Cortical Hyperexcitability: A New Biomarker in Generalized Epilepsy Syndromes

Patterns of Cortical Hyperexcitability in Adolescent/Adult-Onset Generalized Epilepsies.

Badawy RAB, Simon J, Vogrin SJ, Lai A, Cook MJ. *Epilepsia* 2013;54(5):871–878.

PURPOSE: To investigate whether using transcranial magnetic stimulation (TMS) to derive if measures of cortical excitability changes can distinguish between various adolescent/adult-onset generalized epilepsy syndromes at different phases of the disorder. METHODS: One hundred thirty-seven patients with adolescent/adult-onset generalized epilepsy divided into juvenile myoclonic epilepsy, juvenile absence epilepsy, and generalized epilepsy with tonic–clonic seizures only were studied. The cohorts were further divided into drug naive-new onset, refractory, and seizure-free groups. Motor threshold (MT) and paired pulse TMS at short (2, 5, 10, 15 msec) and long (100–300 msec) interstimulus intervals (ISIs) were measured. Results were compared to those of 20 controls. KEY FINDINGS: In the drug-naive cohorts MT was reduced ($p < 0.05$) and cortical excitability increased at 2 and 5 msec and 150, 250, and 300 msec ISIs ($p < 0.01$) in juvenile myoclonic epilepsy compared to other generalized epilepsy groups and controls. Cortical excitability increased to a lesser degree in other generalized epilepsy syndromes compared to controls, but those two syndromes were not distinguishable from one another. The changes in paired pulse TMS were more prominent in the groups with refractory seizures and very small in the groups who were seizure free. SIGNIFICANCE: There are syndrome specific changes in cortical excitability associated with generalized epilepsy. These changes are also dependent on seizure control with medication. Juvenile myoclonic epilepsy has a higher cortical excitability profile compared to other adolescent/adult-onset generalized epilepsy syndromes and can be clearly distinguished from them during all phases.

Commentary

One of the cardinal biomarkers in clinical epilepsy is the interictal epileptiform discharge (IED). The presence of interictal spikes is generally taken to indicate cortical hyperexcitability, but their sporadic appearance means that long periods of EEG recording may be necessary to ascertain spike frequency, and there is little experimental control over their measurement. Noninvasive, repeatable methods of actively probing cortical excitability, then, are potentially valuable tools both in science and in the clinic. In research, they allow us to explore underlying brain physiology in patients with various forms of epilepsy in a quantifiable, robust manner. In practice, such measures could help us to prognosticate seizure-recurrence risk in those who have had a single event or who are considering antiepileptic drug (AED) withdrawal, for example. These clinical circumstances are ones in which routine EEGs are frequently obtained to search for interictal spikes, but their utility is less than ideal, and the result is often interpreted merely in binary form, with discharges either present or absent.

In recent years, the use of transcranial magnetic stimulation (TMS) to determine cortical excitability as measured by motor-evoked potential (MEP) response to single-pulse and paired-pulse stimulation has gained prominence in clinical neurophysiology as a research tool in those with epilepsy and other neurologic conditions (1). In particular, multiple publications have reported differences in TMS-evoked MEP measures between epilepsy patients and healthy controls and have suggested changes in these measures depending on epilepsy type, AED usage, and degree of seizure control (2–5).

The article by Badawy et al. continues a pioneering line of work from these investigators that has established some of these principles. In this article, they report on a study of 137 patients with genetic (idiopathic) generalized epilepsy syndromes and 20 healthy controls. The epilepsy patients comprised those with juvenile myoclonic epilepsy (JME), juvenile absence epilepsy (JAE), and generalized epilepsy with tonic–clonic seizures only (GE-TCS) and were classified as drug naïve–new onset, refractory, or seizure-free. TMS over the vertex was used to determine motor threshold and to obtain measurements of intracortical inhibition and facilitation through the use of paired-pulse stimuli separated by varying interstimulus intervals.

The results demonstrate that new-onset JME patients in the drug-naïve state had a lower mean motor threshold than both healthy controls and drug-naïve patients with the other forms of generalized epilepsy. Patients with JME on AEDs (either well controlled or not) did not have a significantly differ-

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ent mean motor threshold from controls, nor did patients with JAE or with GE-TCS. On measures of intracortical inhibition and facilitation, JME patients showed prominent increases in cortical excitability compared with healthy controls; those with JAE and GE-TCS also showed increased excitability compared with controls but to a lesser degree. Across all groups, patients with medically refractory epilepsy had the most prominent differences compared with controls, while those who were seizure free on AEDs had the most subtle differences, seen primarily in the paired-pulse measures with long interstimulus intervals.

To summarize, several themes are now emerging from this and similar investigations:

- The epileptic brain is characterized by distinct abnormalities in cortical excitability compared with that of healthy controls without epilepsy.
- The use of AED therapy, as well as the degree of success of such therapy in controlling seizures, affects these cortical excitability measures.
- As demonstrated in this article, in particular, specific epilepsy syndromes may be distinguishable from others by differences in at least the degree of cortical excitability.

The clinical utility of these and similar results will likely lie in our ultimate ability to assess cortical excitability noninvasively, even in patients without frequent IEDs, in a controlled manner without having to "wait" for spontaneous spikes to occur. Since patients who are seizure free seem to have demonstrably different profiles on these measures compared with those who are on medications but are uncontrolled, and with those who are drug-naïve, these measures could serve as biomarkers of epilepsy before, during, or after AED withdrawal or could help prognosticate seizure-recurrence risk.

The implications of the syndrome-specific findings in JME noted in this article are not straightforward to interpret however. The TMS protocol of these investigators involved stimulation at the vertex and recording of MEPs; JME would, perhaps more than other generalized epilepsy syndromes, be expected to feature motor cortex excitability in particular. Going forward, the growing use of TMS combined with simultaneous continuous EEG for recording of potentials anywhere from the cortex, not just limited to the motor strip, will expand the importance of these kinds of studies and allow for a broader assessment of individual epilepsy syndromes, especially focal disorders or generalized epilepsies without a prominent motor clinical component (6).

This article's results contribute to our understanding of the pathobiological underpinnings of various epilepsy syndromes. As the field considers moving from a now-historic classification system for seizures and syndromes to one that reflects more up-to-date knowledge regarding epilepsy causes, networks, and genetics (7), evidence such as that presented here will provide us with another type of physiological measure by which these disorders can be categorized. It is possible that signature patterns of TMS-measured cortical excitability will be found that typify particular syndromes in the way that signature epileptiform discharge patterns currently typify certain syndromes, in which case, we may ultimately have a companion measure to the tried-and-true spike-and-wave.

by Bernard S. Chang, MD

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