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The Value of Proton MR Spectroscopy in Pediatric Metabolic Brain Disease

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What is the future for in vivo proton MR spectroscopy in the understanding of pediatric metabolic diseases? To gain a perspective, it is necessary to look back at what has happened, examine the present accomplishments, and try to understand what problems cloud the future.

The invention of magnetic resonance (MR) imaging followed by more than a quarter century the first observations of proton MR in condensed matter. However, the value of MR spectroscopy as an analytic tool for chemists was appreciated soon after the discovery of MR, when it was found that different molecular groups had different chemical shifts (1). Despite this advantage of MR spectroscopy, its clinical application in the study of metabolism in diseases has evolved at a much slower pace than that of MR imaging.

The successful application of proton MR spectroscopy to pediatric metabolic diseases has been around for only the past decade. With the successful implementation of magnetic field shimming, pulse sequence design, and water suppression on 1.5-T magnets, spectroscopy could be performed in a reasonable time frame of 10 to 20 minutes or more, first from single voxels and then, with the development of chemical-shift imaging spectroscopy and the use of longer acquisition times, from multiple voxels, within a single section and then within multiple sections. Initially, echo times (TEs) were long (eg, 135 and 270

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milliseconds), but with improvements in magnetic field gradient coils, TEs of 10 to 40 have become commonplace. The shorter TEs enable more metabolites to be identified and potentially quantitated, either by ratio to one another or by assumptions made relative to quantities of other metabolites or to water or to control solutions. Long TEs allow more precise estimation of lactate without superimposed fat peaks, whereas shorter TEs allow estimation of *myo*-inositol, lipids, and, often with less reliability, glutamine, γ-aminobutyrate (GABA), and glutamate. Both techniques have advantages and disadvantages. For instance, a short-TE sequence minimizes the signal loss and distortion to the spectra from T2 and spin-coupling effects, thereby greatly improving the detectability of inositol, glutamine, glutamate, and other short T2 components and coupled spin systems. However, there are substantial amounts of lipid signal present between 1 and 2 ppm and macromolecules contributing to the baseline. Because thespectrum is crowded and the baseline not well defined, short-TE spectra are not as easily managed as long-TE spectra.

Although the hurdles faced in obtaining and understanding the data remain enormous, they are not unconquerable. First, the pediatric patient that is often of most interest is young and therefore not cooperative. Metabolic brain disease, an inborn error of metabolism that interferes with neurologic function, frequently, but not always, represents a serious medical problem, and, in many instances, the patient can be medically unstable. Imaging these patients often requires sedation and/or medical support, plus time out of the intensive care unit. It requires a more prolonged use of the MR imager for tests that usually are not reimbursable (in the United States, proton spectroscopy is only reimbursed in Ohio and California) and takes potential time away from paying patients, a practice for which hospitals often have little tolerance. In addition, the inborn errors of metabolism, are, for the most part, rare conditions, even at subspecialty tertiary pediatric centers. Thus, for instance, the prevalence of maple syrup urine disease (MSUD) in the general population is given as 1 in 290 000 (2), so accumulating sufficient numbers of patients studied by a standard spectroscopic technique presents a challenge; that is, in order to have statistically significant numbers.

Finally, we are dealing with complex diseases, ones that are for the most part still being unraveled by specialists in many facets of disease: molecular geneticists, metabolic disease specialists, pediatricians, pathologists, neurologists, and so on. These researchers have only some insight into the complexity of the issues, and many issues they do not grasp at all. For instance, the metabolic pathways and the substrates produced within the living, intact, in vivo human brain are still incompletely understood, and it is these metabolites that we, as neuroradiologists and physicists doing proton spectroscopy, are seeking to comprehend. One can imagine the frustration of being confronted with a child with an as yet unknown brain disorder in whom proton spectroscopy reveals yet another peak for a metabolite that is not normally present and that we are not even able to assign a name to.

Technical Aspects of Brain Proton Spectroscopy

Metabolites Detected and Their Significance

On commercial clinical MR imagers, nuclei accessible for MR spectroscopic studies are phosphorus-31 and proton. In vivo MR spectroscopy with carbon-13 and nitrogen-15 provides valuable information, and these studies are also actively pursued in research investigations. Of all these, proton offers both the highest sensitivity and the richest information (3), and it is the most developed for use in clinical examinations. Proton MR spectroscopy allows detection of a variety of metabolites, including *N*-acetylaspartate (NAA), total creatine and phosphocreatine (Cr), choline-containing compounds (Cho), *myo*-inositol, *scyllo*-inositol, glutamine, glutamate, glucose, taurine, GABA, alanine, and lactate. Some metabolites do not appear under normal conditions, but become detectable when they are abnormally prominent in disease states. The Table summarizes the role of various metabolites and the significance of abnormal changes in them.

