

## THALAMIC DYSFUNCTION IN IDIOPATHIC GENERALIZED EPILEPSY: NEW FINDINGS OF OLD NEWS

### Magnetic Resonance Spectroscopy and Imaging of the Thalamus in Idiopathic Generalized Epilepsy

Bernasconi A, Bernasconi N, Natsume J, Antel SB, Andermann F, Arnold DL

Brain 2003;126:2447–2454

Experimental work in animal models of generalized epilepsy and clinical data in humans with idiopathic generalized epilepsy (IGE) indicate that the thalamocortical circuitry is involved in the generation of epileptic activity. The purpose of this study was to evaluate in vivo the chemical and structural integrity of the thalamus in patients with IGE. Thalamic proton magnetic resonance spectroscopic imaging ( $^1\text{H-MRSI}$ ), measuring *N*-acetylaspartate (NAA), choline-containing compounds, and creatine (Cr) was performed in 20 IGE patients and in a group of age-matched healthy subjects. Additionally,  $^1\text{H-MRSI}$  measurements were taken in the insular cortex, the posterior temporal lobe white matter, and the splenium of the corpus callosum. MRI volumetric analysis of the thalamus was performed in all patients. At the time of the examination, seizures were well controlled in 10 IGE patients and poorly controlled in 9. One patient was newly diagnosed and had the MRI and MRSI examination before starting the antiepileptic medication. In IGE patients,  $^1\text{H-MRSI}$  showed a reduction of mean thalamic NAA/Cr ratio compared with normal controls; no difference was found in NAA/Cr in the other examined areas. No difference in NAA/Cr was found between patients whose seizures were well controlled and those in whom seizures were not controlled. No correlation was seen between thalamic NAA/Cr and mean number of spike-and-wave complexes. We found a significant negative correlation between thalamic NAA/Cr and duration of epilepsy. The mean thalamic volume in patients with IGE was not different from that in normal controls. These results show evidence of progressive thalamic neuronal dysfunction in patients with IGE, supporting the notion of abnormal thalamocortical circuitry as a substrate of

seizure generation in this form of epilepsy. The thalamic dysfunction may occur regardless of amount of spike-and-wave activity.

### COMMENTARY

The role of thalamic nuclei in the generation of epileptic seizures of idiopathic generalized epilepsy (IGE) has been recognized for the last 6 decades. The involvement of posterolateral and midline thalamic nuclei in the generation of spike-wave activity has been documented in animal models of absence seizures (1,2) and has been demonstrated with depth electrode recordings in humans (3). Anterior and mediodorsal nuclei have been shown to be closely associated with the generation of generalized convulsive seizures triggered by pentylenetetrazol (PTZ) or bicuculline in animal models (4). Thus it was not surprising that Bernasconi et al. found that thalamic proton magnetic resonance spectroscopic imaging ( $^1\text{H-MRSI}$ ) showed a reduction of the *N*-acetylaspartate (NAA)/creatine (Cr) ratio in 20 patients with IGE, compared with normal controls. This finding, coupled with normal thalamic volumes, was suggestive of a thalamic neuronal metabolic dysfunction and ruled out the presence of structural abnormalities.

Yet this interesting study has only begun to answer the pivotal questions regarding the significance of thalamic neuronal dysfunction. First, is it specific to the convulsive forms of IGE [i.e., juvenile myoclonic epilepsy (JME) and generalized tonic-clonic seizures on awakening] or is it also found in absence seizures? Is it specific to IGE, or can it be identified in localization-related epilepsy? After all, the mediodorsal nucleus of the thalamus is highly connected to limbic structures, such as amygdala, hippocampus, and piriform, perirhinal, and prefrontal cortices, and is well known to mediate limbic seizure propagation (5). Significant increments in glucose utilization have been found in this structure during limbic motor seizures, and degenerative changes have been identified after limbic status epilepticus in experimental animals (6) as well as after prolonged hemic convulsions in humans (7).

Is the low NAA/Cr ratio a trait of IGE or a marker of poorly controlled seizures? Although the authors did not find a difference in NAA/Cr ratio between patients who were and

were not seizure free, the study was not powered to answer this question. Furthermore, to answer the question, patients ought to be recruited from general neurology practices, rather than from specialized epilepsy centers, as the latter are more likely to attract patients with more severe forms of epilepsy and, hence, not be representative of a typical population of IGE patients. This point was one of the weaknesses of this study, as 50% of the patients included had seizures that had failed to respond to pharmacotherapy, compared with 10% to 15% in most general neurology practices.

Finally, the thalamus is not the only neuroanatomic structure to have been found to display neuronal dysfunction in IGE. A study carried out in 15 patients with JME and 10 controls revealed decreased NAA (and normal Cr and choline) in the patients' prefrontal cortex (8), whereas in the present study, the authors found a significant correlation of thalamic and insular cortex NAA/Cr ratios. The abnormal findings in prefrontal cortex are not surprising, as impaired frontal lobe functioning has been demonstrated in patients with JME, by using neuropsychological tests (9) and functional neuroimaging studies with positron emission tomography (10).

by *Andres M. Kanner, M.D.*

## References

1. Gloor P, Fariello RG. Generalized epilepsy: some of its cellular mechanisms differ from those of focal epilepsy. *Trends Neurosci* 1988;11:63–68.
2. Vergnes M, Marescaux C, Depaulis A, Micheletti G, Warter JM. Spontaneous spike and wave discharges in thalamus and cortex of a rat model of generalized petit-mal seizure. *Exp Neurol* 1987;96:127–136.
3. Niedermayer E, Laws ER Jr, Walker AE. Depth EEG findings in epileptics with generalized spike-wave complexes. *Arch Neurol* 1969;21:51–58.
4. Miller JW, Ferrendelli JA. The central medial nucleus: thalamic site of seizure regulation. *Brain Res* 1990;508:297–300.
5. Patel S, Millan MH, Meldrum BS. Decrease in excitatory transmission within the lateral habenula and the mediodorsal thalamus protects against limbic seizures in the rats. *Exp Neurol* 1988;101:63–74.
6. Shimosaka S, So YT, Simon RP. Distribution of HSP72 induction and neuronal death following limbic seizures. *Neurosci Lett* 1992;138:202–206.
7. Mori H, Mizutani T, Toshimura M, Tamanouchi H, Shimada H. Unilateral brain damage after prolonged hemiconvulsions in the elderly associated with theophylline administration. *J Neurol Neurosurg Psychiatry* 1992;55:466–469.
8. Savic I, Lekvall A, Greitz D, Helms G. MR spectroscopy shows reduced concentrations of *N*-acetyl aspartate in patients with juvenile myoclonic epilepsy. *Epilepsia* 2000;41:290–296.
9. Devinsky O, Gershengorn J, Brown E, Perrine K, Vasquez B, Luciano D. Frontal functions in juvenile myoclonic epilepsy. *Neurol Neuropsychol Behav Neurol* 1997;10:243–246.
10. Swartz BE, Simpkins F, Halgren E. Visual working memory in primary generalized epilepsy: an FDG-PET study. *Neurology* 1996;47:1203–1212.