

Magnetic Resonance Spectroscopy in Congenital Metabolic Disorders

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Introduction

Congenital metabolic disorders refer to inherited defects producing metabolic abnormalities in the human body. Disorders that disrupt the central nervous system (CNS) are of great importance. These disorders produce a paradoxical situation for neuroradiologists and imaging scientists investigating them. One would hypothesize that an error in metabolism would produce either an excess or deficit of a given metabolite. Magnetic resonance spectroscopy (MRS) should be ideally suited for recognizing such errors of metabolism. In a few conditions, proton MRS offers a narrow diagnostic differential. However, for the majority of congenital metabolic disorders, non-distinct imaging and proton spectroscopic presentations, such as volume loss, abnormal T2 signal and reduced N-acetyl aspartate (NAA), are found in the brains of children and adults. The ability to observe metabolic alterations and to recognize them as distinct disorders remains difficult. In principal, two factors limit the application: 1) diminished sensitivity in metabolite detection due to inherently low proton signal and/or concentrations, and 2) poor specificity with common features for distinct metabolic disorders. For pediatrics, additional disadvantages include developmental maturation coupled with progression of disease with multiple primary and secondary features. Regardless a primary or secondary metabolic defect, metabolic disorders should impact cellular function, disrupt at least one of the commonly observed metabolites NAA, creatine and phosphocreatine (Cr & PCr), cholines (Cho) or demonstrate a pathological metabolite, such as lactate or alanine. The practical usefulness of MRS exists in offering information on staging pathologic processes such as ischemia, altered myelination, gliosis, and neurodegeneration.

This presentation will review the spectroscopic features associated with mitochondrial disorders, peroxisomal disorders, amino acid disorders, lysosomal disorders, primary white matter disorders and a few novel disorders. Spectroscopic appearances can differ due to technical factors and change with the age of onset and stage in disease progression. Recent texts [1,2] offer reviews of select metabolic entities from an imaging perspective. In select conditions, MRS will provide the only diagnostic feature found with any imaging examination (i.e. creatine deficiency syndromes). In many situations, MRS will provide only confirmatory diagnostic information to the imaging examination. However, recent studies using MRS indicate potentially a more beneficial role in therapeutic monitoring.

Mitochondrial Disorders

Mitochondrial disorders encompass a heterogeneous, polysymptomatic and often, multisystemic group of disorders, caused by defects of intracellular energy metabolism and result in diminished adenosine triphosphate (ATP) production. Proton MRS has been employed to detect lactic acidosis for the diagnosis of mitochondrial disorders. While in some mitochondrial pathologies detection of elevated brain lactate is anticipated, elevated lactate alone does not necessarily signify a mitochondrial disorder. Conversely, the absence of lactate does not exclude a mitochondrial defect.

Mitochondrial disorders often manifest in an intermittent fashion and causing temporal fluctuation of lactate levels, which can be observed during periods of decompensation and fall below the level of detection during remission [3].

Since the 1990's, children clinically diagnosed with Leigh syndrome (however, genetically diverse, i.e. pyruvate dehydrogenase deficiency, cytochrome oxidase deficiency, Complex I deficiency) have been evaluated with proton MRS [4-10]. Spectra obtained from the basal ganglia, occipital cortex, and brainstem reveal lactate elevations coinciding with regions demonstrating T2 signal abnormalities. Proton MRS also demonstrated a decrease in the N-acetylaspartate/creatine and an increase in the choline/creatine, representing neuronal loss and breakdown of membrane phospholipids. There is some evidence that a reduction of lactate levels may correlate with response to therapy, as seen in treatment trials with dichloroacetate (DCA) and Co-enzyme Q10 [11-13].

Dinopoulos reviewed clinical MRI/MRS examinations in 49 children (ages neonate to 15 years) with biochemical evidence of a respiratory chain defect [14]. Using the Modified Adult Criteria for group classification (definite, probable and possible), 81% of patients classified as "definite" demonstrated the presence of lactate, with 31% for the "probable" group and 0% for the "possible" group of patients. All patients with subcortical white matter involvement in the "definite" and "probable" groups had lactate elevation observed on proton MRS in regions with abnormal T2 signal.

