *N* = 66 (38%)	*p**
Myoclonic seizures only	28 (26)	14 (21)	*0.585*
Generalized tonic clonic seizures only	25 (23)	15 (23)	*1.000*
Absence seizures only	10 (9)	5 (8)	*0.788*
Myoclonic seizures + absence seizures	2 (2)	3 (4)	*0.367*
Myoclonic seizures + generalized tonic clonic seizures	36 (33)	16 (24)	*0.396*
Myoclonic seizures + generalized tonic clonic seizures + absence seizures	3 (3)	7 (11)	*0.043**
Absence seizures + generalized tonic clonic seizures	5 (4)	6 (9)	*0.335*

* Statistically significant at $p \leq 0.05$.

Table 4 Outcome and documented seizure types in the year before becoming seizure-free or seizure types of persisting seizures at follow up.

	Seizure-free ≥1year *n* (%) *N* = 109 (62%)	Not seizure-free ≥1year *n* (%) *N* = 66 (38%)	*p*[*]
Myoclonic seizures only	23 (21)	23 (35)	*0.052*
Generalized tonic clonic seizures only	30 (28)	17 (26)	*0.861*
Absence seizures only	5 (4)	2 (3)	*0.712*
Myoclonic seizures + absence seizures	2 (2)	4 (6)	*0.200*
Myoclonic seizures + generalized tonic clonic seizures	40 (37)	10 (15)	*0.003*[*]
Myoclonic seizures + generalized tonic clonic seizures + absence seizures	4 (4)	4 (6)	*0.478*
Absence seizures + generalized tonic clonic seizures	5 (4)	6 (9)	*0.335*

[*] Statistically significant at $p \leq 0.05$.

Seizure outcome and seizure types in the first year of epilepsy

Patients who were not seizure-free at the last follow up were significantly more likely to have had all three seizure types within the first year of their epilepsy compared to seizure-free patients (≥1 year seizure-free at the last follow up; seizure-free 3% vs. not seizure-free 11%, df = 1, $p = 0.043$) (Figure 1, Table 3).

Seizure outcome and persisting seizure types

Seizure-free patients were significantly more likely to have MS and GTCS as their last seizure type before becoming seizure-free (37% vs. 15%, $p = 0.003$), whereas in the not seizure-free group MS only and GTCS only tend to persist (Table 4).

Antiepileptic drug treatment

The majority of patients (66% of seizure-free and 60% of those with persisting seizures) were on VPA monotherapy. Other drugs used in monotherapy were levetiracetam (LEV), topiramat (TPM), primidon (PRM) or lamotrigin (LTG). Patients taking LEV, TPM or PRM did not differ in seizure outcome. In contrast, patients receiving LTG became less frequently seizure-free (15%; $p = 0.024$). Three percent of patients (one patient of the seizure-free group and

Table 5 Antiepileptic drug treatment and outcome, multiple antiepileptic drugs per patient are possible.

Antiepileptic drugs	>2 years seizure-free *n* (%) *N* total = 94 patients	Not seizure-free *n* (%) *N* total = 81 patients	*p*[*]
Valproic acid	62/94 (66)	49/81 (60)	*0.529*
Carbamazepine	1/94 (1)	4/81 (5)	*0.183*
Topiramat	3/94 (3)	7/81 (9)	*0.190*
Levetiracetam	8/94 (9)	13/81 (16)	*0.162*
Lamotrigin	2/94 (2)	9/81 (11)	*0.024*[*]
Primidon	6/94 (6)	8/81 (10)	*0.417*
Clonazepam	1/94 (1)	1/81 (1)	*1.000*
Phenobarbital	2/94 (2)	5/81 (6)	*0.251*
Zonisamide	1/94 (1)	1/81 (1)	*1.000*
Ethosuximide	–	2/81 (2)	*0.212*
No antiepileptic drug treatment	16/94 (17)	3/81 (4)	*0.003*[*]

[*] Statistically significant at $p \leq 0.05$.

Table 6 Overview long-term outcome studies. Abbreviations: MS = Myoclonic seizure; AS = Absence seizure; GTCS = Generalized tonic clonic seizure; JME = Patients with juvenile myoclonic epilepsy; FU = Follow up; sd = Standard deviation; CAE = Childhood absence epilepsy.

