Proton Magnetic Resonance Spectroscopy for the Diagnosis and Management of Cerebral Disorders

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The use of magnetism in medicine has a long and colorful history since its legendary discovery in the Western world by the shepherd Magnes. More recent use of magnetism has centered on nuclear magnetic resonance. Magnetic resonance spectroscopy (MRS) provides chemical information on tissue metabolites. Both hydrogen 1 (1H) and phosphorus 31 resonances have been used to study brain tissue, but the magnetic resonance sensitivity for protons is far greater than it is for phosphorus. One of the most important contributions of 1H-MRS to clinical neurology is its ability to quantify neuronal loss and to demonstrate reversible neuronal damage. 1H–magnetic resonance spectroscopy has been found to be a useful research tool in elucidating the pathophysiology underlying certain diseases. This review focuses on the use of proton MRS to study various neurologic diseases, including epilepsy, multiple sclerosis, brain tumors, human immunodeficiency virus 1–associated neurologic disorders, as well as cerebrovascular, neurodegenerative, and metabolic diseases. It highlights the contributions of 1H-MRS to the diagnosis and the monitoring of these neurologic diseases that make it a useful adjunct in patient management.
ippus Aureolus Paracelsus (1493-1541) said that every person possessed magnetic powers. He deduced that even the cure for epilepsy could be derived by the careful application of magnets (vide infra). Familiar with Paracelsian teachings, the Viennese physician Franz Anton Mesmer (1734-1815) called these innate forces “animal magnetisms.”

The use of magnetism as a diagnostic tool began with Dr John Elliotson (1791-1868), professor of the theory and practice of medicine at London University, London, England. By 1837, he was performing surgical procedures on patients anesthetized (mesmerized) by “magnetic sleep.” In 1838, his magnetic treatments were applied to 2 sisters, Elizabeth and Jane Okey. Not only were they cured of their hysterics, but, supposedly, they were also given clairvoyance and the ability to visualize their internal organs and those of others. The sisters would accompany Elliotson on his medical rounds, and, through magnets, he would place them in a trancelike state. The sisters would then evaluate the state of his patients’ organs and Elliotson would prescribe the appropriate treatment. The University Hospital was less than convinced that his methods were appropriate medical management and passed a resolution preventing the practice of mesmerism within the hospital.

More recent use of magnetism for diagnosis has centered on nuclear magnetic resonance. These new technologies are now “pointing the way” to the anatomical, functional, and biochemical foundations of neurologic disease. This review uses examples from different neurologic disorders to demonstrate how magnetic resonance spectroscopy (MRS) can be used as a tool for the investigation and management of these diseases. The information presented is based on a large body of innovative work from literally hundreds of researchers. It is only the limitations of space that prevent citing them all. However, it is hoped that this review will function as both a context and a catalyst that will excite the reader to explore further this diverse and expanding field.

**MRS IN VIVO**

Whereas magnetic resonance imaging (MRI) provides anatomical information based on signals from water, MRS provides chemical information on metabolites. The atomic nuclei that can be studied by MRS are hydrogen 1 (1H), phosphorus 31 (31P), chlorine 13, fluorine 19, and sodium 23. Both 1H and 31P are present in concentrations in the brain that can be detected by MRS and have been used extensively to study brain metabolites in vivo. This review focuses on the use of 1H-MRS to study neurologic disease because the magnetic resonance (MR) sensitivity is much greater for protons than it is for phosphorus, and it therefore allows for greater spatial resolution, which is better suited for examining cerebral pathologic features.

**PROTON SPECTRA OF HUMAN BRAIN**

In vivo spectroscopy poses additional challenges over those encountered with conventional MRI. First, the metabolites in the brain tissue exist in millimolar concentrations. Therefore, the signals from the water in the brain and in surrounding structures can both overwhelm and distort the signals from the metabolites of interest. To overcome this, techniques are generally used that either suppress the stronger signals or prevent them from being excited in the first place. Second, since abnormalities in the brain are often focal, and because brain tissue is heterogeneous, it is necessary to obtain spectra from localized areas, either from single or multiple volumes. Small voxels, on the order of 1 or 2 cm³, and long acquisition times produce relatively low signal to noise ratios. Third, the power of using MRS is the possibility to quantify the spectra that are generated. This, however, is not a trivial task. Since absolute quantification is difficult to perform accurately, many laboratories calculate the relative quantity of metabolites present by using the ratio of one metabolite to another that is known to be unchanged.