Localization and Quantitation Techniques

Both single-voxel techniques—stimulated-echo acquisition mode (STEAM) (4) and point-resolved spectroscopy (PRESS) (5) (P. A. Bottomley, "Selective Volume Method for Performing Localized NMR Spectroscopy," US patent 4 480 228 1984)—and spectroscopic imaging techniques (6–8) are commonly used in clinical MR spectroscopic studies. Single-voxel studies are easier to perform and have demonstrated reliable quantitation. The absolute signal intensity can be calibrated with an external standard positioned inside the coil with the patient (9), or with a phantom after the patient study is completed (10), or by using tissue water as an internal reference (11).

Although brain involvement in metabolic diseases is often diffuse, the distribution of metabolites in the brain is not uniform, and the pattern of distribution of abnormal metabolites may vary. Chemical-shift imaging, which is used to map metabolite distribution in the brain, can be performed in one, two, or three spatial dimensions. Two-dimensional chemical-shift imaging sequences with short and long TEs are currently available with most commercial MR imagers. Although chemical-shift imaging is capable of absolute quantitation (12), this capability has not been fully realized with routine clinical studies. However, this situation may change in the near future. The internal reference calibration of chemical-shift imaging is not as easy to accomplish as in single-voxel studies. The acquisition of an internal reference signal for each voxel is possible, but requires another chemical-shift imaging acquisition, which is time-consuming. An in vivo chemical-shift imaging signal can also be calibrated by using a phantom before or after the patient study. Before shielded gradient coils were

used in MR imagers, the variation of signal from chemical-shift imaging voxels on a uniform phantom were on the order of 10%. Therefore, the apparent signal variation across the section could be artifactual. With the use of shielded gradients, signal variation across a transverse section on a phantom is much smaller; calibration of chemical-shift imaging signal using a phantom has become a good approach (12). One problem is the nonideal point spread function: a nominal voxel also contains contributions from outside tissue (13). Although one needs to be careful in using chemical-shift imaging to obtain quantitative measurements because of the potential for spectral leakage, this problem does not have serious consequence for most clinical applications, in which the important issue is often whether metabolite levels have changed markedly over volumes larger than the nominal voxel size. A method for eliminating the long-range signal contamination is to apply k-space filtering, which is a feature provided with commercial MR imaging units. However, with this technique, the effective voxel size (volume that contributes to the spectrum of one nominal voxel) is drastically increased. To reduce the size of effective voxels, many investigators perform chemical-shift imaging using 32×32 phase-encoding steps to decrease the nominal voxel size. Because of the long minimal measuring time, it is difficult to use a long repetition time (TR) to acquire signal free of T1 saturation, especially for sedated children.

To cover a three-dimensional volume, several methods are now available to acquire chemical-shift images in multiple sections, including 3-D phase-encoding chemical-shift imaging (14), sequential multisection chemical-shift imaging (15), and a 1-D Hadamard spectroscopic imaging (HSI)/2-D chemical-shift imaging hybrid (16). Each method has advantages and disadvantages. Three-dimensional chemical-shift imaging is a simultaneous data acquisition technique. The position of the chemical-shift imaging grid can be adjusted in all three spatial directions in postprocessing. However, the severity of the spectral leakage increases with the number of dimensions in chemical-shift imaging. K-space filtering may be used in all three directions and the effective voxel volume is much larger than the nominal voxel. The multiple-section chemical-shift imaging technique provides reliable spectral isolation between sections. In this technique, the data acquisition of different sections are interleaved to improve time efficiency. In one TR, data from one phase-encode sequence are acquired for all sections sequentially. Therefore, a longer TR is needed to acquire data for multiple sections. For example, to obtain four sections, the TR is more than four times the spectral acquisition window. Although four sections are commonly used now, it is possible to extend the method to more sections. When absolute quantitation and spectra free of T1 saturation are desirable, and a long TR is needed anyway, this method is advantageous. The HSI-chemical-shift imaging hybrid of 3-D spectroscopy is a simultaneous acquisition technique with optimal efficiency, and signal leakage between adjacent sections is small. Hadamard encoding may be thought of as an extension of the single-voxel localization method of imaging selected in vivo spectroscopy (ISIS) (17), which is a subtraction technique. Therefore, it is important that the patient does not move during the acquisition. In well-sedated children, good results can be obtained in most cases. More recently, chemical-shift imaging measurements have been obtained with the use of echo-planar imaging (18). Chemical-shift imaging using echo-planar techniques can be done in one, two, or three dimensions. The advantage of this method is that the time needed to acquire a complete data set can be reduced to $1/N$, where N is the number of phase-encoding steps in one spatial direction. For example, to obtain a 16×16 2-D chemical-shift image, the minimal measuring time is 1/16 that required for a conventional 2-D phase-encoding chemical-shift image. Because of the short minimal measuring time, this technique has the advantage that planned data acquisition may be interrupted before it has finished, with the data already accumulated still being useful, provided that the signal-to-noise ratio is acceptable.

