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Commentary

Clinical Proton MR Spectroscopy of Neurodegenerative Disease in Childhood

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Magnetic resonance (MR) imaging and MR spectroscopy (MRS) are complementary, but independent, sources of information. MRS reveals information about tissue metabolism not available from MR imaging. For neurodegenerative diseases, the MR findings frequently are nonspecific. Brain tissue biopsy may be required to establish the diagnosis. MRS could prove to be helpful in diagnosing some diseases and in monitoring the effectiveness of treatment instituted for the disease.

The article by Tzika et al in this issue (1) probes these questions. The authors use two MRS techniques: a PRESS technique with long echo times and a stimulated-echo acquisition mode technique with short echo times. The availability of both techniques makes it possible to obtain peaks of many metabolites, and this can be helpful in the interpretation of some biochemical processes. Long echo times allow more precise estimation of lactate without the superimposed fat peaks, whereas shorter echo times allow estimation of myoinositol, lipids and, often with less reliability, glutamine, γ-aminobutyric acid, and glutamate. Both techniques have disadvantages and advantages. For instance, a short echo time sequence minimizes the signal loss and distortion to the spectra because of the T2 effects, thereby greatly improving the detectability of inositol, glutamine, glutamate, and other short T2 components and coupled spin systems. Substantial amounts of lipid signal are present between 1 and 2 ppm. Thymosin β_4, a cerebral protein, shows up at 0.9, 1.2, and 1.4 ppm (2). There is also a broad hump present in the background, extending from 0.5 ppm all the way to the water resonance position. This hump can be seen in the spectra of normal live brain and in dead brain tissue. It may come from protein backbones within the tissue. Because the spectrum is crowded and the baseline not well defined, short echo time spectra are not as manageable as long echo time spectra. When the time constraints for the patient examination allow only one sequence, it is often a difficult decision as to which sequence is most appropriate. However, when time constraints are not an issue, performing both measurements enhances the value of MRS.

This paper by Tzika et al emphasizes the importance of spatial localization. Consequently, small regions of interest were used for the measurements, even though lesions visualized on MR were frequently larger than the region of interest. Small volumes ensure that the tissue type within the region of interest is homogeneous. However, the observation of the signal intensities related to the abnormal metabolites requires a high signal-to-noise ratio. In many cases, these signals are best observed with bigger sampling volumes and, in some instances, with longer echo time sequences.

The authors have been able to observe inositol because of the use of short echo times. They found increased inositols and/or glycine levels in three of five children with x-linked adrenoleukodystrophy, a peroxisomal disorder, and in several lysosomal disorders, Sanfilippo and Hurler syndrome. In another peroxisomal disorder, Zellweg-

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er syndrome, other authors have recently reported as an abnormality a decrease, rather than an increase, in the inositol levels (3). In the discussion regarding hereditary neurodegenerative disorders of peroxisomal nature, Tzika et al state, "The limited presence of lactic acid in the long echo spectra in adrenoleukodystrophy is probably nonspecific and can be attributed to reduced local blood perfusion. This leads to accumulation of lactic acid, which is not effectively removed by the blood circulation. If proton MRS can detect these types of changes in vivo, it may become an important tool in the evaluation of neurodegenerative changes in peroxisomal disorders. This hypothesis, supported by our observations, must be tested in animal models of the disease as well as larger numbers of patients." That the lactate elevation is attributed to insufficient blood perfusion in the region involved remains speculative, the nature of the pathobiochemical process in adrenoleukodystrophy makes it even improbable that this explanation is correct. At present, the evidence given by the authors to support this conclusion is insufficient.

