CHAPTER

3.2

Multiple Sclerosis and Inflammatory Diseases

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INTRODUCTION

Over the past decades, magnetic resonance imaging (MRI) methodologies have been widely applied to the study of inflammatory/demyelinating disorders of the brain, providing important clues to the pathogenesis, course, and diagnostic workup of such conditions. Studies of proton MR spectroscopy (^{1}H MRS) have been particularly important in this setting. Indeed, by providing evidence of early neurodegeneration, based on levels of *N*-acetylaspartate (NAA), such studies led to a reassessment of the role of axonal damage in a primary demyelinating condition such as multiple sclerosis (MS). Further, by showing changes in brain metabolites such as choline (Cho) and myo-inositol (mI), ^{1}H MRS has confirmed the role of myelin damage and repair in MS.

This chapter covers the most relevant applications of ^{1}H MRS in this field, with an emphasis on MS.

MS

MS is a model of inflammatory autoimmune disorder of the central nervous system (CNS). The etiology of MS is still unknown, although it seems the result of an interaction between unspecific environmental factors and susceptibility genes. These factors activate a cascade of pathological events, which are apparent in the CNS as acute inflammation, focal demyelination, neurodegeneration, and partial remyelination.

MS is the major cause of neurological disability in young adults of Western countries. Clinically, it manifests more frequently with a relapsing–remitting (RR) course, which has a wide heterogeneity of symptoms, potentially involving any part of the CNS. The acute episodes (i.e., relapses) are characterized initially by a complete clinical recovery. However, over the years recurrent relapses are followed by only partial recovery, leaving persistent neurological deficits. Then, a progression of clinical disability without relapses (secondary progressive form; SP) ensues. Rarely (10% of cases), the disease has a continuous worsening of neurological status from the onset, without superimposed bouts (primary progressive form; PP). The prognosis of MS is unpredictable, with a high degree of variability in the final outcome, but the disability progression is usually relentless.

Conventional MRI has a major role in the recently developed diagnostic criteria for MS (McDonald et al., 2001; Polman et al., 2011) because of its sensitivity in detecting MS lesions and their changes over time (Filippi et al., 2003b). MS lesions appear on conventional MRI as multiple white matter (WM) foci of various size, irregular shape, asymmetric distribution, and high signal intensity on T_2-weighted images. Signal hyperintensity on T_2-weighted images lacks pathological specificity as it may reflect edema, demyelination, axonal loss, gliosis, or remyelination (Filippi & Rocca, 2007). A subset of these lesions appears hypointense on T_1-weighted images, and more specifically represents axonal loss and severe tissue damage (van Waesberghe et al., 1998). On post-gadolinium T_1-weighted images, some MS lesions can appear hyperintense, reflecting intense inflammatory activity and mononuclear cell infiltration (Katz et al., 1993).

Despite the sensitivity of conventional MRI for detecting MS lesions, some important limitations exist. First, pathological specificity of the MRI-visible MS lesions is low. Second, conventional MRI is unable to detect and quantify the extent of damage in the normal-appearing brain (Peterson & Trapp, 2005). These drawbacks probably explain the limited association between the measures of conventional MRI and clinical status of MS patients (Barkhof, 2002; Filippi & Rocca, 2007). Against this background, modern

quantitative MRI techniques such as ^{1}H MRS have been developed and applied to the study of MS.

^{1}H MRS of MS Lesions

In the last decade, a plethora of ^{1}H MRS studies have provided *in vivo* chemical-pathological characterization of the MR-visible lesions and normal-appearing brain in MS (Arnold et al., 2000; Narayana, 2005). In demyelinating lesions large enough to allow the acquisition of spectra without significant partial volume effect, ^{1}H MRS at both short and long echo times (TE) shows an increase of Cho and sometimes of lactate since the early phases of the focal process (Davie et al., 1994; De Stefano et al., 1995b). Indeed, abnormalities in the resonance intensity of Cho reflect an increase in the steady-state levels of membrane phospholipids released during active myelin breakdown. Increase in lactate may be a primary sign of hypermetabolism of the inflammatory cells. In large acute demyelinating lesions, a decrease of creatine (Cr) can also be detected (De Stefano et al., 1995a). Short TE spectra show transient increase in visible lipids, released during myelin breakdown (Narayana et al., 1998), and more stable increase in mI (Fernando et al., 2004). All these changes are consistently accompanied by marked decrease in NAA, which is a measure of axonal injury reflecting metabolic or structural changes (Matthews et al., 1998). Glutamate levels were also found elevated in acute MS lesions, suggesting a relationship between axonal damage in active lesions and glutamate excitotoxicity (Srinivasan et al., 2005).

