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Leukoencephalopathies and metabolic diseases

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Abstract Leukoencephalopathies and metabolic diseases comprise a great number of heterogeneous disorders. Diagnosis of these disorders may be challenging at times, requiring sophisticated laboratory investigations. Magnetic resonance imaging (MRI) is useful in supporting diagnosis even though it bears problems of specificity. Quantitative MRI techniques, providing information on cerebral metabolites and tissue microstructure within and outside visible lesions, have proven to be important for understanding the pathogenic mechanisms leading to tissue damage and monitoring disease evolution and response to treatment. This has prompted a more extensive use of these techniques in the clinical setting as a complement to the traditional MRI.

Keywords Magnetic resonance spectroscopy · Diffusion tensor imaging · Magnetization transfer imaging · White matter

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Introduction

Magnetic resonance (MR) Imaging (MRI) has played an important role in the assessment of leukoencephalopathies and other brain metabolic disorders. However, findings obtained with conventional MRI may often be lacking in specificity. For example, signal intensity changes on brain MRI scans might not be able to differentiate among the diverse pathological processes occurring in these disorders in the cerebral white matter (WM), namely hypomyelination, demyelination, myelin vacuolation, cystic degeneration, gliosis and oedema.

Over the last decade, the advent of non-conventional or quantitative MRI techniques such as proton MR spectroscopy (^{1}H-MRS), diffusion tensor imaging (DTI) and magnetization transfer imaging (MTI) has overcome some of the drawbacks of conventional MRI.

The growing number of studies using quantitative MRI techniques has allowed us to gain more insights into the pathogenic mechanisms of brain metabolic disorders, also giving the invaluable opportunity to chart disease progression and, in some cases, to monitor response to treatment. In this brief review, we will summarize the main findings obtained by non-conventional MRI techniques in the most frequent leukoencephalopathies and metabolic disorders of the central nervous system (CNS).

Leukoencephalopathies

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 it is due to very different genetic and biochemical abnormalities, most of which are still undefined [1]. In these conditions, the changes detected by non-conventional MRI techniques are often not very specific. However, the ability of quantitative MRI techniques such as ^{1}H-MRS to monitor temporal changes within WM lesions from the very early phases of the pathological process and to detect alterations also in the normal-appearing brain tissue has the potential to help in the differential diagnosis of this complex and often misclassified group of neurological disorders [2].

Metachromatic leukodystrophy (MLD)

MLD, the most common leukodystrophy, is a lysosomal storage disorder characterized by the accumulation of sulphatides due to a deficiency of the enzyme arylsulphatase A. On MRI, signal hyperintensity is bilateral and symmetrical ('butterfly' pattern), with sparing of subcortical U-fibres. A decrease in N-acetylaspartate (NAA, suggestive of neuro-axonal damage and/or loss) and increase of lactate (Lac, suggestive of abnormal oxidative metabolism), choline (Cho, suggestive of membrane breakdown), and myo-inositol (mI, suggestive of gliosis) are present on ^{1}H-MRS. MTI and DTI show a decrease of magnetization transfer ratio (MTR) and fractional anisotropy (FA) and an increase of apparent diffusion coefficient (ADC) [3].

Pelizaeus-Merzbacher disease (PMD)

This belongs to the group of 'sudanophilic' leukodystrophies and it is characterized by the lack of myelin-specific lipids. On MRI, WM signal changes are widespread, due to diffuse lack of myelination, and brain atrophy may be present at later stages of the disease. Elevated levels of Cr and mI and decreased MTR values have been described whereas FA is only slightly decreased [3].

Globoid cell leukodystrophy

Also known as Krabbe disease, globoid cell leukodystrophy is a rare lysosomal disorder characterized by the accumulation of β-galactocerebroside, a fundamental component of myelin, due to a deficiency of the enzyme β-galactosidase. Increased signal intensity is present in the periventricular WM, but it may also be seen in the corticospinal tracts and cerebellum. A long-term increase in Cho, present inside and outside the WM lesions, is probably due to the high cellular membrane turnover occurring in this disease [4]. DTI has provided quantitative measures relevant to clinical status of these patients and is a promising tool for monitoring response to treatment (i.e., bone marrow transplantation) [5].

Niemann-Pick type C (NPC) disease

This is another lysosomal disorder with neurological involvement which shows accumulation of ceramide, caused by a defective metabolism of cholesterol. This can be seen on ^{1}H-MRS as increased resonance intensity in the lipid region of the spectrum [6]. Interestingly, ^{1}H-MRS can also document the decrease of abnormal peaks in the spectrum of patients with NPC disease after appropriate treatment.

