Spectroscopy Evidence of Diffuse Brain Abnormalities in Patients with Epileptogenic Foci

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 excitotoxicity.^{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 encephali-

tis, 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 diffusely 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.

References

1. Duncan JS. Brain imaging in idiopathic generalized epilepsies. *Epilepsia* 2005;46 Suppl 9:108–11
2. Helms G, Ciumas C, Kyaga S, et al. Increased thalamus levels of glutamate and glutamine (Glx) in patients with idiopathic generalized epilepsy. *J Neurol Neurosurg Psychiatry* 2006;77:489–94
3. Meencke H-J, Veith G. Migration disturbances in epilepsy In: Engel Jr J, Wasterlain C, Cavalheiro EA, eds. *Molecular Neurobiology of Epilepsy, Series Epilepsy Research Supplements*, 9. Elsevier; 1992
4. Kuzniecky R. Clinical applications of MR spectroscopy in epilepsy. *Neuroimaging Clin N Am* 2004;14:507–16
5. Hammen T, Stefan H, Pauli E, et al. 1H-MR spectroscopy: a promising method in distinguishing subgroups in temporal lobe epilepsy? *J Neurol Sci* 2003;215:21–25
6. Hammen T, Kerling F, Schwartz M, et al. Identifying the affected hemisphere by (1)H-MR spectroscopy in patients with temporal lobe epilepsy and no pathological findings in high resolution MRI. *Eur J Neurol* 2006;13:482–90
7. Lantz G, Seeck M, Lazeyras F. Extent of preoperative abnormalities and focus lateralization predict postoperative normalization of contralateral 1H-magnetic resonance spectroscopy metabolite levels in patients with temporal lobe epilepsy. *AJNR Am J Neuroradiol* 2006;27:1766–69
8. Burneo JG, Knowlton RC, Faught E, et al. Chronic temporal lobe epilepsy: spatial extent and degree of metabolic dysfunction studied with magnetic resonance spectroscopy (MRS). *Epilepsy Res* 2004;62:119–24
9. Seres W, Li LM, Antel SB, et al. Time course of postoperative recovery of N-acetyl-aspartate in temporal lobe epilepsy. *Epilepsia* 2001;42:190–97
10. Mueller SG, Laxer KD, Cashdollar N, et al. Spectroscopic evidence of hippocampal abnormalities in neocortical epilepsy. *Eur J Neurol* 2006;13:256–60
11. Wellard RM, Briellmann RS, Wilson JC, et al. Longitudinal study of MRS metabolites in Rasmussen encephalitis. *Brain* 2004;127:1302–12
12. Mueller SG, Laxer KD, Barakos JA, et al. Metabolic characteristics of cortical malformations causing epilepsy. *J Neurol* 2005;252:1082–92
13. Eriksson SH, Rugg-Gunn FJ, Symms MR, et al. Diffusion tensor imaging in patients with epilepsy and malformations of cortical development. *Brain* 2001;124:617–26
14. Spencer DC, Szumowski J, Kraemer DF, et al. Temporal lobe magnetic resonance spectroscopic imaging following selective amygdalohippocampectomy for treatment-resistant epilepsy. *Acta Neurol Scand* 2005;112:6–12
15. Vuori K, Kankaanranta L, Häkkinen AM, et al. Low-grade gliomas and focal cortical developmental malformations: differentiation with proton MR spectroscopy. *Radiology* 2004;230:703–08

Mauricio Castillo
Senior Editor

American Journal of Neuroradiology

DOI 10.3174/ajnr.A0715