Sleep-potentiated epileptic discharges, language regression, and pediatric thalamic lesions

Mark Quigg, MD, MS, FANA
Soheyl Noachtar, MD

Correspondence & reprint requests to Dr. Quigg: quigg@virginia.edu

Neurology® 2012;78:1708–1709

Ever since Gloor et al.[1] demonstrated that thalamocortical interactions were responsible for generalized seizures, alterations of thalamic function have been investigated in the pathophysiology of epilepsy. Today, the thalamus (in its regulatory, synchronizing actions with the cortex) has been assigned diverse roles. To name just two: 1) in potentiating seizure occurrence during sleep[2]; and 2) in its electrical stimulation, treatment of seizures.[3] In addition, recent neuroimaging work has demonstrated heretofore poorly documented anatomic thalamic pathology in generalized epilepsy,[4] and perhaps not coincidentally, in autism.[5]

In this issue of *Neurology*®, Sánchez Fernández et al.[6] evaluated the neuroimaging of children who presented with regression of at least 1 domain of development—typically language or behavior—who were suspected of having acquired epileptic aphasia. After dividing the sample into 2 arms, those whose electrophysiologic sleep was interrupted by long runs of epileptiform discharges (electrical status epilepticus of sleep [ESES]) and controls of those without sleep-activated abnormalities, the authors report that ESES was more likely to be present in those with early developmental lesions that usually involved the thalamus. Regardless of exact cause (most commonly, early stroke), children with thalamic lesions had over 7 times the risk of ESES than children without.

The findings of this report have 2 areas of importance.

First, the Venn diagram of acquired epileptic aphasia (AEA) remains complicated. After all, Landau-Kleffner syndrome is a clinically defined syndrome. The cardinal feature is acquired aphasia (most specifically auditory verbal agnosia) in which the majority of children have seizures. In Landau-Kleffner syndrome, the EEG is supportive in diagnosis.[7] ESES, as first described by Patry et al.[8] and expanded by Tassinari et al.[9] and others, is electrographically defined, with non-REM sleep being supplanted by ongoing epileptic discharges. Autistic spectrum disorders, especially in children who present with autistic regression or seizures, can be difficult to distinguish on pure clinical grounds from more "traditional" AEA.[10] Although case reports of causes of AEA or ESES demonstrate a wide range of etiologies, the present article is the largest series to clearly link clinical suspicions of AEA with EEG and neuroimaging findings of early thalamic injury.

Second, the finding of early thalamic injury associated with ESES is a robust clinical demonstration of the regulatory role of the thalamus as a source of synchronizing, oscillatory activity during non-REM sleep and the facilitation of seizure activity through abnormal cortico-thalamic synchronicity.[2] There is some evidence of a "dose-response" in that the proportion of patients with thalamic lesions increases with spike-wave persistence. Of major importance would be the other side, that behavioral and language outcomes may be proportional to the degree of sleep disruption by persistent spike-wave discharges. Such a finding is central to hypotheses of the role of sleep's importance in memory function and a justification for aggressive antiepileptic treatment in ESES and AEA.

Remaining uncertain is how to classify patients: AEA remains a collection of clinically related syndromes with no unitary "final common pathway" pathophysiology. For example, children with autistic traits—in addition to the index symptoms of behavioral or language decline—comprised about a third of the sample. These patients tended not to express sleep-potentiated epileptiform activity, despite having the primary inclusion criteria of behavioral or language decline. Perhaps future functional neuroimaging studies, such as those that detailed changes in thalamic activity in autism,[11] can help bring together clinical and electrophysiologic findings.

Although it is probably too early to make changes in practice, the search for thalamic dysfunction may prove to be a helpful anatomic correlate to symptoms of language regression, behavioral changes, and epilepsy accompanied by sleep-potentiated EEG abnormalities.

See page 1721

From the Department of Neurology (M.Q.), University of Virginia, Charlottesville; and Department of Neurology (S.N.), University of Munich, Germany.
Go to Neurology.org for full disclosures. Disclosures deemed relevant by the authors, if any, are provided at the end of this editorial.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. **Go to Neurology.org for full disclosures.**

REFERENCES

1. Gloor P, Pellegrini A, Kostopoulos G. Effects of changes in cortical excitability upon the epileptic bursts in generalized penicillin epilepsy of the cat. Electroencephalogr Clin Neurophysiol 1979;46:274–289.
2. Beenhakker MP, Huguenard JR. Neurons that fire together also conspire together: is normal sleep circuitry hijacked to generate epilepsy? Neuron 2009;62:612–632.
3. Fisher R, Salanova V, Witt T, et al. Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. Epilepsia 2010;51:899–908.
4. Pulsipher DT, Dabbs K, Tuchsherer V, et al. Thalamofrontal neurodevelopment in new-onset pediatric idiopathic generalized epilepsy. Neurology 2011;76:28–33.
5. Tsatsanis KD, Rourke BP, Klin A, Volkmar FR, Cicchetti D, Schultz RT. Reduced thalamic volume in high-functioning individuals with autism. Biol Psychiatry 2003;53:121–129.
6. Sánchez Fernández I, Takeoka M, Tas E, et al. Early thalamic lesions in patients with sleep-potentiated epileptiform activity. Neurology 2012;78:1721–1727.
7. Landau WM, Kleffner FR. Syndrome of acquired aphasia with convulsive disorder in children. Neurology 1957;7:523–530.
8. Patry G, Lyagoubi S, Tassinari CA. Subclinical "electrical status epilepticus" induced by sleep in children: a clinical and electroencephalographic study of six cases. Arch Neurol 1971;24:242–252.
9. Tassinari CA, Rubboli G, Volpi L, et al. Encephalopathy with electrical status epilepticus during slow sleep or ESES syndrome including the acquired aphasia. Clin Neurophysiol 2000;111:S94–S102.
10. Nass R, Gross A, Devinsky O. Autism and autistic epileptiform regression with occipital spikes. Dev Med Child Neurol 1998;40:453–458.
11. Mizuno A, Villalobos ME, Davies MM, Dahl BC, Muller RA. Partially enhanced thalamocortical functional connectivity in autism. Brain Res 2006;1104:160–174.