Shocking New Insights Into the Epileptic Trait

Capturing the Epileptic Trait: Cortical Excitability Measures in Patients and Their Unaffected Siblings.

Badawy RAB, Vogrin SJ, Lai A, Cook MJ. *Brain* 2013;136:1177–1191.

We used transcranial magnetic stimulation to investigate whether the cortical excitability changes observed amongst the different generalized and focal epilepsy syndromes are reflected in their asymptomatic siblings and if these changes depended on the clinical phenotype. We studied 157 patients with epilepsy (95 generalized and 62 focal) and their asymptomatic siblings (138 and 82, respectively). Motor threshold and paired pulse transcranial magnetic stimulation at short (2, 5, 10 and 15 ms) and long (100–300 ms) interstimulus intervals were measured. Results were compared to those of 12 control subjects and 20 of their siblings. There were no differences in cortical excitability between healthy control subjects and their siblings. Compared with control subjects, cortical excitability was higher in siblings of patients whether generalized (P50.05; short and long interstimulus intervals) or focal (P50.05; long interstimulus intervals). Compared with epilepsy, motor threshold was lower (P50.05) in patients with juvenile myoclonic epilepsy compared with their siblings only early at onset in the drug naïve state. In all groups (generalized and focal) cortical excitability was lower in siblings only at the long interstimulus intervals (250 and 300; P50.05). Cortical excitability is higher in asymptomatic siblings of patients with generalized and focal epilepsy in a similar manner. The disturbance seems to involve intracortical inhibitory circuits even in the siblings of patients with a structural abnormality (acquired epilepsy). This implies there are certain genetic factors that predispose to both generalized and focal epilepsies and a complex genetic/environmental interaction then determines the clinical phenotype.

Commentary

While epilepsy is a condition defined by chronic recurrent spontaneous seizures, a number of phenomena indicate that certain individuals who do not meet criteria for epilepsy nonetheless may have a tendency to have seizures, a "lower seizure threshold." This may include not only people with a single unprovoked seizure but also those with provoked ones, explaining why they have had a seizure while others in the same situation have not. There is also the issue of acquired focal epilepsy: Why do only a portion of patients with a given type of cerebral lesion develop seizures, and why do only some of these patients develop drug resistance? Finally, some first-degree relatives of individuals with epilepsy have interictal epileptiform discharges: in the current study, 8–13% of siblings of those with primary generalized epilepsy and 7% of siblings of refractory focal epilepsy patients. These situations reveal the existence of a subgroup of the "normal," nonepileptic population that has an increased risk of seizures. This could be explained by a genetically determined state, an "epileptic trait" manifested by spontaneous recurrent seizures (epilepsy) in only a portion of those affected. The addition of a CNS lesion, environmental circumstances, or co-occurrence of other genetic factors could lead to emergence of epilepsy in these predisposed individuals.

This current study used transcranial magnetic stimulation (TMS) to address this issue. TMS delivers a brief intense magnetic field to the scalp, inducing depolarizing electrical current in the underlying brain. This technique has been previously reviewed in *Epilepsy Currents* (1). One measure of excitability is the threshold for eliciting a muscle response from motor cortex activation. Excitability can also be measured with paired pulse stimulation, where a conditioning pulse is followed by a second test pulse; the ratio of the amplitude of the response to the test pulse to that of the conditioning pulse is measured as a function of the interstimulus interval (ISI). In this study, both hemispheres were stimulated. Short ISIs of 2–15 ms were performed with subthreshold conditioning stimuli followed by subthreshold pulses, typically producing facilitation at the longer intervals. Long ISIs used suprathreshold stimuli 100–300 ms apart, usually producing some inhibition of the second response. Abnormal cortical excitability was determined from shifts of these short and long ISI response curves for epilepsy patients and nonepileptic sibling groups compared to those of control subjects.

This approach has previously been validated as a useful tool for characterizing epilepsy. Not only does TMS demonstrate abnormal excitability in patients with different forms of epilepsy (1–9) but it also distinguishes between focal and generalized types; although both have increased excitability, this change is greater in the hemisphere ipsilateral to the side

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of seizure origination of focal epilepsy (2). TMS also reveals an additional increase in cortical excitability of epilepsy patients after sleep deprivation, particularly with idiopathic generalized epilepsy (3, 4). Introduction of antiepileptic drugs and achievement of seizure freedom results in near-normalization of cortical excitability, while drug resistance is associated with a broad increase in excitability (5, 6). Therefore, TMS responses are reliable markers of the type, severity, and natural history of epilepsy.

The current study found evidence of abnormal cortical excitability in the asymptomatic nonepileptic siblings of patients with a variety of generalized and focal epilepsy syndromes. Although this excitability was greater in siblings of those with generalized epilepsy, nevertheless, abnormal cortical excitability was present in siblings of those with all types of focal epilepsy, including seizure-free and drug-resistant subgroups. Many of these focal epilepsy patients had CNS lesions. Based on indirect evidence, the authors attributed the observed abnormalities of ISI response curves to defective $GABA_A$ and $GABA_B$ mediated mechanisms. Therefore, these results demonstrate a familial abnormality of cortical excitability even in association with acquired epilepsies.

The TMS responses of the different subgroups of the 220 nonepileptic siblings were pooled and averaged. Although these subgroups, as a whole, had increased excitability, they were undoubtedly heterogeneous, containing individuals with normal cortical excitability as well as others with likely different forms of genetically determined defects affecting the balance between excitation and inhibition. These genotypes have not yet been defined.

There are many mutations known to lead to epilepsy. The most numerous are voltage- and ligand-gated channelopathies, and abnormalities of transmitter release (10). Many known epileptogenic mutations involve GABA transmission (10), congruent with the hypothesis that the abnormal cortical excitability detected with TMS is largely due to defective inhibition.

The current study supports the emerging concept that there are individuals who are susceptible to seizures, a larger group than that of people with epilepsy. Sometimes, this lower seizure threshold is unexpressed and silent; at other times, seizures or epilepsy emerges, depending on the severity of the seizure tendency, comorbidity, or environmental factors. TMS is a tool for detecting and characterizing the invisible population at risk for seizures. Thus, elucidating the different mechanisms underlying this phenotype of the "epileptic trait" may be an important step in unraveling the genetics of epilepsy.

by John W. Miller, MD, PhD

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