Vacuolating megalencephalic leukoencephalopathy (VML)

This is a neurodegenerative disorder clinically characterized by megalencephaly with onset in the first year of life. Its histological hallmark is myelin vacuolation. Conventional brain MRI findings consist of diffusively abnormal WM with subcortical cysts. ^{1}H-MRS has shown inhomogeneous decreases in all normally detected metabolites, with a gradient of lesser severity from posterior to anterior regions of WM [7]. Low FA, high ADC and reduced MTR values are also present [3].

Vanishing white matter (VWM) disease

In VWM disease [8] or childhood ataxia with CNS hypomyelination (CACH) [9], a disorder characterized by rarefaction and cystic degeneration of WM, MRI and DTI findings are similar to those found in VML whereas changes in spectroscopic metabolites and MTR are more pronounced. In addition, increase in glucose resonance intensity may be found as a result of the small amount of cerebral tissue left and the subsequent expansion of extracellular space.

Canavan disease

This is a very rare disorder characterized by a deficiency of the enzyme N-acetylaspartylase which normally breaks down NAA into acetate and aspartate. For this reason, the abnormally high levels of cerebral NAA found by ^{1}H-MRS can be considered pathognomonic [10], although high NAA levels are also found in sialic acid storage disorders and sometimes in Pelizaeus-Merzbacher disease [4].

Adrenoleukodystrophy (ALD)

This is one of the most common WM disorders in children. The classical form affects only males because it is inherited as X-linked recessive trait. There is accumulation of very long fatty acids (VLFA) within peroxisomes leading to damage of myelin. In most cases, abnormalities in the occipito-parietal WM and splenium of the corpus callosum are visible on MRI. However, bilateral corticospinal tract and medial lemniscus may be the only affected WM regions in the first stages of the disease. The intense inflammatory process may show a ^{1}H-MRS pattern with increases of Cho, Lac and lipids and decrease of NAA; sometimes, further peaks may be appreciated in the spectrum, as a result of the accumulation of VLFA [11]. DTI may show a restriction of water diffusion in the lemniscal regions at the early stages and an increase of ADC in the posterior WM with the progression of the disease. Recently, the use of advanced MRI techniques has revealed significant microstructural and metabolic changes in the brain of patients with adrenomyeloneuropathy (AMN) [12,13], previously classified as a 'pure spinal' form of the disease, and thus providing evidence that, even in the absence of visible brain changes on conventional MRI, occult cerebral involvement may occur in this disorder.

Metabolic disorders

The ability of quantitative MRI techniques to detect and monitor microstructural and metabolic brain changes can be exploited also in diagnosing brain metabolic diseases, a group comprising a great number of heterogeneous neurological disorders.

Mitochondrial encephalopathies

Mitochondrial encephalopathies, as a group, are probably the most common form of metabolic disorders. They are caused by a defect in the oxidative respiratory mechanisms leading to accumulation of lactic acid in both cerebral WM and grey matter (GM). Examples of mitochondrial disorders are MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis and stroke), MERFF (myoclonic epilepsy associated with ragged red fibres) and Leigh disease (subacute necrotizing encephalomyelopathy). In all these disorders, ^{1}H-MRS may be helpful in patient management, by showing an extensive pathological increase in Lac both within and outside of MRI lesions indicative of widespread energy failure associated with mitochondrial disorders [14]. DTI also might be useful, by showing an increased ADC in correspondence with acute infarction.

Among the mitochondrial disorders, succinate-dehydrogenase deficiency can be diagnosed by ^{1}H-MRS in the presence of an abnormal peak in the spectrum corresponding to methylene groups of succinate.

Finally, in other rare metabolic disorders such as (i) cerebrotendinous xanthomatosis (CTX) (due to the toxic effect of high cholestanol and/or bile alcohol levels), (ii) ethylmalonic encephalopathy and (iii) a new type of leukoencephalopathy with slowly progressive CNS dysfunction, the finding of diffuse ^{1}H-MRS increase in brain Lac has strongly contributed to the interpretation of the complex pathogenic mechanisms (i.e., primary or secondary mitochondrial defects) of these disorders [4].

Aminoacidopathies

The amino acid disorders, mainly involving childhood, are another important group of rare metabolic disorders. These include phenylketonuria (PKU) (aspecific bilateral WM hyperintensity on brain MRI), maple syrup disease (MSD) (brain MRI changes in both WM and deep GM), homocystinuria (signs of arterial occlusions on brain MRI), and glutaric (cysts at the level of Sylvian fissures and signal changes in WM and deep GM), methylmalonic and propionic acidurias (MRI hyperintensity in bilateral WM and globus pallidus). In many of these conditions, ^{1}H-MRS might be helpful, showing peaks corresponding to amino acids in excess (e.g., phenylalanine in PKU, leucine, isoleucine and valine in MSD) as well as a low NAA.