After the acute phase and during a period of days to weeks, there is a gradual return of raised lactate resonance intensities to normal levels (De Stefano et al., 1995a). Cr also returns to normal levels within a few days (De Stefano et al., 1995a) or, alternatively, may have a small residual increase, presumably related to gliosis (Caramanos et al., 2005). Persistent increase of mI signal in chronic MS lesions may be linked to microglial proliferation (Brex et al., 2000; Helms et al., 2000; Kapeller et al., 2002). Resonance intensities of Cho, lipids, and mI usually return to normal within few months (Brenner et al., 1993; De Stefano et al., 1995a). The signal intensity of NAA may remain low or show partial recovery, starting soon after the acute phase and lasting for many months (De Stefano et al., 1995b). The recovery of NAA within MS lesions may be caused by transient metabolic changes in neuronal mitochondria, resolution of edema, or modification of the relative partial volume of axons caused by increase in the diameter of previously shrunk axons secondary to remyelination (De Stefano et al., 1995b).

^{1}H MRS of the MS Normal-Appearing Brain

Early single-voxel ^{1}H MRS studies focused mainly on MR-visible lesions (Wolinsky et al., 1990; Arnold et al., 2000). However, more recent studies, taking advantage of a better ^{1}H MRS imaging methodology, have shown that metabolic changes are not confined to MS lesions but are present both close to and far from them (Husted et al., 1994; Davie et al., 1997; Narayanan et al., 1997; Fu et al., 1998; Narayana et al., 1998; Sarchielli et al., 1999).

The NAA decrease found in the normal-appearing white matter (NAWM) is usually ascribed to axonal damage (Matthews et al., 1998) and, albeit present at early stages (De Stefano et al., 2001), is more pronounced in advanced stages of MS (Falini et al., 1998; Fu et al., 1998; Matthews et al., 1998).

The diffuse axonal abnormalities seem to result from nonlesional abnormalities either associated with subtle myelin pathology that is not visible on conventional MRI or with subtle axonal pathology, possibly due to the action of diffusible factors associated with inflammation (Hohlfeld, 1997). However, results of other experimental studies reporting that axonal damage may partially occur, via a mechanism related to the presence of an abnormal glia–axonal interaction even with low or absent inflammation (Bitsch et al., 2000; Peterson et al., 2001; Garbern et al., 2002), suggest that a primary neurodegeneration also may have a role in MS.

The degree of such NAA reduction diminishes with its distance from the center of a lesion (Arnold, 2005; De Stefano et al., 1999), in line with the notion that the widespread abnormalities are partially linked to a dying back of transected axons within MS lesions (Trapp et al., 1998). However, lower levels of NAA are also present without any clear-cut relation with T_2-visible MS lesions (De Stefano et al., 2002), and thus independently of focal demyelination, as it occurs in RRMS patients with minimal lesion accrual and in those with PPMS, who usually have low brain T_2-lesion load.

Axonal damage is not the only pathological process occurring in the NAWM of MS brains. Indeed, a number of ^{1}H MRS studies in patients with both clinically isolated syndromes suggestive of MS (Fernando et al., 2004) and established MS (Kapeller et al., 2001; Chard et al., 2002) have demonstrated a large increase in mI remote from T_2-hyperintense lesions, suggesting a significant increase in glial cell activity in the NAWM of MS patients. In addition, some studies show that abnormal magnetization transfer ratio and increases in lipids and Cho resonance intensities can precede new MS lesion formation in the NAWM (Filippi et al., 1998; Goodkin et al., 1998; Pike et al., 2000). Thus, focal WM abnormalities probably develop well before the

MR appearance of gadolinium enhancement and T_2-hyperintense lesions, as a result of microscopic damage to myelin in a macroscopically normal WM.

^{1}H MRS data do confirm such relatively new concepts of MS pathology by showing signal from lipids (which become visible due to demyelination) in regions that later will develop new T_2-hyperintense lesions (Narayana et al., 1998). These data are in agreement with those of another ^{1}H MRS study, which found a focal increase in Cho preceding the development of new T_2-hyperintense lesions (Tartaglia et al., 2002), thus confirming that a low-grade, focal myelin pathology may predate the development of acute, severe inflammation.

More recent ^{1}H MRS studies have focused on metabolic abnormalities in the gray matter (GM), confirming the important contribution of GM pathology in MS (Filippi, 2001). Decrease in NAA in the cerebral cortex may be small or absent in the early stages, but seems to be marked in patients with progressive disease (Sharma et al., 2001; Sarchielli et al., 2002; Adalsteinsson et al., 2003; Filippi et al., 2003a). In contrast, NAA decrease in the deep GM is more consistently found from the early stages (Wylezinska et al., 2003; Inglese et al., 2004; Geurts et al., 2006). In some studies where both ^{1}H MRS and histopathological methods have been applied in RR and SPMS patients, the degree of *in vivo* NAA decrease and *ex vivo* loss of thalamic neurons was similar (Cifelli et al., 2002; Wylezinska et al., 2003). In contrast with this, however, a very recent 1H MRS study (Kirov et al., 2013) on early RRMS patients followed-up semi-annually for 3 years showed that WM glial abnormalities (Cr, Cho, and mI) were larger than axonal (NAA) abnormalities and progressed over time, whereas axonal values showed partial recovery and changes in the global GM were absent. This suggests that a neuronal dysfunction, rather than true damage, may occur in the early stage of MS.

