

PROTON MR SPECTROSCOPY IN BRAIN METABOLIC DISORDERS

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Abstract. Metabolic disorders of the central nervous system (CNS) include pathologies with extremely different pathogenesis. The clinical diagnosis of these disorders is often very difficult and requires sophisticated laboratory investigations. Proton magnetic resonance (MR) spectroscopy (^1H -MRS) has been recently used in a number of clinical studies to supplement conventional MRI as it is able to provide in vivo biochemical assay of a given brain tissue. Brain data on several neurometabolic diseases suggest that ^1H -MRS can provide in vivo chemical-pathological characterization of the abnormality detected by MRI and can detect metabolic alterations in tissue appearing normal on conventional MRI. This may help for differential diagnosis and can be important in the evaluation of disease outcome. Indices provided by ^1H -MRS have been demonstrated to be relevant to patients' clinical status, to represent sensitive indicators of early neurological involvement and to be helpful in monitoring effects of therapeutic interventions. This suggests that, in the next future, a more extensive use of brain ^1H -MRS in the management of patients with metabolic disorders affecting CNS should be encouraged.

Keywords: magnetic resonance spectroscopy, metabolism, white matter

INTRODUCTION

The advent of magnetic resonance (MR) imaging (MRI) has changed the clinical approach to the evaluation of the metabolic disorders. The clinical importance of MRI in the management of patients with metabolic disorders of the central nervous system (CNS) lies in its great sensitivity for detecting brain lesions. However, unfortunately, the brain lesions detected on MRI are often not characteristic enough to allow the diagnosis of these complex disorders [1].

In recent years, *nonconventional* MR techniques have been used to complement conventional MRI and overcome some of its limitations. Proton MR spectroscopy (^1H -MRS) has been particularly useful in patients with metabolic disorders as it can simultaneously provide chemical-pathological correlates of changes occurring within and outside visible MRI lesions. Thus, an expanding number of research groups have been using single voxel ^1H -MRS and multivoxel MR spectroscopic imaging (^1H -MRSI) in vivo to study patients with metabolic disorders [2-4]. These ^1H -MRS techniques have demonstrated to increase diagnostic accuracy and the understanding of the evolution of pathology in many of these disorders. It must also be stressed, however, that ^1H -MRS is complementary to MRI, except in a few cases where a disease-specific pattern could be detected.

We will give an overview on how ^1H -MRS can be used as a complementary method to conventional MRI to detect metabolic changes in the most frequently studied metabolic disorders.

DIAGNOSTIC-SPECIFIC ^1H -MRS CHANGES

As stated before, the ^1H -MRS changes detected in metabolic disorders are, in most cases, not disease-specific. However, in some conditions ^1H -MRS can provide typical brain metabolic patterns able to address the diagnosis.

One example of a disease in which MRS provides a diagnostic pattern is a spongiform leukoencephalopathy known as Canavan's disease. In this disorder, the deficiency of the enzyme aspartoacylase (which breaks down NAA) is responsible for abnormally high levels of NAA in the brain, which can be considered pathognomonic [8; 9]. It must be stressed, however, that high NAA level can be also found in Salla disease and severe infantile sialic acid storage diseases [10; 11], but in these conditions the high NAA signal reflects an accumulation of N-acetyl-neuraminic acid that offsets the possible loss of NAA. Moreover, small increases in NAA can be found in patients with Pelizaeus-Merzbacher disease probably reflecting the elevated density of axons in white matter lacking the oligodendrocytic tissue and normal myelin sheaths between axons [12].

In vanishing white matter disease (VWM, also called childhood ataxia with diffuse CNS hypomyelination) and megalencephalic cystic leukoencephalopathy (MCL) [13-18] conventional MRI findings of extensive white matter abnormalities with sparing of central brain structures are seen together with metabolic changes detected with ^1H -MRS. These changes include the almost complete disappearance of all normally detected

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metabolites in the white matter, presence of small increases in Lac and sparing of gray matter that is structurally and metabolically normal. In MCL, although $^1\text{H-MRS}$ abnormalities tend to be more pronounced with increasing age, these are generally mild and the frontal white matter is significantly less involved than other white matter regions. In patients with VWM disease, increases in glucose resonance intensities (present at 3.4 and 3.8 ppm) may also be present. This $^1\text{H-MRS}$ metabolic profile is probably due to little brain white matter tissue left and the great increase in extracellular spaces.