Choice of Echo Time

For short-TE spectra, the metabolite levels can be quantified with the linear combination model method (19). In this method, solution spectra for each metabolite are measured and used as the base function. The measured spectrum is reconstructed using the model functions by a least-squares curve-fitting procedure. The baseline is determined by a smoothness criterion. This procedure gives satisfactory results in most cases, as evidenced by the low residual small noise level of the difference between the in vivo data and the fit. To obtain reliable metabolite levels, it is crucial to acquire spectra with good shimming and good water suppression. Although a value is returned for all metabolites, some metabolites are determined with higher precision than others. The uncertainty of metabolite levels determined by least-squares curve fitting due to random noise in the spectrum can be calculated (20, 21). For spectra with multiple peaks, overlapping between peaks increases the uncertainty of peak area measurement (Z. Wang, J. Haselgrove, "Determination of Errors in MR Spectroscopy Measurement Caused by Random Noise," in: *Proceedings of the Society of Magnetic Resonance 3rd Meeting and the European Society for Magnetic Resonance in Medicine and Biology 12th Annual Meeting* 1995;3:1949). The metabolites that can be determined most reliably in short-TE spectra are NAA, total Cr, Cho, and *myo*-inositol (S. W. Provencher, W. Hanicke, T. Michaeis, "Automated Quantitation of Localized 1H MR Spectra In Vivo: Capabilities and Limitations," in: *Proceedings of the Society of Magnetic Resonance 3rd Meeting and the European Society for Magnetic Resonance in Medicine and Biology 12th Annual Meeting* 1995;3:1952). The precision with which glutamine, glutamate, and GABA can be determined is not as good, because they have broad resonance line shapes and overlap with one another. In many cases, it is advantageous to acquire spectra with long TEs, if the major interest is NAA, Cho, and Cr. Although the signal intensity is decreased, the precision of these peaks

Major metabolites observed in the brain

Metabolite	Role	Clinical Significance
N-acetylaspartate (NAA)	Present in neuronal cell and synthesized in mitochondria. Physiological role is poorly understood. It is also an osmolite.	NAA is a neuronal marker. Neuronal damage and cell death cause decrease in NAA. Overall, NAA is the most sensitive metabolite to central nervous system disorders. Sometimes a small decrease in NAA is reversible, and may not indicate permanent cell damage. NAA is increased in Canavan disease.
Total creatine and phosphocreatine (Cr)	Involved in energy metabolism of cells.	Level of Cr is relatively stable in metabolic diseases; however, Cr may decrease, and it is not a reliable internal reference.
Choline-containing compound (Cho)	Membrane component and an osmolite.	Cho is sensitive to myelin disorders and is often decreased; however, it may be increased when cell membrane turnover is increased, usually in the early or acute stage of a demyelinating disease. Cho is increased in malignant brain tumors.
Myo-inositol	Present only in glial cells. It is a hormone messenger and osmolite.	*Myo*-inositol is a glial marker. It is sensitive to osmolarity and reflects the serum sodium level. *Myo*-inositol is increased in hypernatremia and decreased in hyponatremia. Its level may change in white matter diseases.
Glutamate and glutamine	Glutamate is an excitatory neurotransmitter, glutamine is involved in the recycle of glutamate	Glutamine is increased in hepatic encephalopathy. Total glutamate and glutamine are increased in human immunodeficiency virus and other viral infections.
Glucose	Fuel for brain cells	Glucose level is low under normal conditions. Elevation of glucose may be observed in diabetics.
γ-aminobutyrate (GABA)	Inhibitory neurotransmitter	Higher GABA as a result of medication helps to suppress seizures.
Taurine	Osmolite and bile acid	Taurine appears to be important in neonates.
Lactate	Product of anaerobic glucose metabolism.	Lactate elevation is found in hypoxia, stroke, and mitochondria diseases. Lactate elevation may be found in other disorders, too, but the reasons for this are not fully understood.

