How to Advance the Debate on Nonspecific vs Specific Seizure Type and Comorbidity Profile

Risk-Taking Behavior in Juvenile Myoclonic Epilepsy.


Objective: Patients with juvenile myoclonic epilepsy (JME) often present with risk-taking behavior, suggestive of frontal lobe dysfunction. Recent studies confirm functional and microstructural changes within the frontal lobes in JME. This study aimed at characterizing decision-making behavior in JME and its neuronal correlates using functional magnetic resonance imaging (fMRI). Methods: We investigated impulsivity in 21 JME patients and 11 controls using the Iowa Gambling Task (IGT), which measures decision making under ambiguity. Performance on the IGT was correlated with activation patterns during an fMRI working memory task. Results: Both patients and controls learned throughout the task. Post hoc analysis revealed a greater proportion of patients with seizures than seizure-free patients having difficulties in advantageous decision making, but no difference in performance between seizure-free patients and controls. Functional imaging of working memory networks showed that overall poor IGT performance was associated with an increased activation in the dorsolateral prefrontal cortex (DLPFC) in JME patients. Impaired learning during the task and ongoing seizures were associated with bilateral medial prefrontal cortex (PFC) and presupplementary motor area, right superior frontal gyrus, and left DLPFC activation. Significance: Our study provides evidence that patients with JME and ongoing seizures learn significantly less from previous experience. Interictal dysfunction within “normal” working memory networks, specifically, within the DLPFC and medial PFC structures, may affect their ability to learn.

Clinical Predictors of the Long-Term Social Outcome and Quality of Life in Juvenile Myoclonic Epilepsy: 20–65 Years of Follow-up.


Objective: The long-term social outcome in patients with juvenile myoclonic epilepsy (JME) is still controversial. The aim of this study was both to investigate the long-term social outcome in relation to clinical variables and to identify epilepsy-related factors that affect the quality of life (QoL) in JME patients with a follow-up of at least 20 years. Methods: A retrospective selection of 33 of 90 patients (21 female) from a tertiary epilepsy center diagnosed with JME and followed for ≥20 years (mean 37.8 years) was studied. All patients were evaluated with a thorough review of their medical records, and a subsequent face-to-face or telephone interview. QOLIE-31-P questionnaire (QoL In Epilepsy) and Beck Depression Inventory-II were used to assess the QoL and the presence and severity of depressive symptoms, respectively. Results: Of 33 patients, 18 (54.5%) became seizure-free; in 4 of the patients (22.2%), antiepileptic drug (AED) treatment was discontinued. Early and long-term seizure freedom improves both social adjustment (p = 0.02) and occupational integration (p = 0.02) and associates with a better QoL (odds ratio [OR] 2.25). A high seizure burden highly affects both aspects of personal life—family and work; notably the occurrence of frequent and/or late onset generalized tonic–clonic seizures increases the risk of concomitant diseases (p = 0.05) and lifelong AED treatment (p = 0.03), decreases the patient’s employability (p = 0.02), increases the rate of employment disability pension (p = 0.05), and considerably increases public/social spending. Seizure freedom significantly increases the QoL (p = 0.001), whereas more severe courses of epilepsy (OR 3.2), AED side effects (p = 0.04), depression (p = 0.02), and sleep disturbances (OR 2.7) considerably decrease the patient’s QoL. Significance: Although patients with JME are a heterogeneous group,
several predictors for the long-term social, family, educational, and occupational outcome have been identified in our study and should be considered in the effort to both improve the patient’s QoL as well as preserve economic resources.

**Commentary**

The findings of these three papers are an important reminder about the functional relevance of seizure control and antiepileptic drug compliance in patients with seizures triggered in the transition between sleep and awakening. The Wandschneider et al. study focuses on short-term daily functioning, measured by decision making/impulsivity, executive functions, and the working memory network. The Schneider-von-Poderwels et al. study describes long-term functioning of juvenile myoclonic epilepsy (JME) patients followed for 20 years using employment, disability, social adjustment, depression, and quality of life measures. As demonstrated in other long-term population and hospital outcome JME studies (see review in [1]), most of these patients continue to have seizures and depression, social isolation, unemployment, and social impulsiveness despite relative educational success.

Poor decision making in JME patients, evident in the Iowa Gambling Task (IGT) used by Wandschneider et al., was associated with increased activation during a visual working memory task in the dorsal lateral prefrontal cortex, but not in other parts of the visual memory network. This might reflect involvement of mainly verbal reasoning in the decision making of the IGT task and/or the lack of significant differences in the executive function skills of the JME and control groups. Increased dorsal lateral prefrontal activation during an executive function task might also represent the increased effort (2) the JME patients needed to perform the visual memory dual n-back task. Since the JME and control groups have similar scores on frontal lobe tasks, Wandschneider et al. stated that their imaging findings suggest that functional imaging might pick up subtle deficits not noted in neuropsychological testing.

