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Focal Lesion in the Splenium of the Corpus Callosum in Epileptic Patients: Antiepileptic Drug Toxicity?

Michael Tennison

At one time neurologists focused narrowly on the control of seizures, with insufficient regard for the adverse effects of therapy. Treatment was recommended for every patient with a seizure, and medications were continued indefinitely. The last two decades have spawned an abundance of research documenting the adverse consequences of antiepileptic drug (AED) therapy, especially their negative cognitive and behavioral effects. Today, epileptologists pay increased attention to the potential negative effects of treatment, and the focus has shifted to maximizing quality of life. Control of seizures is only one aspect of the overall effort. This shift has resulted in a trend toward delaying initiation of AEDs until seizures become recurrent. When seizures have remitted for several years, discontinuation of therapy is frequently recommended, especially in children.

In this issue of the *American Journal of Neuroradiology*, Kim et al report a previously undescribed, rare (60.5% of 1200 subjects), reversible abnormality in the splenium of the corpus callosum (CC) in epileptic patients taking either phenytoin, vigabatrin, or both. The lesions were neither subtle nor apparently artifactual. All but one of these patients had poorly controlled epilepsy, as evidenced by their need for multiple medications. A lesion was seen in one patient 10 days after starting phenytoin. No preexisting lesion was evident on an MR image obtained 20 days earlier. A CC lesion was seen in a second patient 7 days after initiation of vigabatrin therapy, but the study obtained 3 years earlier, when the lesion arose, was negative. Medications were changed in two patients in whom lesions in the CC were no longer present on follow-up scans performed 4 and 6 months later. This report raises further cause for concern about the adverse effects of epilepsy treatments.

Although the patients were treated with a variety of AEDs, all were taking either phenytoin or vigabatrin, and the authors postulate that the MR changes were reversible effects of these two drugs. If confirmed, this observation would be especially alarming because these drug-induced changes would be structural and not simply functional. While provocative, there are a number of problems with the authors' conclusions.

To establish an association between these two AEDs and CC changes would require evidence that the frequency of this finding is significantly increased in patients undergoing phenytoin and vigabatrin therapy compared with the frequency in a reference population. Kim et al obtained MR examinations to evaluate seizures in 1200 patients, but the investigators did not reveal how many performed for other indications failed to show CC changes. If we assume that a similar number of patients had imaging for other reasons, and none had abnormalities in the CC, the difference between zero in the reference group and the finding of six in the AED-treated group would not be statistically significant. MR studies are not usually performed on healthy subjects and never in the numbers needed to detect such rare events, so we have no way of knowing the frequency of CC changes in a healthy population.

There are important limitations of the investigational design of this report. It is an observational study performed on a sample of convenience (patients referred for MR evaluation of epilepsy) and not a prospective assessment of all patients with seizures. Confounding factors and biases, including selection bias, are likely to be present. There are certainly numerous additional conditions shared among the patients reported besides epilepsy and the use of phenytoin and vigabatrin.

An association between the use of AEDs and CC changes does not prove a cause-and-effect relationship. To advance from association to cause and effect would require a consistently strong association across studies and a credible biological explanation for the relationship. MR changes would need to follow a temporal and dose-response relationship with the offending AEDs (1).

The data presented do not suggest a strong association between AEDs and MR changes, but the authors do present evidence for potential biological plausibility that may be the most compelling argument given. Vigabatrin has been associated with vacuolization of myelin in several animal species (2), and this finding has been a significant factor in delayed approval of this drug by the U.S. Food and Drug Administration. MR imaging has documented myelin changes in experimental animals in several areas including the thalamus, hypothalamus, and fornix (3), but no abnormalities in the CC have been revealed by either MR or pathologic study at the time of surgery or autopsy (4). Neurophysiological changes in axonal conduction in the CC of animals exposed to phenytoin have been demon-

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strated experimentally (5), but there are no reports of structural pathologic changes in white matter. The biological plausibility is intriguing, especially for vigabatrin, but far from convincing.

No other study corroborates cause and effect between AEDs and CC changes. The authors, however, give some evidence of a potential temporal relationship, at least in one above-noted patient who had negative findings 10 days before starting vigabatrin and CC changes 20 days later. Lesions resolved in two patients in whom phenytoin or vigabatrin therapy was discontinued. Although this finding suggests a temporal relationship, it is possible that the changes would have resolved spontaneously, and any change that was made after discovery of the lesions would appear to have caused resolution. While several patients had high serum levels of AEDs, this is a common clinical occurrence that does not provide evidence of a dose-response relationship.

The study prompts a number of additional questions. Without sophisticated testing beyond that routinely employed, the splenium of the CC is a clinically silent area. Did the clinicians caring for the patients check specifically for a disconnection syndrome? It is curious that medications would have an effect only on the splenium of the CC. What could be the basis for a particular vulnerability in this area? Phenytoin has been used for

more than 50 years, yet it has never previously been associated with CC or CNS myelin pathology. And why only these two drugs? Phenytoin and vigabatrin are no more closely related chemically or by proposed mechanisms of action than many other AEDs.

What do these findings mean clinically? The reported changes in the CC are rare, reversible, not conclusively due to medications, and cause no apparent symptoms. It would be premature to change prescribing habits on the basis of these preliminary observations. Kim et al remind us that the potential for adverse effects of epilepsy treatment requires continued vigilance. It will be interesting to see if other groups report similar CC lesions, including additional information that might lead to a better understanding of their cause.

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