	Martinez-Juarez et al., 2006. Brain	Baykan et al., 2008. Neurology	Camfield & Camfield, 2009. Neurology	Geithner et al., 2012. Epilepsia	Senf et al., 2013. Neurology
	Long-term follow-up	Long-term follow-up	Population-based study	Long-term follow-up	
N=	222 patients	48 patients	23 patients	31 patients	66 patients
Mean follow-up	12.4 years (range 1—41)	19.6 ± 5.7 years	25.8 ± 2.4 years	39.1 years (sd ± 11.9; range 25—63)	44.6 years (± 13.7; range 20—69)
Definition of seizure-free period	No exact definition of time	Benign course: no GTCS and < 2 MS/month	No exact definition of time	5 years	5 years
Outcome: seizure-free patients with benign course	Classic JME: 58% (93/161) seizure-free (mean FU 12.4 yrs; range 1—41 years) CAE/JME: 9% (3/35) seizure-free (FU 5—52 years) JME ± adolescent onset pycnoleptic AS: 56% (10/18) seizure-free (mean FU 13.4 years; range 5—26) JME and astatic seizures: 62% (5/8) seizure-free (mean FU 11.1 years; range 3—18).	66% (32/48) benign course (mean FU 39.1 years ± 11.9; range 25—63)	78% (18/23) seizure-free (mean FU 25.8 ± 2.4 years; range 20—30 years)	67.7% (21/31) seizure-free (mean FU 39.1 ± 11.9; range 25—63)	59.1% (39/66) seizure-free (mean FU 22.9 ± 10.9; range 5—46)
Seizure-free patients without AEDs	Classic JME: 9% (8/93) patients, duration 1—11 years	8% (4/48) patients, mean duration 5 years	25% (6/24) patients, for 5—23 years	19% (6/31) patients, mean duration 19.2 years (SD ± 8.01, range 8—30)	16.7% (11/66) patients, at least during last 5 years

four of the not seizure-free group) received temporarily carbamazepine (CBZ) once in their medical history. At FU none of them had CBZ anymore. Eight percent of patients were on polytherapy (Table 5).

Nine percent (16 patients) of the patients were seizure-free without any AED-therapy.

The first documented seizure types of these 16 patients were MS only in 46% of patients, AS only in 26%, GTCS only in 8%, AS and GTCS in 8%, AS and MS in 4% and all three seizure types in 8% of the patients.

Discussion

In this long-term study with an observation period of up to 38 years, 62% of patients with JME achieved seizure freedom of all seizure types for more than one — and 53% of patients for more than 2 years. Nine percent of all patients were seizure-free for more than 2 years without any AED, 38% of patients had no seizure control. The presence of AS, MS and GTCS within the first year of epilepsy was associated with poor long term seizure control (seizure-free 3% vs. not seizure-free 11%, df = 1, $p = 0.043$).

In contrast to the commonly held belief, that JME requires lifelong treatment we identified patients with good seizure outcome based on the occurrence of different seizure types (Dreifuss, 1989; Delgado-Escueta and Enrile-Bacsal, 1984; Panayiotopoulos et al., 1994; Penry et al., 1989; Grünewald and Panayiotopoulos 1993; Kleveland and Engelsen, 1998; Martinez-Juarez et al., 2006; Meador, 2008). In the seminal description of JME by Janz and Christian (1957), 43% of patients had MS as first seizure type

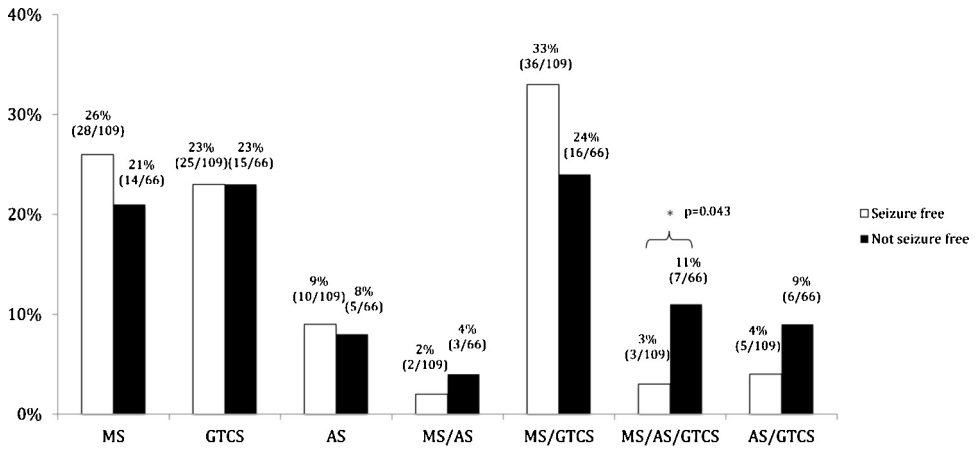

Figure 1 Seizure types in the 1st year of epilepsy. Abbreviations: MS = Myoclonic seizure; GTCS = Generalized tonic clonic seizures; AS = Absence seizures; * = Statistically significant.