**Compounds Observable in Proton Spectra**

Resonances in MR spectra are identified primarily by their frequency, i.e., position in the spectrum, expressed as the shift in frequency in parts per million (ppm) relative to a standard. Water-suppressed, localized proton MR spectra of a healthy human brain at “long” echo times (TE) (commonly, TE, 136 or 272 milliseconds) reveal 4 major resonances (Figure 1):

- one at 3.2 ppm that arises mainly from tetradeuteromethanes, especially choline-containing phospholipids (Cho);
- one at 3.0 ppm that arises primarily from creatine (Cr), either alone or as phosphocreatine;
- one at 2.0 ppm that arises from N-acetyl groups, especially N-acetylaspartate (NAA); and
- one at 1.3 ppm that arises from the methyl resonance of lactate and is normally barely visible above the baseline noise. In certain pathological conditions, a methyl resonance from lipids or alanine can also be detected in this region.

Shorter TEs are better for detecting compounds with short T$_2$ relaxation times, such as lipids, myoinositol, glutamate, and γ-amino-butyric acid.

**Cho AND OTHER LIPIDS ARE MARKERS OF MYELIN BREAKDOWN**

Changes in the resonance intensity of Cho appear to result mainly from increases in the steady state levels of soluble choline compounds, including choline, phosphocholine, glycerophosphocholine, and, in some cases, betaine. Choline levels increase in acute demyelinating lesions because these membrane phospholipids are released during active myelin breakdown. Many brain tumors are also associated with high signals from Cho, presumably associated with their increased cellular density.

**BRAIN PATHOLOGY AND VARIATIONS OF Cr INTENSITY**

Total Cr concentration is relatively constant throughout the brain and
tends to be relatively resistant to change. Therefore, Cr is often used as an internal standard to which the resonance intensities of other metabolites are normalized. Care must be taken, however, not to use local Cr signals as an internal standard for some destructive pathological processes, such as malignant tumors, which can result in focal decreases of measured Cr.

NAA INTENSITY IS A MARKER OF NEURONAL INTEGRITY

The resonance from NAA is arguably the most important \(^1\)H-MRS signal in the measurement of brain pathological processes. Normal developmental changes in proton spectra have been described.\(^3,4\) N-acetylaspartate can be detected in the cerebral cortex and white matter of fetuses as early as 16 weeks' gestation. Levels of NAA-Cr increase rapidly in the first few years of life. However, adult values are not completely attained until 16 years of age.\(^4\) N-acetylaspartate is found primarily in mature neurons and neuronal processes, such as axons, and therefore has been used as a neuronal marker in mature human brains. Decreases in the relative NAA concentrations are observed in pathological processes well known to involve neuronal loss such as degenerative disorders, stroke, and glial tumors. Low NAA signals are also observed in other brain pathological processes in which the loss or damage to neurons and axons is less well known and less evident, even at postmortem examination. The ability to quantitatively evaluate neuronal loss or damage in vivo is one of the most important potential applications of MRS in cerebral disorders.

LACTATE IS A MARKER OF ANAEROBIC METABOLISM

Lactate is the end product of glycolysis and accumulates when oxidative metabolism is unable to meet energy requirements. Certain brain neoplasms can cause increased levels of lactate because they have elevated relative rates of glycolysis. Lactate also accumulates in the extracellular environment of necrotic tissue and fluid-filled cysts. A third circumstance in which lactate levels may be elevated is inflammatory reactions that are associated with cellular infiltrates. It is thought, for instance, that the prolonged elevation of lactate levels following ischemic infarction results from the metabolism of infiltrating macrophages.

