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Frequency, causes and phenomenology of late seizure recurrence in patients with juvenile myoclonic epilepsy after a long period of remission

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Summary

Purpose: To determine frequency, causes, and phenomenology of late seizure recurrence (SR) in patients with juvenile myoclonic epilepsy (JME) after remission of at least 1 year.
Methods: Among 2722 epileptic patients from tertiary referral center, we retrospectively identified 105 patients (62 females; mean age 22.3 ± 7.2 years) with an established diagnosis of JME. All patients were treated with valproates (83.3%), or lamotrigine, topiramate, phenobarbital, add-on clobazam, or combinations (16.2%).
Results: The median period of follow-up was 4.2 ± 3.2 (range: 1—17) years. SR occurred in 74 patients (70.5%) after median period of 2.4 ± 3.2 years. Twenty-two patients (29.7%) experienced myoclonic seizures (MS), 13 (17.7%) generalized tonic—clonic seizures (GTCS), 37 (50%) a combination of MS and GTCS, and two (2.6%) a combination of MS, GTCS and absence seizures. SR was associated most frequently with sleep deprivation and AED withdrawal, and rarely with alcohol intake, drug abuse, photostimulation, or menstruation. No provoking factors for SR were identified in 31.1% and 45% of cases with MS and GTCS, respectively. The majority of patients (59/74) had a single SR. A second SR occurred less frequently in patients in whom valproate dosage was increased after the first SR ($p = 0.0048$).
Conclusion: Late SR (mainly MS and GTCS) is detected frequently after prolonged follow-up in patients with JME despite the use of best-known therapy, usually due to AED withdrawal or erratic life style. Instead of futile efforts to persuade the patient to conform to restrictive life style, it is probably more efficient to use initial higher doses of AEDs.

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Introduction

Juvenile myoclonic epilepsy (JME) is an age-related, idiopathic, generalized epileptic syndrome presenting with bilateral, arrhythmic myoclonic seizures (MS), generalized tonic–clonic seizures (GTCS), and less frequently typical absence seizures (AS).[1,2] The most common factors that provoke seizures are sleep deprivation, fatigue, excessive alcohol intake, stress, photostimulation, and menstruation.[1,3–5] Valproate (VPA) is the drug of choice that leads to complete remission of seizures in a majority of patients.[2,6,7] However, the frequency of seizure recurrence (SR) during long-term follow-up, despite VPA therapy, is not well known.

The aim of this study is to estimate frequency, causes, and phenomenology of late SR in patients with JME after at least a 1-year period of remission.

Patients and methods

Among 2722 epileptic patients from the Department of Epileptology of the Institute of Neurology CCS (tertiary referral center) hospitalized between January 1987 and December 2003, we retrospectively identified 137 patients with established diagnoses of JME. We used the clinical charts archive and electronic database containing all data regarding the first and all follow-up visits.

The diagnosis of JME was made if patients fulfilled all criteria according to Panayiotopoulos:[4] (1) presence of single or repetitive, arrhythmic, irregular MS, mainly occurring after awakening, predominantly in the arms; (2) normal neurological examination; (3) abnormal EEG findings presenting with generalized SW discharges (focal or background abnormalities were acceptable if other clinical criteria were justified); (4) normal CT/MR scans. Exclusion criteria were: (1) clinical and/or EEG evidence of myoclonic jerks secondary to brain hypoxia, metabolic diseases or other structural brain abnormalities;[8] (b) eyelid myoclonia with absence seizures; (c) self-induced epilepsy; (d) pure forms of photosensitive epilepsy; (e) poor drug compliance and (f) without remission during the first year.

Twenty patients satisfied exclusion criteria (two with eyelid myoclonia with absences, four with structural brain abnormalities; nine with poor drug compliance; five did not gain remission in the first year). Ten patients were lost for follow-up, and two patients dropped out due to their refusal to comply with AED regimen. Finally, 105 patients entered our cohort.

All patients were treated with antiepileptic drugs (AED) and followed on 6 month scheduled visits for at least 1 year. Additional visits were undertaken during 1 week following SR. Compliance was verified as reported by patients and by monitoring of plasma drug levels at each visit. Authors performed all follow-up visits, governed the therapy, determined SR, and estimated provoking factors (PF).

We defined SR as appearance of any type of solitary or repeated seizures that characterized JME (MS, GTCS, AS). Single SR completed during 24 h and multiple SR recurred in more than one 24 h period. AED withdrawal was diagnosed if the patient could confidently recall cessation in AED intake for more than 3 days (five times plasma half-life of VPA). Low plasma levels of AED (less than 50% of the level obtained at the 1-year visit) without clear anamnestic data of therapy cessation were also considered as AED withdrawal. The definition of other PF (sleep deprivation, photostimulation, menstruation, alcohol abuse, drug abuse, and emotional stress) is obvious by its name.

After a follow-up period of at least 1 year, all patients were divided into three groups according to the association of SR with PF. Patients without any SR during the follow-up period formed the first group (No_SR). Patients who had SR associated with obvious PF (usually with only one GTC in 6 months and less than five MS or AS per month) formed second group (PF_SR). Patients who had SR associated with no obvious PF (usually with two or more GTC in 6 months and more than five MS, or AS per month) formed the third group (NoPF_SR). Our policy was not to change the AED or its dose in the first two groups. However, in the third group, our policy was either to increase the dose of the original AED, to add another AED or to change therapy to different AED. After the dose had been changed, patients were followed for at least one additional year.

All patients signed forms of informed consent, approved by the Ethical Committee. Chi square, Mann–Whitney's, Kruskal–Wallis's test, Spearmen's coefficient of correlation, and descriptive statistics were used when indicated.

Results

After the introduction of AEDs, average period of follow-up was 4.2 ± 3.2 (range: 1–17) years. Demographic characteristics of the population, the number of patients with SR, and its timing are shown in Tables 1 and 2.

During the first year, VPA was used as the first monotherapy in 91 (83.8%) patients (dose range 250–2500 mg). Half of the patients treated with VPA needed 500 mg or less and 3/4 needed 1000 mg or less for complete abolition of all seizures. Lamotrigine (up to 400 mg), topiramate (up