persisting for several months or years; 32% had MS and GTCS; 25% had GTCS as the first seizure type followed by MS after several years (Janz and Christian, 1957). However, they did not report on different outcomes depending on the type of the first seizure and the evolution at the early phase of the disease. In a retrospective study of the Marseille group, patients with a lifetime history of all three seizure types were significantly more often not seizure-free (Gelisse et al., 2001). Another prospective study (Guaranha et al., 2011) has also confirmed this as a negative predictor. Two other studies did not find any association between seizure types in JME and outcome (Baykan et al., 2008; Geithner et al., 2012).

In our study, AS had a tendency to remit, while MS and GTCS persisted longer. MS and GTCS were the most prevailing combination of seizure types in those who became eventually seizure-free (seizure-free 37% vs. not seizure-free 15%, $p = 0.003$).

Only few patients had MS only: the occurrence varies from 1% in our study to 11.7% in an observational study (Canevini et al., 1992). Janz and Christian described an antagonism of MS and GTCS: some patients had more isolated MS and less frequently GTCS preceded by MS, the other group of patients had more GTCS preceded by MS and rare isolated MS. The predominance of isolated MS was regarded as indicator of good prognosis of seizure outcome (Janz and Christian, 1957). The total number of GTCS was not predictive in two other studies (Baykan et al., 2008; Geithner et al., 2012).

In our study 14% (24/175) of patients showed photosensitivity, 71% (17/24) of them were seizure-free. In the literature the number varies from 8% (Canevini et al., 1992) to 90% (Appleton et al., 2000), as reported in a review from Kasteleijn-Nolst Trenité et al. (2013). Responsible for this different prevalence are factors like sex (photoparoxysmal response was mainly found in female, Kasteleijn-Nolst Trenité, 1989), medication (VPA is effective in patients with photoparoxysmal response, Jain et al., 1997), time of EEG (there seems to be a higher sensibility of EEG in the morning, Labate et al., 2007), methodology of photic stimulation (a continuous performance for up to 5 min seems to increase the prevalence of photoparoxysmal response, Appleton et al., 2000) and occurrence of sleep deprivation (Scollo-Lavizzari and Scollo-Lavizzari, 1974).

Consistent with the findings of other studies (Baykan et al., 2008; Geithner et al., 2012) the presence of photosensitivity in our study was not considered as a prognostic factor.

A prospective study showed the implication of reflex traits (eye-closure, intermittent photic stimulation, neuropsychological tasks like mental calculations, language and praxis induction). In five patients seizures were triggered by intermittent photic stimulation and none were seizure-free compared to 18.5% of those without such seizures ($p = 0.005$). Similarly six patients with eye closure induced seizures had a poor seizure outcome (21.4% vs. 0.0%, $p = 0.025$) (Guaranha et al., 2011).

So far five studies focused on the long-term evolution of seizure types in JME (Martinez-Juarez et al., 2006; Baykan et al., 2008; Camfield and Camfield, 2009; Geithner et al., 2012; Senf et al., 2013). In these studies, the outcomes varied from 66% (32/48) of patients with a benign course (Baykan et al., 2008: mean follow-up 39.1 years $\pm$ 11.9; range 25—63) up to 78% (18/23) (Camfield and Camfield, 2009: mean follow-up 25.8 $\pm$ 2.4 years; range 20—30 years), 67.7% (21/31) seizure-free patients (Geithner et al., 2012: mean follow-up 39.1 $\pm$ 11.9; range 25—63 years) and 59.1% (39/66) (Senf et al., 2013: mean follow-up 44.6 $\pm$ 13.7; range 20—69 years). In a multicenter long-term follow-up study with a subgroup analysis on different seizure types, seizure-freedom was found in 58% patients with classical JME (93/161 patients; mean follow-up 12.4 years; range 1—41 years), 9% patients with childhood absence epilepsy evolving into JME (3/35 patients; follow-up from 5 to 52 years), 56% patients with JME and adolescent onset pyknoleptic absences (10/18 patients; mean follow-up 13.4 years; range 5—26) and 62% patients with JME and astatic seizures (5/8 patients; mean follow-up 11.1 years; range 3—18) (Martinez-Juarez et al., 2006).