may even improve owing to a lack of interference from other metabolites and a well-defined baseline at long TEs (Provencher et al, "Automated..."). The area of the peak can also be calibrated, but the peak areas are subject to T1 and T2 effects. Recently, the PRESS technique was combined with the Carr-Purcell-Meiboom-Gill sequence to eliminate effects of J coupling at long TEs (T. Thiel, O. Speck, J. Hennig, "Improved Sensitivity to Overlapping Multiple Signals in In Vivo Proton Spectroscopy Using a Multiecho Volume Selective (CPRESS) Experiment," in: *Proceedings of the International Society for Magnetic Resonance in Medicine Fifth Scientific Meeting and Exhibition* 1997:242). The spectra are similar in appearance to the short-TE spectra, but the macromolecular contribution is much smaller.

Editing Techniques and Correlation Spectroscopy

Proton spectra contain rich information. However, because of overlap between the peaks, reliable detection of interesting metabolites, such as glutamine, glutamate, and GABA, is difficult. Even lactate signal can be contaminated by lipids. Taking advantage of a J coupling (22) between protons in the same molecule, specially designed "editing" pulse sequences can be implemented to selectively detect a metabolite. Most editing sequences rely on the generation and manipulation of double quantum or zero quantum coherence, longitudinal spin order, or phase modulation caused by J coupling. Long TEs are needed to generate the multiple quantum coherence and spin orders. For an interaction with strength J to take full effect, a time on the order of 1/J is needed. For example, the J coupling strength between CH and CH3 protons in lactate is approximately 7 Hz (23), and all lactate editing techniques use a TE of 135 to 144, independent of B_0 field strength and regardless of whether it is based on zero quantum, double quantum, and so on. The question of lactate editing has been studied by a number of investigators, and many articles have been published on this subject. Editing sequences for detection of GABA (24), glutamine, and glutamate are also being developed (25). In many cases, the editing procedure introduces significant signal loss, as a combined effect of the long TE and intrinsic loss due to editing. Because of the high specificity of these techniques, they have considerable clinical potential in the diagnosis and treatment monitoring of metabolic diseases. However, their application to clinical studies is still at a very early stage. They require additional time to perform after the basic MR spectroscopic study has been obtained, and these sequences are not currently provided by commercial manufacturers.

Another frequent problem of proton spectroscopy is the assignment of unknown peaks. Although peak assignment can sometimes be made by using information based on clinical diagnosis and other clues, it is desirable to make an unambiguous peak assignment on the basis of MR spectroscopy alone. This is difficult with a 1-D spectrum. Two-dimensional correlation spectroscopy is a promising technique for solving this problem. It has routinely been used by chemists to unravel spectra of complicated molecules, revealing which peaks in the spectrum belong to the same molecule by the presence of cross peaks arising from J coupling, which facilitate peak assignment. Initial results of the technique in the in vivo human brain have been demonstrated (26, 27). Its difficulty comes from the short T2 of the in vivo lines, and, as a consequence, the signal is weak, requiring long examination times. However, with improvements in the technique and in signal detection sensitivity, by going to a higher B_0 field and by the use of phased-array coils, such studies will become possible and thereby increase our understanding of certain metabolic diseases.

Clinical Applications of Proton Spectroscopy to Metabolic Diseases

A relatively simplistic system for classifying metabolic disorders affecting the brain, both gray and white matter, is used in looking at the existing literature on pediatric metabolic diseases of the central nervous system. This classification includes peroxisomal, lysosomal, mitochondrial, aminoacidopathic, and primary white matter disorders.

Peroxisomal Disorders

Peroxisomal disorders include X-linked adrenoleukodystrophy (ALD), neonatal ALD, and Zellweger syndrome. Of these, there is a small body of literature on ALD, which includes two series, that by Tzika et al (28), with 11 patients, and that by Kruse et al (29), with 25 patients. ALD has several presentations: 1) the severe, cerebral form of child ALD (cALD), which occurs most often between the ages of 4 and 8 years, leads to a rapid vegetative state, and accounts for 50% of ALD patients (30); 2) adrenomyeloneuropathy (AMN), which occurs in young adults, represents 25% of ALD patients, and involves the spinal cord and peripheral nerves (31); 3) ALD in which there is adrenal involvement or in which patients are asymptomatic, accounting for 20% of ALD patients; and 4) adolescent or adult cerebral forms (aALD), which include 8% of ALD patients. In addition, disabilities similar to AMN develop in 20% of women who are heterozygous for ALD (32).