Other rare metabolic conditions also may provide diagnostic-specific $^1\text{H-MRS}$ findings. In phenylketonuria, patients show a specific peak due to the elevated phenylalanine at 7.37 ppm and, despite the diagnosis is easily reached testing the enzyme involved in the disease, the size of this peak can be used in patients with this metabolic disorder to follow the influx of phenylalanine from blood into brain tissue as well as to monitor the response of diet therapy [19-21]. In the leukoencephalopathy associated with the disturbance of the metabolism of the polyols [22], the diffuse decrease of all normally detected metabolites is associated with the increases of arabitol and sorbitol in both white and grey matter regions. In maple syrup disease, a relatively specific broad peak is detectable at 0.9 ppm. This region of the spectrum is usually attributed to lipids, but in maple syrup disease is believed to represent resonances of methyl protons from branched-chain aminoacids and branched-chain alpha-keto acids that accumulate as a result of defective oxydative decarboxylation of leucine, isoleucine and valine [23]. Also $^1\text{H-MRS}$ studies on patients with Niemann-Pick type C disease have shown increased resonance intensity of the lipid region of the spectrum, probably due, in this case, to a defective metabolism of cholesterol with ceramide accumulation [24; 25]. In both maple syrup and Niemann-Pick type C diseases, the abnormal broad peak detectable at 0.9 ppm seem to decrease with appropriate therapy [23; 24]. In non-ketotic hyperglycinemia, the elevated glycine signal at 3.55 ppm detected by $^1\text{H-MRS}$ is particularly meaningful when depicted with long echo time sequences [26; 27]. In this disorder, defective glycine cleavage causes elevated concentrations of glycine in plasma, urine, and cerebrospinal fluid. In earlier studies [28; 29], the reduction of glycine in brain tissue corresponded more reliably with clinical findings than the stable values in plasma and cerebrospinal fluid, indicating that $^1\text{H-MRS}$ can be a valuable tool in the diagnosis and monitoring of treatment effects in patients with this rare disorder. In succinate-dehydrogenase deficiency, a rare cause of mitochondrial encephalomyopathy, the presence of an abnormal peak at 2.4 ppm (originating from the two equivalent methylene groups of succinate) in the cerebral and cerebellar white matter can provide a metabolic pattern distinctive of the disease [30]

Finally, specific metabolic syndromes have been recently revealed by using proton MRS. This is the case of the creatine deficiency syndromes, which include

defects in the guanidinoacetate methyltransferase and in the arginine-glycine amidinotransferase [31; 32], and the X-linked creatine deficiency syndrome [33]. In the first two forms of the diseases, the Cr resonance intensity is undetectable in the brain on $^1\text{H-MRS}$, but cerebral levels of Cr do increase after creatine supplementation. In the X-linked form of creatine deficiency, as the metabolic defect is due to the transport of creatine into the central nervous system, patients are unresponsive to treatment and the Cr resonance intensity levels are unchanged after creatine supplementation. Another condition with very specific $^1\text{H-MRS}$ spectrum is the unique case of a child with minor developmental delay and absence of cerebral NAA, in whom the most prominent peak of $^1\text{H-MRS}$ at 2.02 ppm was undetectable [34]. Both creatine deficiency syndromes and the absence of NAA are characterized by mild or absent abnormalities on conventional MRI suggesting the unique potential of $^1\text{H-MRS}$ in revealing metabolic abnormalities in MRI normal-appearing tissue.

$^1\text{H-MRS}$ IN THE DIFFERENTIAL DIAGNOSIS OF MITOCHONDRIAL DISORDERS

In the clinical suspect of a mitochondrial disorder, $^1\text{H-MRS}$ can offer information useful for the differential diagnosis beyond what is currently available in routine clinical use.

For example, the intra-parenchymal levels of Lac are usually elevated in mitochondrial disorders [3; 35], although it must be also stressed that Lac levels are not unequivocally elevated in all patients and/or in all the brain structures. In general, Lac levels are transiently increased in a number of acute pathological conditions associated with inflammatory cells [2; 36; 37], but extensive pathological increases in Lac both within and outside of MRI lesions may be indicative of widespread energy failure associated with mitochondrial dysfunction [38; 39]. In addition, as $^1\text{H-MRS}$ can provide advantages in the interpretation of the pathological processes underlying the brain tissue, this can be used to differentiate brain lesions appearing similar on MRI. That is, much larger increased levels of brain parenchymal Lac can be found in hypoxic-ischemic white matter lesions with a complex pathogenesis such as of the mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS) than in acute and chronic cerebrovascular disorders [40].

In other very rare metabolic disorders such as the ethylmalonic encephalopathy [41] and a new type of leukoencephalopathy with slowly progressive pyramidal, cerebellar, and often dorsal column dysfunction [42] the findings of diffuse brain mitochondrial impairment have strongly contributed to the interpretation of the complex pathogenetic mechanisms of these disorders. In both cases, the diffuse $^1\text{H-MRS}$ increase in brain Lac detected in a multi-voxel $^1\text{H-MRSI}$ study was underlying a primary mitochondrial disorder, as demonstrated by biochemical and genetic studies [43; 44]. Furthermore, in a very rare metabolic disorders such as the cerebrotendinous xanthomatosis, the diffuse $^1\text{H-MRS}$ increase in brain Lac detected in a single-

voxel ^1H -MRS study [45] add to morphological and biochemical evidence of mitochondrial dysfunction, probably secondary to the toxic effect of high cholestanol and/or bile alcohol levels [46; 47].