Imaging and spectroscopy of patients with MELAS can demonstrate variable results as stroke-like lesions emerge and evolve. With proton MRS, lactate elevation in the acute and sub-acute stages is often observed. Subsequently, declines in NAA and Cr, consistent with neuroaxonal injury, which may or may not be reversible, are appreciated. Proton MRS indicates energy failure with increased lactate and decreased creatine. [15-28]. Kaufmann investigated 91 individuals meeting partial or full criteria for MELAS who underwent standardized neurologic examination, neuropsychological testing, MRS, and leukocyte DNA analysis. There was a significant correlation between degree of neuropsychological and neurologic impairment and cerebral lactic acidosis as estimated from ventricular MRS lactate levels [29].

Peroxisomal Disorders

Peroxisomes are organelles within a cell that contain enzymes responsible for critical cellular processes, including biosynthesis of membrane phospholipids (plasmalogens), cholesterol, and bile acids, conversion of amino acids into glucose, reduction of hydrogen peroxide, oxidation of fatty acids, and prevention of excess oxalate synthesis. Peroxisomal disorders are subdivided into two major categories: 1) biogenesis disorders (PBDs) arising from a failure to form viable peroxisomes, resulting in multiple metabolic abnormalities, and 2) disorders resulting from the deficiency of a single peroxisomal enzyme.

Four different disorders comprise the genetically heterogeneous PBD group: Zellweger syndrome (ZS), infantile Refsum's disease (IRD), neonatal adrenoleukodystrophy (NALD) and rhizomelic chondrodysplasia punctata (RCDP). Zellweger syndrome presents with cortical dysplasia and neuronal heterotopia on imaging. Proton MRS illustrates the neuropathologic aspects of Zellweger syndrome, which include neuronal degeneration, abnormal myelination, and compromised liver

function. Bruhn et al. reported MRS of infants (N=4) with impaired peroxisomal function classified as variants of Zellweger syndrome revealed a marked decrease of N-acetylaspartate in white and gray matter, thalamus, and cerebellum with two patients also demonstrating an increase of cerebral glutamine and a decrease of the cytosolic polyol myo-inositol (ml) in gray matter and striatum reflecting impaired hepatic function [30]. Two subjects in the Bruhn study exhibited a notable elevation of mobile lipids and/or cholesterol in white matter. For rhizomelic chondrodysplasia punctata, two studies report elevations of mobile lipids, myo-inositol-glycine, acetate and reduced choline levels as consistent with a deficiency in plasmalogen biosynthesis [31,32]. In contrast to ZS, IRD and NALD, rhizomelic chondrodysplasia punctata does not feature liver disease which is significant when accounting for the ml differences.

X-linked adrenoleukodystrophy patients evaluated with proton MRS demonstrate abnormal spectra within regions of abnormal signal as well as normal appearing white matter (NAWM). The spectral profile for NAWM of neurologically asymptomatic patients is characterized by slightly elevated concentrations of composite choline compounds at 3.2 ppm, with an increase of both Cho and ml reflecting the onset of demyelination. Markedly elevated concentrations of Cho, ml, and glutamine in affected white matter suggest active demyelination and glial proliferation. A simultaneous reduction of the concentrations of NAA and glutamate is consistent with neuronal loss and injury. Elevated lactate is consistent with inflammation and/or macrophage infiltration. The more severe metabolic disturbances in ALD correspond to progressive demyelination, neuroaxonal loss and gliosis leading to clinical deterioration and eventually death. The detection of MRS abnormalities before the onset of neurological symptoms may help in the selection of patients for bone marrow transplantation (BMT) and stem cell transplant. Stabilization and partial reversal of metabolic abnormalities is demonstrated in some patients after therapies. The spectral profiles can be used to monitor disease evolution and the effects of therapies [33-47].

Disorders of Amino and Organic Acid Metabolism

A large number of imaging and spectroscopy studies have investigated patients with phenylketonuria (PKU) [48-77]. White matter alterations revealed by imaging in patients with phenylketonuria (PKU) correlated to blood phenylalanine (Phe) concentrations as well as to brain Phe concentrations measured by proton MRS. The clinical significance of the white matter changes is uncertain. MRI alone has limited impact on therapeutic recommendations for adolescents and adults with PKU. However, kinetic investigations of patients performed using proton MRS revealed individual differences in brain Phe concentrations despite similar blood Phe levels. Interindividual variations of blood-brain barrier Phe transport constants and Phe consumption rate are responsible for differences and thus, seem to be causative factors for the individual outcome in PKU [48-77].