THE APPLICATION OF \(^1\)H-MRS TO SPECIFIC NEUROLOGIC DISEASES

Brain Tumors

MRS as a Tool for Diagnostic Classification of Cerebral Space-Occupying Lesions. Magnetic resonance spectroscopy is a promising method for improving the specificity of noninvasive diagnosis of brain neoplasms.\(^3\) Although conventional MRI has greatly increased the sensitivity by which it is possible to detect tumors, gains in sensitivity have not been paralleled by gains in specificity. Figure 2 illustrates the problem with MRI scans from 2 elderly patients who rapidly developed symptoms suggestive of focal cerebral space-occupying lesions. The MRI images demonstrate the presence of lesions but cannot discriminate between the meningioma seen in Figure 2, A, and the glioblastoma seen in Figure 2, B. In contrast, by providing chemical profiles of the tumors, proton spectra from the MRS imaging add another dimension by which the space-occupying lesions can be differentiated.

Changes in the intensity of individual resonances are generally not sufficiently specific for diagnostic classification of lesions. Therefore, it is necessary to look at the pattern across multiple resonances. Spectra from the somewhat atypical meningioma seen in Figure 2, A, show features consistent with the absence of neurons (low NAA levels) and necrosis (high lactate and lipid levels). The spectra also reveal a resonance from alanine. Although alanine may be present in a number of tumor types, it is only clearly visible separate from lactate in vivo in meningiomas. The spectra from this meningioma can be compared with the distinctive metabolic profile of the glioblastoma. While the spectrum of the glioblastoma also consists of low NAA, high lactate,
It is known that the metabolism and high lipid levels, these resonances occur in different relative proportions to those of the meningioma. In studies with good MRS imaging data, pattern recognition also has been able to identify different grades of gliomas, radiation necroses, abscesses, and focal lesions in patients with acquired immunodeficiency syndrome (AIDS).

MRS as a Tool for Surgical Guidance and Monitoring Therapeutic Response. Proton MRS also has been used to predict the location of histopathological features important for brain tumor histological diagnosis. Therefore, it can be helpful for stereotaxically guided biopsies and selective tumor resections. Changes in the chemical-pathological profile of spectra also have been used to monitor the response to drug and radiation therapy, and even to predict the response to chemotherapy.

Epilepsy
Ictal Changes in Energy Metabolism. It is known that the metabolic demands of a seizure may exceed the capacity of the brain to provide the required energy oxidatively. The activation of anaerobic glycolysis that results leads to a local accumulation of lactate. Accordingly, in the rare instances when it has been possible to obtain spectra from active seizure foci, the expected increase in the lactate resonance intensity has been observed. In humans, these increases of lactate levels persist for several hours after the seizure.

Interictal Changes in MR Spectra Are Useful for Lateralization of Seizure Foci. Temporal lobe epilepsy (TLE), the most common form of partial epilepsy, is refractory to medical treatment in approximately 40% of patients. Many of these patients can be helped by surgical removal of the epileptic focus, provided that (1) all or most of the patient's seizures originate from 1 temporal lobe and (2) the remaining temporal lobe can compensate for the functional loss of the removed side. Lateralization of the seizures has generally been based on clinical and electroencephalographic (EEG) recordings, which usually include video telemetry. If surface EEG is unsuccessful, electrodes may need to be placed intracerebrally.

This traditional approach is being modified by modern neuroimaging techniques. Both MRI and positron emission tomography analyses have been used successfully for lateralization of seizure foci, but their results can vary widely between studies. Magnetic resonance spectroscopy detection of decreased NAA levels in one or both temporal lobes (Figure 3) compares favorably with these techniques and may be the most sensitive and accurate single method for lateralization of TLE. Interestingly, in those patients with TLE who have not had any seizures for at least 6 months following surgery on the anterior temporal lobe, the decrease in NAA levels within the adjacent mid and posterior temporal lobes normalizes. This must mean that the regional decreases in NAA levels detected interictally reflect neuronal dysfunction associated with the epileptic state, rather than irreversible neuronal loss associated with hippocampal sclerosis. The hypothesis that the regional decrease in NAA levels that occurs in the temporal lobe is not due to axonal degeneration following hippocampal damage is supported by observations that patients with infarctions within the hippocampus have normal levels of NAA in the posterior temporal lobe. The fact that the epileptic state itself is responsible for the decrease in NAA levels in epileptic temporal lobes may explain its high concordance with EEG lateralization of TLE and the fact that decreases of NAA levels can be present in the absence of any detectable abnormality on MRI.

