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Juvenile myoclonic epilepsy-what does the future look like?

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Juvenile Myoclonic Epilepsy—What Does the Future Look Like?

Prognosis of Juvenile Myoclonic Epilepsy 45 Years After Onset: Seizure Outcome and Predictors.

Senf P, Schmitz B, Holtkamp M, Janz D. *Neurology* 2013;81:2128–2133.

OBJECTIVES: Juvenile myoclonic epilepsy (JME) is the most common idiopathic generalized epilepsy subsyndrome, contributing to approximately 3% to 11% of adolescent and adult cases of epilepsy. However, little is known about the long-term medical evolution of this clinical entity. The aim of this study was to analyze long-term outcome in a clinically well-defined series of patients with JME for seizure evolution and predictors of seizure outcome. METHODS: In this retrospective cohort study, we analyzed seizure outcome in 66 patients who had JME, were treated at the Department of Neurology, Charité–Universitätsmedizin Berlin, and were initially diagnosed by a single senior epileptologist. RESULTS: After a mean follow-up time of 44.6 years (20–69 years), 59.1% of patients remained free of seizures for at least 5 years before the last contact. Among the seizure-free patients, 28 (71.8%) were still taking antiepileptic drugs and 11 (28.2%) were off medication for at least the last 5 years. We identified manifestation of additional absence seizures at onset of JME as an independent predictor of an unfavorable outcome regarding seizure freedom. CONCLUSIONS: A significant proportion of patients with JME were seizure-free and off antiepileptic drug therapy in the later course of their disorder. Patients with JME and additional absence seizures might represent a different JME subtype with a worse outcome.

Commentary

Best management of juvenile myoclonic epilepsy (JME) over the long term is inherently challenging. Since JME patients by definition have no underlying structural cause of epilepsy and have normal neurologic examinations, most risk factors for seizure recurrence do not apply in making the decision to stop antiseizure medication. Long-term observational studies or historical reviews are therefore imperative for revealing the natural course of the illness. Only the persistent EEG abnormalities remind us that JME patients carry seizure risk with them as they do their own fingerprint, both patterns predestined by their DNA. As the authors of the recent paper "Prognosis of juvenile myoclonic epilepsy 45 years after onset" point out, information on long-term outcome has thus far been available for only 5 years of follow-up. The current study reports on the outcome of 66 patients, at a single center, with JME whose seizure course was analyzed retrospectively for a minimum of 20 years and a median of 46 years. These 66 patients comprised 80% of their entire JME population of 82 patients and were determined to be representative of such. Their findings were that 39 (59%) of these patients were seizure-free for at least 5 years before the last contact and that 11 of these, or 17% of the entire cohort, were seizure-free while not taking antiseizure medications during this period of time. The presence of absence seizures at epilepsy onset was an adverse predictor for seizure freedom. A surprising finding was that primidone was quite effective, with 11 of 15 patients taking primidone monotherapy reported as seizure-free. This demonstrates a treatment approach in this center that may deserve more broad geographic consideration.

In the Revised Terminology and Concepts for Organization of the Epilepsies from 2010, JME stands as an electroclinical syndrome with onset in adolescence and meets the criteria for syndrome since it is a "complex of clinical features, signs, and symptoms that together define a distinctive, recognizable clinical disorder" (1). The modern age of this syndrome began with its description published in 1957 by Janz and Christian in the journal *Deutsche Leitschrift fur Nervenheilkunde*, in an article entitled "Impulsiv-Petit mal" (2). It was named for Janz after this date, however the name was changed to Juvenile Myoclonic Epilepsy by the International League Against Epilepsy in 1975 (3).

Prognosis is often included as part of a syndromic complex, but the long-term course of JME has never been very clear. With due respect to the Revised Terminology creators, the name JME contributes to a confounded perception of its prognosis. The term "juvenile" refers to the age of onset, but for many patients, families, and even practitioners, the term implies that as the patient matures, the syndrome will resolve. JME is not a pediatric epilepsy syndrome likely to remit with the passing of adolescence, but this is belied by its very nomenclature.

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The risk factors associated with seizure recurrence, which in turn influence the decision to continue treatment long term, are fairly straightforward. They include structural lesions, neurologic disability, persistently abnormal EEGs, and a history of frequent or difficult to control seizures (4–6). These factors are also those that prompt initial treatment of seizures and are important for making an early diagnosis of epilepsy (7). They are intuitive and concrete and make sense to both the neurologist and the patient. Discussing the risks for seizure occurrence with a patient may be hard, but understanding the prognostic factors makes the medication decisions relatively easy.

JME is thought to be a genetically imparted syndrome. Five JME genes have autosomal dominant inheritance. These cause primarily channelopathies and are comprised as follows: calcium channel beta4 subunit, (CACNB4) calcium channel sensor receptor (CASR), GABA receptor alpha one subunit (GABRα1), GABA receptor delta subunit (GABRD), and myoclonin 1/one EF-hand containing gene (myoclonin1/EFHC1). There are multiple susceptibility genes that participate in the genetic epistasis that produces JME, including malic enzyme 2, connexin 36, and bromodomain-containing 2, but many more are thought to be as yet unraveled (8). Epistasis is when the effect of one gene depends on the presence of one or more "modifier genes" (9). The effect of epistasis is due to influences of multiple genes, in which the independent effect of the gene is subserved by the interaction between the genes. The result, among other options, may be synergistic or completely opposite of the effect of one of the involved genes. This complexity accounts for the obscured inheritance patterns, which must be present in JME.

And yet, known JME genes account for less than 10% of patients. EFHC1 detection is available via Athena Neurodiagnostics (Worcester, MA), which is expected to be present in less than 7% of JME patients. How do we advise JME patients, with no family history, regarding their prognosis when their risk factors are locked in their DNA? A reasonable explanation is that JME is "multigenic." The scientific term "epistasis" is probably best avoided at least in part because it sounds very close to the medical term for "nosebleed."

This commentary is focused on the long-term prognosis of JME and application of risk assessment in the decision to continue treatment. In another recent report on the long-term outcome of JME, in which a mean of 40 years of patient follow-ups were reviewed, similar outcomes were found: 18 of 35 patients (55%) were seizure-free for the terminal 5 years of evaluation and 4 (22%) of these were off antiseizure medications (10). The next question then is, Does guidance from risk factors make a difference in outcomes? Evidence suggests perhaps not greatly, since 60% of epilepsy patients in general can be expected to enter remission with treatment (11). Even in a cohort of 246 refractory epilepsy patients followed prospectively for 3 years, 15% had experienced a 6-month remission during the study (12). These rates of remission surely reflect interactions between external and internal factors: judicious management and the underlying severity spectrum of the epilepsies. Without the application of risk-factor consideration, the results would likely be worse.

On the whole, we (using the royal "we") are grateful for the information provided in the current article, albeit a fairly small study from one center. It aims to fill an important gap in our understanding of JME.

by Cynthia Harden, MD

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