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Spectroscopy Evidence of Diffuse Brain Abnormalities in Patients with Epileptogenic Foci

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COMMENTARY

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In the study included in this issue of the *AJNR*, Dr. Leite and her colleagues from Brazil used proton MR spectroscopy in the evaluation of patients with malformations of cortical development (MCD, also known as cortical dysplasias). They set out to evaluate these lesions directly and, more importantly, they looked for metabolic changes in an opposite but symmetrical location in brain tissues with a normal MR imaging appearance. Their working hypothesis was that the normal-appearing brain will show an abnormal MR spectroscopy pattern indicating that it may not be used as an internal control (a method commonly employed in all brain MR spectroscopy studies).

It has long been believed that patients with generalized epilepsy show no findings on imaging studies. While that may be true of MR imaging, MR spectroscopy does show abnormalities in these patients. Diffusely low *N*-acetylaspartate (NAA) correlates with suppression of neuronal activity. Their thalami show low NAA and high glutamine/glutamate (Glx), probably related to effects of excitoxicity.[1,2] While the clinical significance of these observations is uncertain, data obtained from patients with focal epileptogenic foci is important. MR spectroscopy is an important tool in the work-up of patients with refractory seizures. Nearly 15% of such patients will eventually harbor brain malformations; many will be potentially curable by surgical resection.[3] First, these data may help to identify, lateralize, and/or confirm a seizure focus. MR spectroscopy lateralizes temporal lobe epilepsy in 65%–96% of patients.[4] Patients with seizures whose MR spectroscopy studies show metabolite aberrations in their mesial basal temporal lobes, tend to have higher rates of concomitant contralateral abnormalities (though the clinical and treatment-related significance of this is uncertain).[5] In a small group of patients whose MR spectroscopy clearly showed low NAA in the affected side, high choline levels were present in the contralateral hemispheres.[6] Curiously, in patients with preoperative MR spectroscopy abnormalities and a right-sided focus, contralateral metabolic abnormalities will resolve after resection of the primary seizure focus.[7] It has been suggested that this is due to the withdrawal of the effect that seizures have on the brain as a whole. However, MR spectroscopy abnormalities are not time-dependent; that is, patients with chronic epilepsy have similar metabolite levels at the start of their disease and years after.[8] This latter observation is valid for the seizure focus itself, but not for the rest of the brain. In patients with temporal lobe epilepsy in whom remote low NAA is found, the levels of this metabolite will recover to normal or near-normal levels within 6 months of being seizure-free.[9] The hippocampus may be damaged by seizure activity beginning elsewhere (kindling effect). Unilateral hippocampal damage/dysfunction is present in about 50% of patients with distant neocortical epileptogenic foci.[10] Seizures are known to result in variable MR spectroscopy profiles. In patients with Rasmussen encephalitis, MR spectroscopy profiles are known to fluctuate in relation to seizure activity.[11]

The findings reported in this issue of the *AJNR* are not completely new. Mueller et al found that metabolic abnormalities in the perilesional zone share the characteristics of MCD and that these abnormalities may be related to areas of microscopic malformations and/or intrinsic epileptogenicity.[12] In addition, MCD are metabolically heterogeneous because they may contain abnormal as well as normal areas. Abnormal diffusion anisotropy has also been found beyond the visualized limits of MCD.[13] The fact that Leite and her colleagues found abnormal MR spectroscopy profiles even in the contralateral hemisphere is important but not surprising. The most important observation from their study is that one needs to be very cautious when using the contralateral brain as an internal control in patients with focal epilepsy. This is a technique commonly employed in all brain MR spectroscopy studies and reinforces the need for age-matched control normal values. The explanation as to why NAA, a neuronal marker, should be diffusively abnormal in patients whose seizures originate from a single focus, remains elusive.

So far, we have not been able to pinpoint the function of NAA. This metabolite is found in the central nervous system exclusively, particularly in neurons, where it is synthesized in their bodies, travels through their axons and dendrites and is eventually broken down by oligodendrocytes. NAA has the following qualities: it is presumably a precursor for excitatory amino acids that act via the *N*-methyl-D-aspartate receptors; is related to neuronal and neuropil integrity; participates in the functioning of the mitochondria, and regulates protein and myelin-lipid synthesis. Thus, the etiology for low NAA in epilepsy patients is multifactorial. Seizure activity impairs oxygenation and metabolism. Malfunctioning mitochondria may result in low NAA; impaired intraneuronal energy-dependent transport of NAA may make this metabolite less "MR spectroscopy-visible"; and re-arrangements of dendritic connections by pruning and sprouting may also lower its levels, but overall, low NAA is generally felt to be related to neuronal loss. Abnormal metabolism of NAA may contribute to the high Glx seen in some patients with seizures, damage to the cell membranes may make the fraction of MR spectroscopy-visible choline higher, and the development of gliosis may result in elevations of myoinositol.[6] It is also possible that local electrical disturbances related to seizure activity may introduce minute currents which result in susceptibility effects leading to metabolite peak height abnormalities, particularly if higher field strengths (3T and above) are used to obtain MR spectroscopy studies at the time of seizures or soon thereafter.

What is the meaning of bilateral or diffuse MR spectroscopy abnormalities in patients with epileptogenic foci? It certainly does not represent dual pathology, because most patients will clinically improve after lesionectomy. Additionally, many of the distant MR spectroscopy abnormalities may improve when patients become seizure-free. The relationship between diffuse/contralateral MR spectroscopy abnormalities and the success of pharmacologic and/or surgical treatments has not been evaluated. Surgical failure may occur when a neocortical focus has "kindled" a hippocampus, leading to its atrophy and gliosis, thus making it a new seizure focus. Extensive temporal lobe MR spectroscopy abnor-

malities are also more common in patients who fail selective amygdalohippocampectomies.[14]

A benefit that MR spectroscopy offers when evaluating patients with MCD is that it allows to distinguish between these benign lesions and cortical-based low-grade gliomas.[15] Tumors show lower NAA and higher choline than MCD. Furthermore, changes in choline and creatine may also help to differentiate among cortical-based glioma subtypes (astrocytoma versus oligodendroglioma).

What can the neuroradiologist learn from these observations? Clearly, the metabolic and electrical abnormalities associated with seizure foci extend beyond the anatomic lesion. The exquisite sensitivity of MR spectroscopy allows the identification of these abnormalities, but their significance remains uncertain. This uncertainty offers innumerable research possibilities and opens the door to gain further in-depth and in vivo understanding of this common disease (epilepsy), which was not formerly possible.

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