Impulsivity, poor future planning, difficulty making choices based on both implicit and explicit information, and incorporating this information into future planning (impaired executive functions) are features of JME patients, as well as of patients with other seizure types (see review in [3]). Different epilepsy syndromes are also associated with the same wide range of psychiatric disorders (depression, anxiety, and psychosis) and suicidal behavior (see review in 3). Attention deficit hyperactivity disorder (ADHD) is prevalent in children and youth with epilepsy (4), and continues into adulthood in children without epilepsy (5). Nevertheless, this disorder has not been studied in adults with epilepsy, despite the high rates of inattention on neuropsychological testing (see review in 3) and impulsivity (6) on behavioral testing.

Furthermore, patients with the previously mentioned psychiatric disorders and with suicidality also have increased prevalence of epilepsy (7). Like patients with epilepsy, patients with psychiatric disorders but no epilepsy have varying degrees of impaired cognition and executive function, poor social adjustment, and problems with employment. Therefore, the similar cognitive, psychiatric, social, and occupational profile of epilepsy patients, irrespective of syndrome implies that the comorbidities are part of the disorder, reflect large scale brain involvement, and not the type of seizure. However, we still do not yet know if the brain mechanisms underlying each of the comorbidities are the same or different across epilepsy syndromes. The psychiatric literature clearly indicates that there are similarities and differences in the regional cortical and subcortical structural and functional abnormalities, and their association with the clinical, cognitive, social, and outcome in schizophrenia, depression, bipolar disorder, anxiety disorders, and ADHD.

To examine the similarities and differences in the mechanisms of the comorbidities of epilepsy, future studies should involve multimodal imaging and EEG, and recruit large representative samples of epilepsy patients with different epilepsy syndromes with and without the comorbidities who have variable seizure burden and include seizure-free patients. Prospective well-powered studies will help identify structural and functional brain biomarkers that determine if and how the comorbidities in different epilepsy syndromes evolve over time and respond to treatment of seizures and of the comorbidities.

In addition, transitions from sleep to awakening in JME (8), and in generalized tonic-clonic seizures on awakening, play a role in the pathophysiology of these epilepsy syndromes. Sleep disturbances are also found in patients who do not have epilepsy but have depression, bipolar disorder, anxiety disorder, schizophrenia and other psychoses, and ADHD (9).
Abnormal sleep is found in different epilepsy syndromes (see review in [10]) and is also associated with impaired cognitive functioning and behavior (11, 12). Therefore, studies that examine if the sleep abnormalities in these seizure disorders contribute to the associated psychopathology and cognitive impairments found in epilepsy would advance our knowledge on the underlying mechanisms of these comorbidities.

In terms of take home clinical messages, in their 20-year follow-up of JME patients Schneider-von-Poderwelis et al. found that poor quality of life was related to a severe course of epilepsy (recurrent uncontrolled seizures), antiepileptic drug adverse effects, depression, and sleep disturbances. Several studies have shown that epilepsy patients with depression experience increased adverse effects for antiepileptic drugs (13), and sleep disturbance is a common symptom of depression. In addition, in JME adverse effects of antiepileptic drugs can lead to pseudoresistance due to treatment noncompliance with subsequent poor seizure control (1). The association among these different variables (poor seizure control, depression, antiepileptic drug adverse effects, sleep disturbances, and pseudoresistance) underscores the need to rule out depression in all JME patients with poor seizure control and/or adverse antiepileptic drug effects.

An additional clinical take home message is Wandschneider and colleagues’ conclusion regarding the implications of the poor decision making of the JME patients who were not seizure free. Furthermore, clinicians should be aware of the far-reaching effects on daily living in epilepsy patients with deficits on neuropsychological testing. For example, impaired executive function and decision making, together with slow learning from experience (evident in the IGT test) and impulsivity, can lead to poor judgment, which in turn, impacts behavior and emotional responses, social interactions, educational achievements, and occupational functioning. Long-term outcome findings in epilepsy studies demonstrate dysfunction in these domains that appears to be unrelated to the epilepsy syndrome (14, 15).

by Rochelle Caplan, MD

References
Instructions
The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in four parts.

1. **Identifying information.**
Enter your full name. If you are NOT the main contributing author, please check the box “no” and enter the name of the main contributing author in the space that appears. Provide the requested manuscript information.

2. **The work under consideration for publication.**
This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking “No” means that you did the work without receiving any financial support from any third party – that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check “Yes”. Then complete the appropriate boxes to indicate the type of support and whether the payment went to you, or to your institution, or both.

3. **Relevant financial activities outside the submitted work.**
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American Epilepsy Society

Epilepsy Currents Journal
Disclosure of Potential Conflicts of Interest

Section #1 Identifying Information

1. Today’s Date: March 27, 2014

2. First Name  Rochelle     Last Name Caplan  Degree MD

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

If no, enter your name as co-author:

4. Manuscript/Article Title: How to advance the debate on non-specific vs. specific seizure type and comorbidity profile

5. Journal Issue you are submitting for:  Epilepsy Currents 14.4

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Did you or your institution at any time receive payment or services from a third party for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

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* This means money that your institution received for your efforts on this study.
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* This means money that your institution received for your efforts.
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