Other metabolic disorders

It is important to point out that the use of ^{1}H-MRS has revealed the existence of specific metabolic syndromes such as creatine deficiency syndromes [15] and absence of NAA [16], both of them characterized by mild or absent abnormalities on conventional MRI. This is particularly important in the case of creatine deficiency due to defects in the guanidinoacetate methyltransferase and arginine-glycine amidinotransferase (enzymes involved in the creatine metabolism), as cerebral levels of Cr do increase after creatine supplementation. This emphasizes the importance of an early diagnosis of such conditions and underlies the value of advanced MRI techniques such as ^{1}H-MRS in the management of patients with this type of complex neurological disorder.

Conclusions

Advanced MRI techniques of the brain provide important information for diagnosis and management of patients with rare brain disorders such as leukoencephalopathies

and metabolic disorders. They are able to quantitatively assess metabolic and microstructural tissue damage in visible WM lesions and in the normal-appearing brain tissue, providing more insights into underlying pathological changes. These techniques are complementary to the traditional brain MRI and their extensive use in the clinical setting should be encouraged.

Conflict of Interest statement The Authors declare that they have no conflict of interest related to the publication of this manuscript

References

1. Kolodny EH (1993) Dysmyelinating and demyelinating conditions in infancy. Curr Opin Neurol Neurosurg 6:379–386
2. De Stefano N, Mortilla M (2007) Proton magnetic resonance spectroscopy in brain metabolic disorders. Clin Neurorad 17:223–229
3. van der Voorn JP, Pouwels PJ, Hart AA et al (2006) Childhood white matter disorders: quantitative MR imaging and spectroscopy. Radiology 241:510–517
4. Kruse B, Hanefeld F, Christen HJ et al (1993) Alterations of brain metabolites in metachromatic leukodystrophy as detected by localized proton magnetic resonance spectroscopy in vivo. J Neurol 241:68–74
5. Provenzale JM, Escolar M, Kurtzberg J (2005) Quantitative analysis of diffusion tensor imaging data in serial assessment of Krabbe disease. Ann N Y Acad Sci 1064:220–229
6. Sylvain M, Arnold DL, Scriver CR et al (1994) Magnetic resonance spectroscopy in Niemann-Pick disease type C: correlation with diagnosis and clinical response to cholestyramine and lovastatin. Pediatr Neurol 10:228–232
7. De Stefano N, Balestri P, Dotti MT et al (2001) Severe metabolic abnormalities in the white matter of patients with vacuolating megalencephalic leukoencephalopathy with subcortical cysts. A proton MR spectroscopic imaging study. J Neurol 248:403–409
8. van der Knaap MS, Barth PG, Gabreels FJ et al (1997) A new leukoencephalopathy with vanishing white matter. Neurology 48:845–855
9. Tedeschi G, Schiffmann R, Barton NW et al (1995) Proton magnetic resonance spectroscopic imaging in childhood ataxia with diffuse central nervous system hypomyelination. Neurology 45:1526–1532
10. Grodd W, Krageloh-Mann I, Petersen D et al (1990) In vivo assessment of N-acetylaspartate in brain in spongy degeneration (Canavan's disease) by proton spectroscopy. Lancet 336:437–438
11. Rajanayagam V, Grad J, Krivit W et al (1996) Proton MR spectroscopy of childhood adrenoleukodystrophy. AJNR Am J Neuroradiol 17:1013–1024
12. Dubey P, Fatemi A, Huang H et al (2005) Diffusion tensor-based imaging reveals occult abnormalities in adrenomyeloneuropathy. Ann Neurol 58:758–766
13. Marino S, De Luca M, Dotti MT et al (2007) Prominent brain axonal damage and functional reorganization in "pure" adrenomyeloneuropathy. Neurology 69:1261–1269
14. De Stefano N, Narayanan S, Matthews PM et al (2000) Proton MR spectroscopy to assess axonal damage in multiple sclerosis and other white matter disorders. J Neurovirol 6[Suppl 2]:S121–S129
15. Schulze A (2003) Creatine deficiency syndromes. Mol Cell Biochem 244:143–150
16. Martin E, Capone A, Schneider J et al (2001) Absence of N-acetylaspartate in the human brain: impact on neurospectroscopy? Ann Neurol 49:518–521