

## MAGNETIC RESONANCE SPECTROSCOPY IN GENERALIZED EPILEPSY

### Proton MRS Reveals Frontal Lobe Metabolite Abnormalities in Idiopathic Generalized Epilepsy

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**OBJECTIVE:** To assess  $\gamma$ -aminobutyric acid (GABA) plus homocarnosine (GABA+) and glutamate plus glutamine (GLX) concentrations in the frontal lobes of patients with idiopathic generalized epilepsy (IGE).

**METHODS:** Twenty-one patients and 17 healthy volunteers were studied. A single voxel was prescribed in each frontal lobe for each subject. Point-resolved spectroscopy (PRESS)-localized short echo time MR spectroscopy (MRS) was performed to measure GLX and the metabolites *N*-acetylaspartate plus *N*-acetylaspartylglutamate (NAAt), creatine and phosphocreatine (Cr), choline-containing compounds (Cho), and myo-inositol (Ins). A double quantum GABA filter was used to measure GABA+. Segmented T<sub>1</sub>-weighted images gave the tissue composition of the prescribed voxel.

**RESULTS:** Group comparisons showed elevation of GLX and reduction of NAAt in the patient group ( $p < 0.05$ ). The metabolite ratios GLX/NAAt and GLX/Ins also showed elevation in IGE ( $p = 0.01$ ). No group effect was observed for GABA+, Cr, or Cho. Ins concentrations were not significantly reduced in the patient group but were less in the subgroup of patients who were taking sodium valproate.

**CONCLUSIONS:** IGE was associated with bilateral frontal lobe metabolite changes. Elevation in GLX was observed, which may imply increased neuronal excitability, whereas reduction in NAAt suggests reduced overall neuronal numbers or neuronal dysfunction.

### Thalamic Dysfunction in Juvenile Myoclonic Epilepsy: A Proton MRS Study

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**SUMMARY:** **PURPOSE:** To investigate neuronal dysfunction in the thalami of patients with juvenile myoclonic epilepsy (JME) by using proton magnetic resonance spectroscopy (MRS).

**METHODS:** We performed single-voxel proton MRS over the right and the left thalami of 10 consecutive patients (five women) with JME (mean age, 31.6 years) and 10 age-matched healthy volunteers (five men). All patients had seizure onset in late childhood-teenage, normal neurologic examination, typical EEG of JME, and normal high-resolution MR imaging (MRI). We determined ratios of *N*-acetylaspartate (NAA) over creatine-phosphocreatine (Cr). Values  $< 2$  standard deviations from controls were considered abnormal. We performed analysis of variance to evaluate group differences.

**RESULTS:** Group analysis showed that thalami NAA/Cr ratios were significantly decreased in JME patients (left side,  $1.58 \pm 0.26$ ; right side,  $1.5 \pm 0.15$ ) as compared with controls (left side,  $1.98 \pm 0.18$ ; right side,  $1.88 \pm 0.15$ ;  $p = 0.001$  and  $p = 0.007$ , respectively). Individual analysis showed that nine of the 10 patients had abnormal NAA/Cr in at least one of the thalami.

**CONCLUSIONS:** This study shows evidence of neuronal dysfunction in the thalami of patients with JME, which may have relevance for the mechanisms of seizure generation in this form of generalized epilepsy.

## COMMENTARY

The idiopathic generalized epilepsies have been less fertile territory for imaging studies than localization-related epilepsies. Routine structural magnetic resonance imaging (MRI) in patients with idiopathic generalized epilepsies almost always is unrevealing, although a subtle increase in cortical grey matter in the mesial frontal lobes has been reported (1). Limited positron emission tomography (PET) studies showed normal interictal glucose metabolism, and global ictal activation. Cerebral blood flow (CBF), measured with [<sup>15</sup>O]-H<sub>2</sub>O, increased to a greater degree in the thalamus than cortical regions during absence seizures (2).

Magnetic resonance spectroscopy (MRS) may have the potential to detect physiologic abnormalities in patients with

generalized epilepsy syndromes. MRS shares some of the advantages and disadvantages of PET: compared with structural MR, spatial resolution is limited; and, both data acquisition and analysis are relatively complex. However, MRS can measure *N*-acetylaspartate (NAA), a marker that seems to reflect neuronal functional integrity as well as number, and compounds that play a role in neuronal transmission, including  $\gamma$ -aminobutyric acid (GABA) and glutamate. Resolving the MRS spectral peaks individually can be difficult, and the GABA peak, measured by Simister and associates, included homocarnosine and glutathione. The NAA peak included both *N*-acetylaspartate and *N*-acetylaspartylglutamate.

Simister et al. studied 17 controls and 21 patients (age range: 17–51) with a variety of idiopathic generalized epilepsy (IGE) syndromes, including juvenile myoclonic epilepsy (JME) and juvenile absence epilepsy (JAE). Classification was not possible in six patients. The patients were taking a variety of antiepileptic drugs. Epilepsy onset age ranged from 6 to 17 and duration from 4 to 35 years. Spectra were acquired in a single voxel measuring  $40 \times 35 \times 25$  millimeters in each frontal lobe.