In patients with non-ketotic hyperglycinemia, elevated cerebral glycine can be measured with proton MRS [78-83]. Using long echo times, such as 288 ms, MRS reveals predominately glycine at 3.5 ppm. Employing short echo times, the resonance at 3.5 is a composite of myo-inositol and glycine. Ratios comparing glycine with creatine correlate with patient course.

Neurological proton MRS appears to be useful for examining patients suffering from maple syrup urine disease in different metabolic states [84-87]. The accumulation of abnormal branched-chain amino acids (BCAA) and branched-chain alpha-keto acids (BCKA) peak at 0.9 ppm accompanied by elevated lactate are manifested in patients. The presence of cytotoxic or intramyelinic edema as evidenced by restricted water diffusion on DWI, with the presence of lactate on spectroscopy, could imply cell death. However, in the context of metabolic decompensation in MSUD, it appears that changes in cell osmolarity and metabolism can reverse completely after metabolic correction [84].

A triad of hyperammonemia, encephalopathy, and respiratory alkalosis characterizes urea cycle disorders. Five disorders involving different defects in the biosynthesis of the enzymes of the urea cycle have been described: ornithine transcarbamylase deficiency, carbamyl phosphate synthetase deficiency, argininosuccinate synthetase deficiency or citrullinemia, argininosuccinate lyase deficiency, and arginase deficiency. The key feature for proton MRS of the brain is the elevation of glutamine. In the clinical setting, distinguishing urea cycle disorders from hypoxic ischemic encephalopathy in the neonate can employ a combination of laboratory abnormalities (elevated ammonia) and pattern of injury as described by Barkovich [1] with urea cycle disorders having predominant injury within the putamen and globus pallidus, bilaterally. The regions sampled with MRS should include the basal ganglia, however, other regions should also reveal the key abnormalities. The hyperammonemia found in the urea cycle defects converts glutamate to glutamine in the brain. As cerebral edema develops, declines in myo-inositol may be appreciated along with elevated lactate levels.

The first application of proton MRS studies in patients with methylmalonic aciduria and propionic aciduria utilized *in vitro* methods for discriminating the respective acids and therapeutic monitoring of metabolic perturbations in urine [88-91]. These disorders are defects in the conversion of isoleucine, valine, methionine and threonine to propionic acid, methylmalonic acid and succinic acid. *In vivo* brain proton MRS of the acidurias revealed reduced ml and NAA with elevated glutamate, glutamine and possibly lactate [92-97]. These findings correspond to hyperammonemia, ketoacidosis and mitochondrial dysfunction.

Proton MRS in the striatum and white matter revealed decreased NAA/Cr, increased Cho/Cr, and increased ml/Cr for glutaric aciduria I. These changes represent neuroaxonal damage, demyelination, and astrocytosis in these areas [98]. No dedicated studies of glutaric aciduria II have been performed using MRS [99]. Hanefeld demonstrated in a patient with L-hydroxyglutaric aciduria a decrease in NAA and Cho with an elevation of ml in white matter [100]. Two case reports indicated recognition of an elevated resonance at 2.5 ppm, which could be attributed to glutamate, glutamine or hydroxyglutaric acid [101].

Lysosomal Disorders

The lysosomes are intracellular organelles responsible for degrading lipids, proteins and complex carbohydrates. A genetic mutation resulting in the absence or partial deficiency of an enzyme or protein leads to the accumulation of undigested compounds which can disrupt the normal functioning of cells. When cellular division is

impaired from the accumulation of undegraded material, secondary changes to the spectral markers, NAA, Cho and ml are expected. Proton MRS of lysosomal disorders, such as metachromatic leukodystrophy, globoid cell leukodystrophy (Krabbe's disease), neuronal ceroid lipofuscinosis and Sandhoff's disease, have demonstrated reduced NAA expected with neuroaxonal loss but have also revealed disturbances in glial cell metabolism associated with demyelination [102-110]. In Salla disease, a free sialic acid storage disorder, an accumulation of N-acetylneuraminic acid in the lysosomes of brain parenchyma produces an elevation of the N-acetyl methyl group resonance at 2.0 ppm, usually attributed to N-acetyl aspartate [111]. Depending upon its composition, the often complex, undegraded material may contribute to the lipid (0.8-1.3 ppm) and macromolecular resonances (0.8-2.6 ppm) observed on proton MRS, as reported in Sjogren-Larsson's syndrome [112-114] and neuronal ceroid lipofuscinosis (infantile CLN1) [109,115]. However, it is important not to confuse pathologic lipid resonances with susceptibility and chemical shift artifact.