Multiple Sclerosis
The pathology of multiple sclerosis (MS) is usually described as demyelination with relative preservation of the integrity of the axon shaft. The conduction block resulting from demyelination is traditionally believed to account for the neurologic impairment of MS. However, measurements of NAA levels with MRS have emphasized that in addition to demyelination, substantial axonal damage does occur in this...
logic impairment in MS. These observations, along with physiological evidence showing that demylinated axons regain function once they adapt their sodium channels and pathological data reemphasizing the prevalence of both axonal damage and wallerian degeneration in MS, have led researchers to focus increasingly on axonal damage as a cause of neurologic impairment in MS.

Acute MS Lesions. Magnetic resonance spectroscopic studies show that concentrations of NAA are substantially reduced within acute MS lesions. Furthermore, these decreases in NAA levels usually show partial recovery over time. Both the decline and the recovery of NAA levels have been found to correlate strongly with alterations in neurologic impairment observed in patients with MS. These results reinforce the hypothesis that axonal dysfunction is associated with neurologic dysfunction and its subsequent recovery in the acute phase of MS.

Although the focus above emphasized alterations of NAA levels, acute lesions also show changes in other metabolites. Large increases in the Cho resonance occur early and are, at least in part, associated with increased mobility and MR visibility of membrane phospholipids. Moderate increases in lactate levels are also observed and probably result from both the presence of inflammatory infiltrates themselves and their effects on local vasculature. During the hyperacute phase of MS plaques, there is also a transient and substantial decrease in Cr resonance intensity. Magnetic spectroscopic images show that the Cr signal returns to normal in subacute and chronic plaques. Short TE spectra show increases in myoinositol and lipids with greater sensitivity than long TE spectra. Preliminary data suggest that increases in lipids detected by MRS may occur before the development of lesions that can be observed using T2-weighted MRI.

Chronic MS Lesions. Incomplete recovery of axonal damage in MS eventually leads to the accumulation of irreversible disability. In patients with chronic MS lesions, NAA levels are not only decreased within the MS plaques, but also within the adjacent white matter that appears normal in T2-weighted MR images. The decline of NAA levels within this so-called normal-appearing white matter varies progressively with distance from the center of the lesion. Indeed, it is the reduction of NAA within the normal-appearing white matter that correlates best with the extent of disability of patients with chronic MS.

The ability of MRS to demonstrate metabolic changes that appear to be specific for axonal damage, demyelination, and inflammation may have important implications for measuring the outcome of new treatments for MS. Current treatments are directed primarily at reducing the initial stages of inflammation and do not completely arrest the disease. Future treatments may target the different components of the inflammatory process that result in axonal damage, and that thus far only MRS can measure specifically.

Neurologic Disorders Associated With Human Immunodeficiency Virus 1 (HIV-1)

Human immunodeficiency virus 1–infected patients are susceptible to a number of neurologic complications. Following infection, the virus may directly invade the brain and cause a diffuse encephalopathy, variably called HIV-encephalitis, AIDS encephalopathy, AIDS dementia complex, AIDS-related dementia, or HIV-1–associated cognitive/motor disorder (see Chang for reviews). 1H-magnetic resonance spectroscopy detects early decreases in levels of NAA and increases in Cho levels, even before abnormalities are detected by MRI and before clinical symptoms have manifested. Later on, cognitive dysfunction develops and MRI may show atrophy and nonspecific white matter changes associated with further reductions in NAA and increases in Cho levels.

In the later stages of AIDS, the most common diseases affecting the brain parenchyma are secondary to opportunistic infection or malignancy and are predominantly focal, such as progressive multifocal leukoencephalopathies, cerebral toxoplasmosis, and primary cerebral lymphomas. Magnetic resonance spectroscopy may be able to distinguish between these different space-occupying lesions based on their chemical profiles. 1H-magnetic resonance spectroscopy may also be used for monitoring the efficacy of antiretroviral therapy and may even be used to predict the responsiveness to drug therapy.
Cerebrovascular Injury

Although the brain can metabolize glucose anaerobically for brief periods in the absence of oxygen, this is done at the expense of the accumulation of lactate. This lactate, or the associated acidosis, may actually exacerbate the extent of neural damage. N-acetylaspartate resonances can be used to estimate the extent of the neuronal damage that occurs, both immediately and in the stages following an acute ischemic event. A consistent picture that emerges is that within the area of infarcted tissue there is an elevation of levels of lactate and diminished levels of NAA.