It is evident that the role of inositol is still not fully understood (4), other than as a messenger for hormone actions. Furthermore, inositol and glycine cannot be resolved from each other in the 1.5-T in vivo spectra. It is also known, and therefore always a consideration in the interpretation of spectra, that the inositol level in infants is relatively high. In Sanfilippo syndrome, spectra shown are of interest apart from the high inositol level, because there are two peaks, at approximately 1.7 and 1.4 ppm, in the short echo spectra. The origins of these two peaks is not identified. For metabolic disorders, the appearance of unknown peaks is not unusual. Interpretation of these signals represents both difficulties and opportunities. High-field resolution MR spectroscopy of the tissue extract may help to identify the unknown metabolites. High-resolution nuclear MR spectra of urine and blood may also be very useful in providing clues for peak assignments, although metabolites in the brain are not necessarily present in the blood or urine. Once understood, the abnormal resonances may be more specific to the disease and more sensitive to the effectiveness of treatment. In the case of Gaucher disease, a lysosomal disorder, the authors indicate that the glutamine and glutamate levels are elevated. However, compared with spectra in Figs. 1 and 2, this does not seem to be the case. The spectra looked normal.

The authors present one case of Leigh syndrome as an example of mitochondrial dysfunction with elevation of lactate without a decrease in *N*-acetyl aspartate. The high lactate level here is striking. In the experience at the Children's Hospital of Philadelphia, we have examined three cases of Leigh syndrome; the first case has been reported (5). The results of later follow-up studies in this patient show changes in the MR patterns. The initial high signal intensity in the basal ganglia was resolved after several months; however, the MRS results did not change. This case demonstrated the role of MRS relative to MR in monitoring the effect or lack of effect of treatment.

Tzika et al present their MRS findings by visual impression of the spectra and refer only occasionally to ratios, which are, however, not presented numerically. It remains unclear in this paper how the ratios were calculated, at peak height or by area, and which assumptions about the baselines were made. The spectra obtained by the authors show good quality and the clinical material brought together in this manuscript is of great interest. However, the question arises, are global impressions about what MRS can and cannot do still valid, or is a more demanding approach concerning the techniques of data acquisition, quantification, and comparison with comparable normal values required? Proton MRS has the unique capability of showing in vivo concentrations of a number of biochemical compounds and therefore has the potential of elucidating the biochemical basis of encephalopathy and assisting in diagnostic assessment and therapeutic monitoring. To achieve this purpose, many technical requirements have to be fulfilled and some general pathologic and pathobiochemical considerations taken into account. Bottomley (6) lays down some rules that need to be kept in mind. Not all problems concerning calculation of accurate concentrations in metabolites have been solved, but several sensible approaches are available, including that of Kreis et al (7).

As difficult and demanding as are the technical aspects of MRS, so are the considerations regarding interpretation of data. With few exceptions, proton MRS in neurodegenerative disorders has not been shown to be more specific than MR imaging. Findings of ^{1}H and ^{31}P MRS in degenerative cerebral disorders are nonspecific, and the results are mainly indicative of destruction of neuronal tissue (*N*-acetyl aspartate decrease) or demyelination, most clearly visible in ^{31}P MRS (8). Only in very few instances does ^{1}H MRS yield

more specific results, as in phenylketonuria, where phenol alanine can be measured, in Canavan's disease with excessive concentrations of *N*-acetyl aspartate, and in maple syrup urine disease with high concentrations of branch-chain amino acid. Many other findings are less specific and indicate only a disturbance of certain biochemical pathways: higher lactate in mitochondrial disorders (and all other conditions of energy failure), higher glutamine in hepatocerebral syndromes and in inborn errors of urea cycle metabolism, and myoinositol and glutamine-glutamate increase in excitotoxic syndromes.

The only way to progress in the evaluation of these neurodegenerative diseases is to collect sufficient material from homogeneous populations examined with good technique and quantification of data. To do this it is necessary to have data on a sufficient number of healthy volunteers in all age classes to compare and determine normal (absolute) values and confidence levels. Especially in inborn errors of metabolism, two-dimensional chemical shift imaging may be helpful in assessing large volumes of brain tissue. Tzika et al are to be commended for their efforts to stimulate the use of MRS to understand the neurodegenerative diseases of childhood.

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