Kruse et al (29) used multisection proton MR spectroscopy to study three patients with severe cALD or ALD, five patients with AMN, 12 patients with no neurologic deficits, and five women with the heterozygote and disabilities similar to those that accompany AMN. Abnormalities included decreased NAA, increased Cho, and intermittently elevated lactate. Five patients with normal MR imaging studies had abnormal MR spectroscopic findings; and in eight patients with abnormal MR imaging studies, the MR spectroscopic abnormalities were judged as more severe than the MR imaging abnormality.

Tzika et al (28) studied 11 patients, seven with cALD and four who were asymptomatic. MR spectroscopy in six patients with abnormal MR imaging findings showed a decrease of 65% in NAA/Cr and an elevation of 55% of Cho/Cr. In the four asymptomatic patients, Cho/Cr was elevated 51%, indicating that MR spectroscopy was more sensitive than MR imaging for detecting active early disease.

Cho elevation in patients with ADL appears to be a marker of active demyelination. That MR spectroscopy may be a more sensitive indicator of early central nervous system involvement and that it may furthermore give a measure of the degree of activity of the demyelination has important bearing on treatment of ADL. Bone marrow transplantation (BMT) as a therapeutic method is reserved only for children with early CNS involvement, as patients with advanced disease do worse with BMT (29). Furthermore, since clinically unaffected children may be destined for the milder AMN phenotype and not cALD, and BMT is not indicated in this group, MR spectroscopy and MR imaging can be combined to monitor the population at risk at 6- to 12-month intervals for detection of the earliest signs of disease during the period of vulnerability (29).

Lysosomal Disorders

Lysosomal disorders include, among others, the lipidoses such as Krabbe disease, metachromatic leukodystrophy, Niemann-Pick disease, and the mucopolysaccharidoses. Of these, metachromatic leukodystrophy was described by Kruse et al (33) in seven patients and by Wang et al (34) in one patient, while Sylvain et al (35) described a patient with Neimann-Pick disease.

Kruse et al (33) performed proton MR spectroscopy in seven children, four with the late infantile form and three with the juvenile form of metachromatic leukodystrophy. In six patients, MR spectroscopy was performed more than 6 months after the onset of symptoms, and the MR images showed severe findings. Decreased NAA was found in gray and white matter, and lactate was elevated at the sites of demyelination. The decreased NAA was thought to reflect neuronal-axonal degeneration and therefore loss of functional brain parenchyma. A generalized increase in *myo*-inositol (two to three times normal) in white matter stood out in contrast to MR spectra of other leukodystrophies. The increased *myo*-inositol may have reflected instabilities due to a change in myelin lipid composition, possibly the *myo*-inositol was a primary event rather than a secondary one. Active gliosis was thought to be responsible for the increase in lactate.

In a patient with Neimann-Pick disease, Sylvain et al (35) found an abnormal lipid peak at 1.2 ppm at age 9 months. After treatment with cholesterol-lowering agents, this peak was gone at age 13 months, suggesting that MR spectroscopy could be beneficial as a noninvasive means

of monitoring the response of the central nervous system to treatment.

Grodd et al (36) reported one case of mucopolysaccharidosis type II in which the NAA was decreased; this was a nonspecific finding that was associated with supratentorial atrophy and white matter loss.

Mitochondrial Disorders

Mitochondrial disorders include such diseases as Leigh disease; Kearns-Sayre syndrome; mitochondrial myopathy, encephalopathy, lactacidosis, and stroke (MELAS); and myoclonus epilepsy with ragged red cell fibers, among others. Leigh disease and MELAS have been addressed by various authors, including Barkovich et al (37), Castillo et al (38), Detre et al (39), Wang et al (34), Grodd et al (36), and Krageloh-Mann et al (40). A total of six patients with Leigh disease and seven with MELAS were examined with proton MR spectroscopy, which revealed elevated lactate within gray matter, especially at the sites of recent onset of elevated T2 signal intensity abnormalities. In Leigh disease, this is commonly in the lentiform nuclei (37), but, as shown by Detre et al (39), can also be found in normal T2-appearing gray and white matter as compared with normal control subjects. Castillo et al (38) also found that two patients with negative MR imaging findings had elevated lactate. Barkovich et al (37) found that in patients with MELAS, the lactate elevations were found by to be more often within the affected parietooccipital cortex. Depending on the state of the injury to the brain, both Grodd et al (36) and Detre et al (39) reported a decrease in NAA of the affected tissue.