In the pediatric population, 1H-MRS has been used to study neonatal hypoxia during delivery, hypoxic encephalopathy following near drowning, and following various other acute insults to the central nervous system, including shaken baby syndrome. Low levels of NAA-Cr ratios and elevated lactate concentrations were consistently demonstrated in the areas of infarction and have been shown to predict adverse neurologic status in both the short and long term.

In the adult population, a similar pattern of low NAA levels and high lactate levels is seen acutely following infarction. Clinically less important and smaller changes in Cho and Cr levels may also occur. Levels of NAA and lactate continue to decline up to a week after the infarct, suggesting that the “window” for salvage of damaged neurons may be greater than expected. These biochemical markers may also provide a surrogate for monitoring therapeutic intervention in the acute stroke period. Low levels of NAA and high levels of lactate correlate with and predict impaired neurologic function.

The observation of lactate levels remaining elevated for many months following infarction is intriguing but of uncertain clinical significance as it may not reflect ongoing ischemia but rather anaerobic metabolism of inflammatory infiltrates. Preliminary data suggest that 1H-MRS may be used as a clinical tool for monitoring chronic ischemia as well.

Neurodegenerative Diseases

Amyotrophic Lateral Sclerosis.

Amyotrophic lateral sclerosis (ALS) is a neurologic disorder that affects both upper and lower motor neurons of the central nervous system. As expected, 1H-MRS imaging has demonstrated decreases of NAA levels within the cortex and the brainstem of patients with ALS. In the cortex, the decreases were maximal in the motor strip but were also present in the sensory and premotor areas, consistent with the origins of the corticospinal tract. Neuronal damage, as reflected by a decrease in NAA levels in the motor strip of these patients, was proportional to the severity of neurologic impairment.

One theory about the pathogenesis of ALS is that neuronal loss is induced by glutamate excitotoxicity. Riluzole, a drug that prolongs survival in ALS, is believed to inhibit glutamate release from presynaptic terminals. 1H-magnetic resonance spectroscopy reveals that following treatment with riluzole, the level of NAA increases within the motor cortex of patients with ALS, presumably reflecting the reversal of sublethal motor neuron injury (Figure 4). This again demonstrates the potential value of MRS as a tool for monitoring and quantifying the effectiveness of drug therapy.

Alzheimer Disease.

The differential diagnosis of Alzheimer disease (AD) from other forms of dementia is difficult and still relies on a constellation of clinical information. The role of computed tomographic and MRI scans has generally been restricted to ruling out the presence of space-occupying lesions and subcortical vascular disease. Many recent studies have been performed to establish whether there are metabolic markers that either alone, or in combination with the structural information from MRI, can be used to aid in the diagnosis of AD. Decreases of NAA levels have been observed in various regions of the cerebral cortex. The combination of hippocampal atrophy and decreases in NAA levels may help differentiate AD from normal aging but not from other forms of dementia. There have been studies that suggest that the multidimensional analysis of MRS data, particularly in combination with morphometric MRI data, may help distinguish AD from other dementias. It is likely,

![Figure 4. Magnetic resonance imaging (MRI) spectra can be used to monitor therapeutic interventions. The conventional MRI of a patient with amyotrophic lateral sclerosis is shown (left) with the precentral gyrus delineated. Averaged spectra from the voxels within the precentral gyrus before and after 3 weeks of treatment with riluzole are shown (right). The antisuicide therapy produces a significant increase in N-acetylaspartate (NAA) suggesting either recovery of a population of sublethally injured neurons or reversal of dendritic atrophy. Cho indicates choline-containing phospholipids; Cr, creatine.](https://www.jamaeuro.com/article.aspx?doi=10.1001/jama.1999.00680621039055)
however, that the most promising role of MRS lies in its potential to track the progression of this disease and to monitor the response to therapeutic intervention.