The controls had reduced concentrations of NAA, creatinine, choline, and glutamate plus glutamine (measured as one peak) in the left frontal voxel compared with the right, probably reflecting methodological problems related to positioning of the voxels. Glutamate plus glutamine was significantly increased (both voxels and mean value), and NAA (right voxel and mean value) and inositol (left voxel and mean value) decreased in patients compared with controls. The GABA/homocarnosine peak did not differ between patients and controls. Seizure frequency, age of onset, and epilepsy duration did not affect the results. Inositol was significantly lower in patients on valproic acid—the only AED taken by enough patients to make analysis worthwhile. Subanalysis of the groups with JME and JAE showed effects similar to the patients as a whole.

Mory et al. measured thalamic NAA and creatine plus phosphocreatine (Cr) in 10 patients with JME (mean age 31.6) and 10 controls (mean age 30.6), using a 20 cubic millimeter voxel. The results were expressed in terms of the NAA/Cr ratio, which is thought to be a more stable indicator of neuronal and axonal loss or dysfunction than NAA alone. Overall, there were significant group decreases in thalamic NAA/Cr in the patients compared with controls. Nine of the patients had a value at least two standard deviations below the control mean, four were unilateral, and five were bilateral. Effects of seizure frequency and AEDs could not be evaluated.

These two studies provide evidence for thalamic and frontal lobe dysfunction in patients with generalized epilepsy syndromes. In both studies, structural MRI, including the voxel-based analysis by the same investigators that had previously shown some subtle increases in gray matter, was normal.

Several previous studies have used NAA measurements obtained by MRS to evaluate generalized epilepsy syndromes. Patients with JME had reduced frontal, but not thalamic or occipital, NAA (5). However, NAA/Cr values were normal in frontal lobes in this report. Another recent MRS study, comparing 10 IGE patients with well-controlled seizures and 9 with poorly controlled seizures to normal controls, showed reduced mean thalamic NAA/Cr (6). Insular cortex, posterior temporal lobe white matter, and the splenium of the corpus callosum were normal. Neither seizure control nor spike and wave complex counts affect the results, but there was a significant negative correlation between thalamic NAA/Cr and epilepsy duration. This study suggested progressive thalamic dysfunction in patients with IGE.

Simister and associates previously had found that occipital lobe glutamate plus glutamine and GABA plus homocarnosine were elevated in IGE, but the difference appeared to be due to differences in cortical gray matter proportions, and there was no relation between measurements and seizure control (7). In another study, 14 adult patients with JME had reduced occipital GABA but not homocarnosine, while 12 patients with complex partial seizures showed reductions in both measures (8). Valproic acid and lamotrigine had no effect on the results. Poor seizure control was associated with greater reduction of GABA levels in patients with complex partial seizures but not JME.

By finding evidence for thalamic and frontal lobe dysfunction, while other regions appear to be unaffected, the MRS data lends some support to the thalamocortical hypothesis for the generation of epileptiform discharges in generalized epilepsy syndromes (9). Some evidence suggests that hypersynchrony within the thalamocorticothalamic circuit depends on GABA-mediated mechanisms that may pace burst firing. Unfortunately, the MRS data for GABAergic function in IGE patients are partially conflicting. Simister and associates, for example, found that the measure of GABA plus homocarnosine was normal in frontal lobes and glutamate plus glutamine was elevated, while Petroff reported reduced occipital GABA but normal homocarnosine (8). The differences in some of the findings among these studies might be due, in part, to the relatively small number of patients included as well as to differences in the details of the MRS data acquisition and analysis paradigms. Different brain regions were studied. Our normative MRS data are very limited, and we do not know whether there may be differences in metabolite levels among brain regions. Moreover, the mix of epilepsy syndromes and the AEDs that the patients were taking varied among studies as well. The effect of age on MRS measurements is uncertain, but each study included its own set of age-matched controls. The controls were not sex-matched in all studies; the importance of this factor is unknown.

The relationship between excitatory and inhibitory mechanisms in IGE remains uncertain (9). The effect of alterations in

relative levels of excitatory and inhibitory transmitters on neuronal activity may be hard to infer from measurements of levels in large cortical volumes. MRS measurements reflect not just the neurotransmitter pool, but also overall brain levels, of the compounds. Thus, brain metabolism as well as synaptic activity influences MRS results. In addition, current techniques make it more difficult to distinguish the role of individual amino acids that have closely linked MRS peaks. If technical advances would permit simultaneous acquisition of spectra from several compounds in multiple brain regions, with ongoing EEG recording, pharmacologic challenge experiments might be carried out that could address these issues.

*by William H. Theodore, M.D.*

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