DEMYELINATING AND DISMYELINATING DISEASES

Myelinogenesis is a complex process that can be altered by various hereditary metabolic defects resulting in disorders that are generically grouped under the term of *leukodystrophies*. This congenital failure in myelinogenesis is comprehensive of several mechanisms of myelin disruption such as hypomyelination, demyelination, dysmyelination, etc., and is due to very different genetic and biochemical abnormalities, most of which are still undefined [48]. In these conditions, the ^1H -MRS pattern is often not very specific. However, it might show temporal changes indicative of the metabolic alterations occurring within and outside the abnormalities visible on MRI.

Changes in several metabolites can be seen within demyelinating lesions since the very early phase of the pathological process [6]. Changes in the resonance intensity of Cho result mainly from increases in the steady state levels of phosphocholine and glycerol-phosphocholine, both membrane phospholipids released during active myelin breakdown. Increases in Lac are likely to reflect the metabolism of inflammatory cells. In acute demyelination, decreases in Cr can also be seen [6]. Short echo time spectra give evidence for transient increases in mI [49] and lipids [50], also released during myelin breakdown. After the acute phase, metabolic modifications in the demyelinating lesion show a variable time course [6]. Usually, resonance intensities of Cr and lipids return to normal within a few days. At this stage, small increase in Cr, due to changes in cellularity, can be found inside the demyelinating lesion [51]. Resonance intensities of Lac show a progressive reduction over a period of weeks, whereas Cho and mI return to normal in months. The signal intensity of NAA decreases and, later, may remain decreased or may show a partial recovery [52]. Recovery of NAA may be related to resolution of edema, increases in the diameter of previously shrunken axons that are secondary to remyelination and clearance of inflammatory factors, and reversible metabolic changes in neurons [52].

In progressive disorders, such as many leukodystrophies, the loss of myelin can be very slow and released membrane phospholipids might not accumulate. Thus, ^1H -MRS changes such as those detected in acute demyelination are not seen. In some cases, however, (i.e. adrenoleukodystrophy, Krabbe disease) the high membrane turnover may cause long-term increases in Cho [53]. In contrast, decrease in Cho or increase in Cr can be detected in hypomyelination [54]. In dysmyelinating diseases such as the Pelizaeus-Merzbacher disease both increases and decreases in Cho have been described [12; 55]

A number of brain ^1H -MRS studies of patients with white matter disorders have also shown changes in

the relative resonance intensity of mI. The function of mI in the human brain is not clear, but increases of this metabolite seem to be related to the presence of white matter gliosis and appear consistently in disorders associated with impaired myelination such as adrenoleukodystrophy, metachromatic leukodystrophies, phenylketonuria and Zellweger syndrome [53; 56-58].

Finally, a constant finding of all metabolic disorders affecting the brain white matter is the large decrease in cerebral NAA [3]. This, however, might be mild or absent in hypomyelination [54].

^1H -MRS TO MONITOR DISEASE OUTCOME AND RESPONSE TO THERAPY

As NAA is found almost exclusively in neurons and their processes in mature brains decreases in this metabolite are interpreted as an index of axonal damage, dysfunction or loss [59; 60]. Neuro-axonal damage represents the most important substrate of functional impairment in neurological disorders. Thus, it is not surprising that a number of ^1H -MRS studies have demonstrated highly significant correlations between decreasing NAA and increasing clinical disability in patients with many of these disorders [3; 59]. NAA may offer a highly sensitive, clinically-relevant surrogate of pathological change useful for monitoring disease progression [61].

Unfortunately, therapy is not an easy task in the metabolic disorders involving the CNS. Despite this, ^1H -MRS has been proposed in trials of patients with adrenoleukodystrophy [62] and changes over time in levels of NAA have been used as endpoint after aspartoacylase gene transfer [63]. These recent data add to those previously mentioned such as such creatine deficiency [31], mitochondrial disorders [39] and phenylketonuria [64] and other rare conditions, where ^1H -MRS has been used to monitor response to therapy. In addition, guidelines for a multi-centre use of ^1H -MRS in clinical trials of multiple sclerosis have been recently provided [65]. All together, these data suggest that ^1H -MRS can be easily performed in routine clinical settings to monitor treatment, when this is possible.

CONCLUSIONS

^1H -MRS of the brain provides chemical-pathological information that has the potential to improve both diagnostic classification and management of patients with metabolic disorders affecting the CNS. Metabolic indices provided by ^1H -MRS could be sensitive indicators of early neurological involvement and are relevant to patients' clinical status. A more extensive use of ^1H -MRS (possibly with short echo time sequences) in combination with other nonconventional MR techniques might yield a more complete description of the dynamics responsible for pathological changes in this heterogeneous group of disorders and may allow a more accurate evaluation of disease progression and response to therapeutical intervention.

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