Juvenile Myoclonic Epilepsy: When Will It End

Predictors for Long-Term Seizure Outcome in Juvenile Myoclonic Epilepsy: 25–63 Years of Follow-up.

PURPOSE: The long-term seizure outcome of juvenile myoclonic epilepsy (JME) is still controversial; the value of factors that are potentially predictive for seizure outcome remains unclear. The aim of this study was both to investigate the long-term seizure outcome in patients with JME after a follow-up of at least 25 years and to identify factors that are predictive for the seizure outcome. METHODS: Data from 31 patients (19 women) with JME were studied. All of them had a follow-up of at least 25 years (mean 39.1 years) and were reevaluated with a review of their medical records and direct telephone or face-to-face interview. KEY FINDINGS: Of 31 patients 21 (67.7%) became seizure free, in six of them (28.6%) antiepileptic drug (AED) treatment was discontinued due to seizure freedom. The occurrence of generalized tonic–clonic seizures (GTCS) preceded by bilateral myoclonic seizures (BMS) (p = 0.03), a long duration of epilepsy with unsuccessful treatment (p = 0.022), and AED polytherapy (p = 0.023) were identified as significant predictors for a poor long-term seizure outcome, whereas complete remission of GTCS under AED significantly increased the chance for complete seizure freedom (p = 0.012). The occurrence of photoparoxysmal responses significantly increases the risk of seizure recurrence after AED discontinuation (p = 0.05). SIGNIFICANCE: This study shows conclusively that JME is a heterogeneous epilepsy syndrome. Life-long AED treatment is not necessarily required to maintain seizure freedom. Several long-term outcome predictors that can potentially increase the ability of clinicians and their confidence to recommend different treatment options to patients with JME were identified.


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Commentary
Juvenile myoclonic epilepsy (JME) has long been considered to be the most common chronic idiopathic generalized epilepsy syndrome, requiring life-long antiepileptic drug (AED) therapy (1–4). Long-term seizure freedom on appropriate AED medication has been reported between 75 and 90 percent diagnosed with JME (5–7). Janz (1985) reported seizure recurrence in 91% of patients studied when AED dosages were lowered or withdrawn completely (6). More recent patient datasets are emerging supporting the notion that the seizures seen in JME do not tend to recur following discontinuation of AED medications (5, 8).

The recent review by Geithner et al. (2012) is a retrospective study summarizing the natural history of JME in 31 patients followed over several decades (mean follow-up, 39.1 years) in the northeast region of Germany. The study is unique in that it establishes several predictors of seizure remission and reaffirms that JME is a heterogeneous syndrome. As a brief review, semiological criteria required to diagnose JME must include, at least, bilateral myoclonic seizures that typically occur upon awakening. JME often includes generalized tonic–clonic seizures and, less commonly, absence seizures. Geithner et al. complements recently published studies demonstrating that the natural course of JME depends on its semiology frequency. For example, Martinez-Juarez et al. (2006), subclassified JME into four subtypes or subsyndromes: 1) classic JME, 2) childhood absence epilepsy (CAE) persisting as JME, 3) JME with adolescent onset pyknoleptic absences, and 4) JME with astatic seizures. Classic JME demonstrated the most favorable outcomes: 58% were completely controlled on AED therapy, and 5% remitted following discontinuation of medications. CAE evolving to JME has been shown to exhibit the worst clinical outcome.

Such clinical classifications may complement linkage studies demonstrating JME has a high genetic predisposition. Seven loci have so far been associated with JME. These loci include 1) CACNB4 encoding a calcium channel β subunit, 2) GABRA1 encoding an α subunit of the GABA-A receptor, 3) CLCN2 encoding a chloride channel densely expressed in brain regions inhibited by GABA, 4) GABRD encoding the δ subunit of the GABA receptor, and 5) a poorly understood EFHC1 gene associated with JME; in addition, 6) chromosome 15q14, and 7) the BRD2 gene on chromosome 6p21 have also been linked to JME.

Geithner et al. reported that 21 of the 31 patients identified in the study became seizure free with an appropriate AED regimen, predominantly monotherapy. AED therapy was withdrawn (initiated by either patient or physician) in nine of the individuals in the cohort. Seizures in six of the nine patients (28.6% of the 21 seizure-free patients) remitted without AED therapy for a mean of 19.1 years (range, 8–30 years). These
Juvenile Myoclonic Epilepsy

data are higher than in the study by Camfield and Camfield (2009), who reported total seizure remission in 17% of their sample of 24 patients (5). Geithner et al. reported a recurrence of seizures in three of the nine patients after 1, 10, and 38 years. This important finding suggests that the probability for breakthrough clinical seizures in these patients may remain at some significant level above the normal population. That is, the expressed phenotype converted to a stable or dormant epileptic network even in the absence of an AED regimen. However, the genotype was obviously unchanged and capable of reverting to a pathophysiological state.

A unique feature of the study by Geithner et al. is the identification of significant predictors of long-term seizure outcome. An unfavorable outcome was strongly associated with the following: 1) appearance of generalized tonic-clonic seizures in the presence of bilateral myoclonic seizures, 2) demonstration of a photoparoxysmal response, and 3) intractability of the epilepsy to multiple AEDs.

Of interest, no clear consistency yet exists for EEG as a predictor of response to AEDs (9). Several recent studies have explored structural alterations in JME involving frontothalamic networks as identified by neuroimaging. In particular, diffusion tensor imaging (DTI) has demonstrated that fractional anisotropy in the supplementary motor cortex predicted disease severity (10). Furthermore, this emerging literature has attempted to correlate DTI findings with subtle cognitive dysfunction. Geithner et al. does not discuss the neuropsychological profile of their patients, nor the evolution over time of any neurocognitive deficits recently discussed in the literature (11).

The natural history of JME as presented by Geithner et al. sets the stage for attempting to better understand a specific generalized epilepsy as a heterogeneous syndrome likely involving extensive cortical-subcortical epileptic circuitry. This study demonstrates a diagnostic superiority to other retrospective datasets by requiring not only review of the medical records, but also a telephone interview or a physical presence visit for all enrolled patients. The lack of neuroimaging as a prerequisite for enrollment can potentially contaminate idiopathic generalized epilepsy with cryptogenic etiologies. In addition, as reported by the authors, the inclusion of CAE in the study may have biased the study by introducing a subclass of JME with the worst outcomes.

This study sets the stage for future work utilizing genetic testing of patients diagnosed with the idiopathic generalized epilepsies. Such studies can demonstrate the expression of multiple gene loci associated with variable susceptibilities to medical treatment and outcome. Additionally, this study complements data generated by both cutting-edge neuroimaging techniques, such as DTI, and neuropsychological studies for understanding network connectivity and neurocognitive function seen in a common class of epilepsies.

by Marvin A. Rossi, MD, PhD

References

Instructions
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3. Are you the Main Assigned Author?  ☒ Yes ☐ No

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Marvin A Rossi MD, PhD

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