MRS may be useful in monitoring therapeutic interventions of these disorders. DeStefano used proton magnetic resonance spectroscopic imaging (MRSI) to investigate patients with cerebrotendinous xanthomatosis (CTX), a defect in the metabolic pathway of cholesterol [116]. The findings suggested widespread axonal damage revealed by a decrease in NAA and diffuse brain mitochondrial dysfunction with an increase in lactate. A correlation between levels of the putative axonal marker NAA and patients' disability scores suggests that proton MRS can provide a useful measure of disease outcome in CTX. In Niemann-Pick type C (NPC), a storage disorder with defective cholesterol esterification, reduction of an abnormal lipid resonance on proton MRS correlated with the short-term improvement in an infant patient treated with cholesterol-lowering agents [117]. Using proton MRSI in NPC, Tedeschi reports changes in regional metabolite ratios (NAA/Cr and Cho/Cr) correlating with clinical stage scoring [118]. Takahashi found for the mucopolysaccharidoses, proton MRS reveals a broad resonance at 3.7 ppm attributed to mucopolysaccharide molecules. After bone marrow transplant, the resonance at 3.7 ppm decreases in the brain of some patients, which may aid in determining the efficacy of the therapy [119].

White Matter Disorders

White matter disorders can present as hypomyelinating, dysmyelinating and demyelinating superimposed on a background of normal maturation of myelination. Here, we discuss a few prominent disorders of white matter encountered in children.

Brockmann et al. [120] used localized proton MRS to assess metabolic abnormalities in grey and white matter, basal ganglia, and cerebellum of four patients with infantile Alexander's disease (AD) identified with heterozygous *de novo* mutations in the gene encoding glial fibrillary acidic protein (GFAP). Elevated concentrations of ml combined with normal or increased choline compounds in grey and white matter, basal ganglia, and cerebellum implicate astrocytosis and demyelination. Neuroaxonal degeneration, as reflected by a reduction of NAA, was most pronounced in cerebral and cerebellar white matter. The accumulation of lactate in affected white matter is consistent with infiltrating macrophages. Metabolic alterations revealed by in vivo proton MRS are in excellent agreement with known neuropathological features of AD [121,122].

In Canavan's disease, the lack of a functional enzyme, aspartoacylase (ASPA), leads to an increase in the central nervous system of the substrate molecule, N-acetyl-aspartate, which impairs normal myelination and results in spongiform degeneration of the brain. Detection of this disorder within the brain, CSF and urine is available with *in vivo* and *in vitro* methods. Urinary NAA levels are also increased because of the deficiency of aspartoacylase (N-acyl-L-aspartate aminohydrolase). MRS employed with mouse models of Canavan's disease provide a means evaluating gene therapy [123-137].

A new leukodystrophy with a distinct magnetic resonance imaging pattern of inhomogeneous cerebral white matter abnormalities and selective involvement of brainstem and spinal tracts has been described [138]. Leukoencephalopathy with brain stem and spinal cord involvement and high lactate (LBSL) demonstrates significant elevation of lactic acid, cholines and ml with reduction of NAA within the white matter suggesting axonal damage and gliosis.

Childhood ataxia with diffuse CNS hypomyelination (CACH), also known as vanishing white matter disease, is currently regarded as a primary axonopathy rather than a primary demyelinating process with marked decrease in NAA, Cr, Cho and lipids in white matter [139-141]. In the advanced stage, a virtual absence of all parenchymal metabolites with the presence of CSF metabolites, lactate and glucose has been reported. In contrast, proton MRS in hypomyelination with atrophy of the basal ganglia and cerebellum (H-ABC) reveals normal levels of NAA and Cho with elevated Cr and ml in white matter [142].

