

## A FRONTAL ASSAULT ON THE GENERALIZED NATURE OF JUVENILE MYOCLONIC EPILEPSY

**Frontal Cognitive Dysfunction in Juvenile Myoclonic Epilepsy.** Piazzini A, Turner K, Vignoli A, Canger R, Canevini MP. *Epilepsia* 2008;49(4):657–662. **PURPOSE:** The aim of the present study was to investigate the possible frontal cognitive dysfunction in patients with juvenile myoclonic epilepsy (JME) and to compare the results with those of patients with frontal lobe epilepsy (FLE) and temporal lobe epilepsy (TLE), as well as with controls. **METHODS:** A total of 50 patients with JME, 40 patients with FLE, 40 patients with TLE, and 40 normal controls, all matched for age, education, and IQ, were administered tests to assess frontal functions (the Word Fluency Test and the Wisconsin Card Sorting Test [WCST]). All participants had a normal intelligence level based on the Wechsler Adult Intelligence Scale, and did not take medications other than antiepileptics (AEDs) or have a psychiatric history. **RESULTS:** Patients with JME had severe impairment in all administered tasks, similar to that of patients with FLE; TLE patients and controls followed in order. Multiple regression analysis did not disclose any significant effect of clinical variables on the cognitive deficits. **DISCUSSION:** These results clearly suggest that JME patients can show some frontal dysfunction, which may affect both epileptogenic features and cognitive processes. Further studies are needed to confirm these findings.

### COMMENTARY

Juvenile myoclonic epilepsy (JME) is considered the prototype of an idiopathic generalized epilepsy because the seizures are generalized, EEG discharges have a generalized distribution over the entire head, neurological examination is normal, and there is no evidence of focal brain pathology on routine neuroimaging. Nevertheless, there is emerging anatomic, physiological, and now cognitive evidence of focal frontal lobe abnormalities in JME. These findings could have far reaching implications: if focal abnormalities exist in JME, then it is possible that they exist in other idiopathic generalized epilepsies, fundamentally changing current understanding of their pathophysiology.

It is presumed that the basic pathophysiology of seizures associated with idiopathic generalized epilepsies, including JME, involves thalamocortical interactions that set up a reverberatory circuit between specific thalamic nuclei and broad (i.e., “generalized”) regions of cortex. However, there is some physiological evidence of preferential frontal lobe involvement with JME. In the simplest sense, generalized discharges in JME often are maximally negative in the bifrontal regions. A lack of normal frontal lobe PET activation during visual working memory tests with JME patients suggests that the frontal cortex may not be functioning properly (1).

Frontal cortex has properties that could account for the generalized appearance of JME, including regional connectivity with the thalamus, widespread connections to ipsilateral and contralateral cortical regions, and motor cortex that could mediate myoclonus. The location and convoluted appearance of

the frontal lobes make it difficult to identify subtle anatomic abnormalities. Similarly, impairment of frontal lobe executive functions, such as organization, planning, and complex social interactions, are often not noticed by patients and are difficult to detect by routine neurological examination. Thus, microscopic anatomic abnormalities or subtle defects of frontal lobe functions, if present in JME, could go unnoticed without careful quantitative assessment.

There is anatomical evidence of subtle frontal lobe abnormalities in JME. A few case series report focal cortical microdysgenesis in the frontal cortex; however, it is clear that this finding is only present in a small minority of cases (2). A more generally applicable observation is the increase in mesial frontal grey matter thickness seen in JME patients compared with controls, using quantitative MRI voxel-based morphometry (3). Similarly, MRS demonstrates reduced frontal lobe concentrations of *N*-acetyl aspartate in JME patients (4).

Evaluation of cognitive function for idiopathic generalized epilepsy is gaining attention because it provides evidence of focal brain dysfunction, which as mentioned, is counter to the traditional view that cognitive function is normal. Furthermore, it reveals the possibility that seizures arise from focal brain pathology in what appear otherwise to be truly generalized epilepsy syndromes. Some studies have reported psychiatric symptoms or cognitive deficits in patients with JME. There is greater impairment in frontal lobe test performance seen with JME patients compared with temporal lobe epilepsy patients as well as specific deficits in executive function for individuals with JME (5,6). A common problem in these studies is a lack of appropriate controls. Thus, it is possible that some deficits are due to antiepileptic drugs, the presence of seizure activity, or other phenomena generically related to epilepsy.

Piazzini et al., in the report reviewed here, performed a prospective assessment with JME patients using two commonly

accepted neuropsychological tests of frontal lobe function: the Wisconsin Card Sorting Test and the Word Fluency Test. The investigators chose controls carefully to avoid problems present in previous studies; thus, patients with frontal lobe epilepsy were selected as a positive control group and a normal population without epilepsy also was used. A group with temporal lobe epilepsy was included to account for confounders common to all types of epilepsy, such as antiepileptic drug use and duration of epilepsy. The authors found a meaningful degree of cognitive deficit in the JME patients, who performed almost as poorly as the patients with frontal lobe epilepsy and much worse than the individuals with temporal lobe epilepsy.

The clinical implication of impaired frontal lobe function identified in the JME patients is not clear. The degree of deficit found by Piazzini et al. is significant for the group, but it is not obvious from the data presented what proportion of JME patients are affected. Are a few patients affected to a large degree or many patients affected to a moderate degree? As discussed, others have reported psychiatric problems in patients with JME, and frontal lobe dysfunction could contribute to this finding. It is important to recognize that at least some patients with JME may have psychosocial problems resulting from frontal lobe impairment.

How can the obvious clinical observation of JME as a generalized epilepsy be reconciled with the electrographic, imaging, and cognitive evidence of frontal lobe abnormalities? One hypothesis is that ongoing epileptiform activity alters frontal lobe physiology, resulting in altered neuropsychological function. This hypothesis seems unlikely since seizures are rare in JME and there is no simple reason why altered neuropsychological function would increase cortical thickness. A more likely hypothesis is that JME results from a fundamental abnormality of

inhibitory neurotransmission that creates recurrent inhibition in circuits between the thalamus and susceptible neurons in the frontal cortex (7). Thus, the fundamental pathology could be in a multitude of locations, including thalamic neurons, frontal cortical neurons, or their connections—all of which result in the same phenotype. This theory could account for the variability of inheritance observed in JME, with some investigations suggesting JME is monogenic, while most cases are apparently polygenic. These hypotheses are speculative; however, overall the finding of focal frontal lobe dysfunction on neuropsychological testing in JME expands the possible explanations for its pathophysiology.

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