**Idiopathic Parkinson Disease vs Other Parkinsonian Syndromes.** The most consistent observation from MRS studies of idiopathic Parkinson disease (IPD) thus far is that IPD does not significantly alter the major cerebral metabolite resonances as measured by 1H-MRS. Technical limitations continue to restrict the detailed metabolic analysis of the substantia nigra and other areas within the brainstem. Consequently, efforts to determine whether proton spectra from patients with clinically diagnosed IPD differ from those of age-matched, healthy controls have been directed toward structures like the striatum to which the substantia nigra is known to send dense afferent projections. Such studies consistently demonstrate that patients with IPD have normal NAA-Cr and NAA-Cho ratios within subcortical structures like the striatum and the lentiform nucleus. However, preliminary results from a multicenter study indicate that the ratio of striatal NAA-Cho is significantly lower in a subset of patients with IPD compared to controls. This finding suggests that the substantia nigra is affected in these patients, although the precise mechanism is not yet clear.

**Huntington Disease.** Although the gene for Huntington disease (HD) has been located, neither the effect of the mutation nor the pathophysiology of the disease is well understood. Huntington disease may affect neurons throughout the brain but targets cells in the basal ganglia first.

Several groups have used MRS to explore the metabolic consequences of HD in humans and in animal models. In humans, the NAA-Cho ratio is reduced both in the basal ganglia as well as in the cortex of patients with symptomatic HD. Some studies have used MRS to support the hypothesis that mitochondrial oxidative dysfunction plays a role in the pathogenesis of HD. Elevated levels of lactate have been found in both the basal ganglia and cerebral cortex of patients with HD, at least in some studies. Other studies have demonstrated that the elevation of lactate levels can be reversed by treatment with coenzyme Q and/or nicotinamide. Glutamate excitotoxicity has also been implicated in the pathogenesis of HD. Evidence of excessive glutamate and glutamine in the basal ganglia of patients with HD has been found, but most of these signals come from the metabolic pool rather than the neurotransmitter pool, and the relationship to excitotoxicity is still unclear.

**Metabolic Disorders**

There are an extremely large number of inherited and acquired metabolic disorders that affect the brain, only some of which are currently diagnostically identifiable. With a few exceptions, such as hepatic encephalopathy, the sensitivity of MRS in vivo is too low to measure the specific metabolite, neurotransmitter, enzyme, or structural protein responsible for the disorder. Magnetic resonance spectroscopy can, however, detect the secondary chemical pathological changes, such as demyelination, neuronal loss, and gliosis, that result from many metabolic disorders. (For reviews of childhood diseases, see Frahm and Hanefeld and Grodd et al.) Although not specific, these changes may still contribute significantly to the differential diagnosis in a specific clinical context where it is necessary to distinguish between a few likely possibilities that may have different chemical profiles.

Rarely, however, the secondary changes may be pathologically specific for the metabolic disorders. Examples of such situations include high levels of NAA in Canavan disease, high phenylalanine levels in phenylketonuria, abnormal lipids in Niemann-Pick disease type C, low Cr levels in guanidinoacetate methyltransferase deficiency, high glycine levels in nonketotic hyperglycinemia, and high lactate levels in a variety of mitochondrial disorders, including Kearns-Sayre syndrome and pyruvate dehydrogenase deficiency. In some of these disorders, MRS has been used to monitor the efficacy of therapeutic intervention on the abnormal metabolite.

**CONCLUSIONS**

Magnetic resonance spectroscopy is technically difficult to perform and produces weak signals that provide low spatial resolution and low signal-to-noise ratios. However, its rewards are a chemical specificity that is simply unavailable from any water-based imaging technique. We believe that its most important contribution to clinical neurology is the quantification of neuronal loss and its ability to demonstrate reversible neuronal damage. These are not only nonquantifiable by conventional MRI but are largely indistinguishable. Progress continues to be made with respect to the hardware, soft-
ware, and pulse sequences for single voxel spectroscopy and spectroscopic imaging. Use of these techniques is becoming increasingly feasible in more hospital settings.

The future of noninvasive neuroradiological techniques holds greater reliance on multimodal imaging, which combines the structural specificity of conventional MRI with the greater pathological specificity of different contrast mechanisms (eg, diffusion anisotropy or magnetization transfer) and the chemical specificity of MRS, thereby yielding a multidimensional view of the clinical problem. Each of these different perspectives provides additional features that can be combined until the picture is clear enough to answer the clinical question.

Far from the medieval superstitions that surrounded the powers of the ancient lodestones, modern medicine is now harnessing the potential of magnetism to diagnose and to manage neurologic diseases and to uncover the very pathological basis underlying them.

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