Plecko et al. [143] found heterogeneous cerebral metabolite patterns in patients with Pelizaeus Merzbacher disease (PMD) and Pelizaeus Merzbacher-like disease (PMLD) indicating a mixture of unspecific changes due to primary hypomyelination and secondary gliosis and demyelination. However, neither MRI nor MRS provided unique patterns to allow differentiation between PMD and PMLD patients.

A deficiency of ribose 5-phosphate isomerase was identified in a patient who presented with leukoencephalopathy and peripheral neuropathy after proton MRS of the brain and urine revealed a highly elevated level of the polyols - ribitol and D-arabitol [144,145].

Proton MRS studies in patients with vacuolating megaencephalic leukodystrophy with subcortical cysts (MLC) demonstrate variability with the vacuolizing myelinopathy and diffuse swelling of cerebral white matter [146,147]. The spectra pattern demonstrates reduced parenchymal signal with vacuolization. The residual pattern can appear as reduced NAA, elevated Cho and ml.

Miscellaneous Disorders

Treated Wilson's disease, an inborn error of copper metabolism, reveals no significant differences from healthy controls when studied by proton MRS. However, in patients with acute hepatic disease and subclinical hepatic encephalopathy, decreases in Cho/Cr and ml/Cr can be observed [148-150]. Changes in glutamine would also be expected with impaired hepatic function.

Brain edema may occur in infants with galactosemia and has been associated with accumulation of galactitol [151,152]. In a newborn infant with galactose-1-phosphate uridyltransferase deficiency and encephalopathy, MRI revealed cytotoxic edema in

white matter. Using *in vivo* proton MRS, Berry detected approximately 8 mmol galactitol per kilogram of brain tissue, an amount potentially relevant to the pathogenesis of brain edema [152]. Wang used proton MRS to study 12 patients (four newly diagnosed neonates and eight patients on galactose-restricted diets, age range 1.7-47 years) and control subjects to measure brain galactitol levels *in vivo* and correlate them with urinary galactitol excretion [151]. The results demonstrated that a markedly elevated brain galactitol level is present only in newborn infants with galactosemia who exhibit massive urinary galactitol excretion.

An unusual source of mental retardation has been revealed with proton MRS. Inborn errors of creatine metabolism, specifically defects in creatine synthesis and transport, have recently been reported [153-161]. Several patients with markedly diminished or absent creatine signal have been found with proton MRS. Genetic analysis has revealed novel mutations in the creatine transporter located at Xq28 [154,156,162]. Other autosomal recessive disorders of creatine metabolism involve defects in the hepatic enzymes guanidinoacetate methyltransferase (GAMT) and arginine glycine amidinotransferase (AGAT) [157,159-161]. These disorders manifest with developmental delay, seizures and absence or retardation of language skills, and MR imaging can remain unremarkable. If proton MRS reveals absent brain creatine, serum and urine creatine assessments may give preliminary indication whether there is a synthesis defect (diminished Cr) or a transport defect (elevated Cr). In patients with synthesis defects, proton MRS can monitor increasing brain creatine concentrations afforded with oral supplementation. While there is some motor improvement, neurological damage persists with supplementation in persons with creatine synthesis defects. At this time, there are no treatment options available for persons with creatine transporter defects. A recent study investigated the prevalence of creatine transporter deficiency by DNA sequence analysis in a panel of 290 patients with nonsyndromic X-linked mental retardation (XLMR) archived by the European XLMR Consortium [163]. Six pathogenic mutations, of which five were novel, were identified in a total of 288 patients with XLMR, showing a prevalence of at least 2.1% (6/288). They report the frequency of SLC6A8 mutations in the XLMR population is close to that of CGG expansions in FMR1, the gene responsible for fragile-X syndrome.

Conclusions

The implementation of magnetic resonance spectroscopy in the study of congenital metabolic disorders offers additional insight by providing a method to analyze cellular processes altered by the presence of metabolic abnormalities. While many conditions have a similar presentation, MRS offers valuable information for the individual patient in diagnosis and therapy when fully integrated into the clinical environment. Neurological proton MRS provides markers of axonal swelling, axonal stretching, axonal and neuronal dysfunction and loss with NAA; gliosis, astrogliosis, and osmolytic function with mI; myelin integrity, membrane metabolism and injury with Cho and lipids; and cellular energetics with creatine and lactate. The continued development and application of this technique offers enormous potential in the study of inborn errors of metabolism.

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