Aminoacidopathies

Aminoacidopathies include, among others, phenylketonuria (PKU), MSUD, homocystinuria, methylmalonic acidemia, and glutaric acidemia type I. Various instances of these disorders have been reported, but for the most part as one or two cases, with the exception of the eight cases of PKU reported by Pietz et al (41, 42). These authors were able to detect elevated phenylalanine at 7.37 ppm on proton MR spectra in the white matter, as were Novotny et al (43). Otherwise, the MR spectra were normal. The potential exists for the synergistic use of MR imaging and MR spectroscopy to elucidate the pathogenesis of brain dysfunction and provide guidelines for clinical treatment in PKU. The potential therefore exists to use MR spectroscopy to monitor the effect of sodium benzoate therapy in PKU.

One case each of MSUD has been reported by Heindel et al (44), Wang et al (34), and Felber et al (45). Each group observed a peak at 0.9 ppm, which represents the branched chain amino acids and branched chain 2-oxoacids that accumulate as a result of defective oxidative decarboxylation of leucine, isoleucine, and valine. The proton MR spectroscopic findings are positive even when MR imaging is negative but the patient shows signs of neurologic decompensation and the peripheral blood analysis is positive. With successful treatment, the peak at 0.9 ppm decreases. Thus, proton MR spectroscopy can be used to evaluate the state of disease in MSUD and its response to therapy. Heindel et al (46) reported two infants with nonketotic hyperglycinemia, identified as a large glycine peak at proton MR spectroscopy at 3.55 ppm and further found that proton MR spectroscopy in one patient revealed a different time course for cerebral glycine content than the plasma and cerebrospinal fluid did. The continuing reduction of glycine in brain tissue corresponded more reliably with the clinical picture.

Engelbrecht et al (47) found mildly decreased NAA at MR spectroscopy and hypomyelination at MR imaging in a 10-month-old girl with methylenetetrahydrofolate reductase deficiency. While both MR imaging and MR spectroscopic findings were nonspecific relative to this disease, therapy with betaine as a methyl donor did produce a decrease in hypomyelination at follow-up MR imaging. Potentially, MR spectroscopy may also be useful in monitoring response to therapy. In patients with glutaric acidemia, Grodd et al (36) found both decreased NAA and increased lactate.

Primary White Matter Disorders

In the primary white matter disorders, which include, among others, Canavan disease, Alexander disease, and Pelizaeus-Merzbacher disease (PMD), a number of case reports or small series have been reported.

Canavan disease has received the most attention and has been characterized by an increase in NAA. At proton MR spectroscopy, this has been reported to be in the 20%-to-100% range (48–50), while biochemically in the brain it is often increased by a factor of five. Cho is decreased and *myo*-inositol is elevated (34, 51). Thus, for patients with diffuse white matter disease and macrocephaly who have decreased NAA, the diagnosis has been other than Canavan disease (51). In one family, the MR spectroscopic findings and clinical features led to the description of a new autosomal dominant disorder of white matter (51). Takanashi et al (52) found that in early PMD, the MR spectra are distinct from those of Canavan disease, in that they are normal. However, Grodd et al (36) had different results in PMD. In patients with advanced disease, the NAA was decreased and the Cho was elevated. In two patients with Alexander disease studied by Grodd et al (36), NAA was decreased in the frontal lobes whereas it was close to normal levels in the occipital lobes. Lactate was elevated in the frontal lobe of the child with the most advanced disease.

Conclusion

Technological developments and clinical research in this field have been proceeding at a rapid pace. It has been demonstrated, repeatedly, that MR spectroscopy can provide specific information that is not available from MR imaging. MR spectroscopy has evolved into a valuable clinical tool (53), and is now widely available in major university medical centers. Useful clinical information can

be obtained for disorders involving the central nervous system in children (4, 34, 54). Because MR spectroscopy can noninvasively characterize the biochemistry of brain tissue, and because of the continuing development and improvement of this technology, together with the accumulation of knowledge and experience, this technique will play an increasingly important role in the evaluation of metabolic diseases.

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