According to literature the rate of seizure freedom in our study (53% seizure-free patients for more than 2 years) was low. One possible reason could be the retrospective design of the study. When patients become seizure-free they may

fail coming to the follow-up. Comparing to Martinez-Juarez et al. (2006) our outcome correlates to the ''classical JME'' subgroup. Maybe the other subgroups were underdiagnosed in our population. Finally in a specialized clinic, there is a higher proportion of difficulty to treat patients.

The decision when to start tapering off or eventually withdraw AEDs is discussed controversially, and so far there is no reliable prognostic marker. Previous studies reported following numbers of seizure-free patients without AEDs: Baykan et al. (2008) — 8% (4/48) of patients, mean 5 years without AEDs; Geithner et al. (2012) — 19% (6/31) of patients (mean duration 19.2 years; SD ± 8.01, range 8—30); Senf et al. (2013) — 16.7% (11/66) of patients (at least 5 years); Camfield and Camfield (2009) — 25% (6/24 patients, duration for 5—23 years); Martinez-Juarez et al. (2006) — 9% (8/93) of patients with classic JME (duration 1—11 years); (Martinez-Juarez et al., 2006; Baykan et al., 2008; Camfield and Camfield, 2009; Geithner et al., 2012; Senf et al., 2013) (Table 6).

In our study the presence of all three seizure types (MS, AS and GTCS) within the first year of JME onset predicted a poor seizure outcome. The recognition of this prognostic marker is of major clinical value when the decision to withdraw AEDs has to be made.

According to the literature (Janz and Christian, 1957) patients with MS only at JME onset followed later by GTCS may have a more favorable prognosis. In our study 77% (135/175) of the total patient cohort had MS and later GTCS in the first year of epilepsy. The majority (66%; 89/135) of patients had a benign course and was seizure-free at the last follow-up.

To predict the clinical course of JME poses a challenge as only few reliable clinical prognostic markers are known. One well described marker is the relationship between psychiatric comorbidity in JME and drug resistance (Gelisse et al., 2007; Trinka et al., 2006; Baykan et al., 2008; De Araújo Filho et al., 2008). Another positive prognostic factor seems to be MS only at onset (Jain et al., 1997). In our study, two out of 16 patients who were seizure-free without AEDs had MS only at the last follow-up.

However, it would be necessary to have clinical or biological prognostic factors in the early stage of a disease. Until now, clinical markers which are easy to evaluate like photoparoxysmal response, family history of epilepsy, sex, age at onset of seizures, neuroimaging data, delayed diagnosis and total number of GTCS could not be identified as prognostic factors (Gelisse et al., 2001; Baykan et al., 2008; Geithner et al., 2012).

A prospective study showed the implication of reflex traits (eye-closure, intermittent photic stimulation, neuropsychological tasks like mental calculations, language and praxis induction) on prognosis. Patients with precipitant factors in praxis induction and language were significant less seizure-free. There was no correlation between the presence of focal EEG abnormalities and seizure outcome, but interestingly there was an association between focal EEG abnormalities and the type of reflex traits. The majority of patients with frontal EEG abnormalities had praxis induction, one patient with occipital abnormalities was photosensitive and all three patients with temporal abnormalities had psychiatric disorders (Guaranha et al., 2011).

The major limitation of our study is the retrospective nature with possibly missing information in the patients' charts. Due to the lack of consistent criteria in terms of tapering off medication, there would always be a bias towards a longstanding treatment and the true proportion of complete seizure-free patients without medication cannot be assessed. In fact, we propose that a long-term seizure-freedom of 5 years should be achieved.

As discussed by Geithner et al. (2012) most of the follow-up studies including ours represent only easy-to-follow patients. In face of the known underlying psychological pathology with behavioral abnormalities and compliance problems in JME, the investigated hospital cohort represent a selective population of those who prefer to stay in outpatient care, even if they are seizure-free (Perini et al., 1996; Trinka et al., 2006; Gelisse et al., 2007; De Araújo Filho et al., 2008; Baykan et al., 2008; Camfield and Camfield, 2009). Only large scale prospective multicenter studies with long observational periods can inform clinicians about the long-term course and help determine the time when to taper off the AED treatment. Further prospective controlled studies are needed to define the long-term prognosis with and without AED treatment and to set up prognostic factors.

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