^{1}H MRS of the Spinal Cord

The role of spinal cord damage in MS and its contribution to permanent disability is well known. Indeed, histopathological studies have demonstrated atrophy and axonal loss in the lateral columns of the cervical cord, although the correlation between these two measures is not particularly close. ^{1}H MRS can provide valuable information on true axonal damage in the spinal cord of MS patients.

Technical hurdles exist, however, in performing ^{1}H MRS of the spinal cord due to magnetic field inhomogeneities, physiological movements, and small cross-sectional area. This explains the paucity of ^{1}H MRS studies of the spinal cord performed thus far.

A recent study on a 3 T scanner showed in cervical MS lesions a significant decrease of NAA/Cho and an increase in Cho/Cr and mI/Cr in comparison with cervical spine tissue of healthy subjects (Marliani et al., 2010). In addition, normal-appearing cervical cord in MS patients showed a significant decrease in NAA when compared to healthy subjects (Kendi et al., 2004). In particular, a 32% reduction of NAA levels alongside a 15% volume loss was present in the cervical cord, indicating significant neuroaxonal injury. Importantly, spinal cord NAA showed a correlation with the cerebellar subscore of the Extended Disability Status Scale (EDSS) whereas no correlations were found with cord atrophy or brain lesion load (Blamire et al., 2007).

In another ^{1}H MRS study (Ciccarelli et al., 2007) on MS patients with cervical cord relapse and lesions, patients had reduced levels of NAA. Significant correlations were found between EDSS and mI, Cho and Cr, and between 9-hole peg test (9-HPT) and Cr. The concentration of mI was independently associated with the EDSS.

Interestingly, recovered patients from a cervical cord relapse showed a sustained increase in NAA after 1 month and a greater increase was associated with better recovery, especially in patients with short disease duration (Ciccarelli et al., 2010a). This was interpreted as the presence of a repair mechanism that may be driven by increased axonal mitochondrial metabolism.

NAA can be considered as a combination of axonal structural integrity and mitochondrial metabolism. Thus, by modeling NAA with imaging measures of axonal structural integrity (axial diffusivity and cross-sectional area) it was shown that lower residual variance in NAA, reflecting reduced mitochondrial metabolism, was associated with greater clinical disability, independently of structural damage (Ciccarelli et al., 2010b).

While the few ^{1}H MRS studies on MS cervical cord conducted thus far have offered useful information on tissue damage, this method, if further exploited, can potentially provide a more complete picture of neurodegeneration in the spinal cord of MS patients.

^{1}H MRS and Clinical Status in MS

Since the pathological mechanisms underpinning disability in MS are obvious targets for novel treatments, their understanding is crucial. ^{1}H MRS, by providing quantitative measures for noninvasively detecting axonal injury/loss in patients with MS,

allows the exploration of dynamic relations between such measures and disability *in vivo*.

By and large, such correlation is explained by changes of NAA/Cr in the NAWM (Fu et al., 1998), in line with evidence of widespread pathology gleaned from other MRI methodologies.

Thus, a number of longitudinal ^{1}H MRS studies have demonstrated highly significant associations between changes in NAA/Cr and worsening of clinical disability in patients with isolated acute demyelinating lesions (De Stefano et al., 1995a) and in those with established MS and RR (Davie et al., 1995; De Stefano et al., 1997, 1998). It must be stressed, however, that the relationship of NAA/Cr with disability is far from perfect, probably due to a number of important factors. First, to determine the total axonal loss based on the measure of the NAA per unit volume (NAA density), it is necessary to correct for the axonal loss associated with brain atrophy. Second, although the location of axonal damage/loss in the NAWM is relatively homogeneous across the brain, the contribution of spinal cord pathology is not strongly reflected by changes in brain NAA. Third, the brain has plasticity mechanisms that can be recruited in order to mask axonal damage/loss at early stage of MS. Indeed, axonal injury occurs in MS even in the absence of clinical disability and becomes clinically relevant only when a "threshold" of axonal loss is reached and mechanisms of compensatory reserve in the CNS are exhausted.

In addition to NAA and Cr, other metabolites seem to have clinical relevance. Indeed, Cho and lipid signals show good prediction toward development of acute and severe inflammation. Further, widespread mI increase in patients with the different disease forms suggests the presence of glial proliferation in MS brains and its relevance to clinical disability. In contrast, increases of glutamate in lesions and normal-appearing brain seem to be related, at least in part, to ongoing neurodegenerative processes.

Alongside physical disability, ^{1}H MRS has also shown a good sensitivity for the cognitive status of patients with MS, especially in the normal-appearing brain, enabling the differentiation between MS patients with and without cognitive impairment. Level of NAA/Cr showed a closer correlation with cognitive scores in the right than in the left hemisphere (Christodoulou et al., 2003). A recent study on genotype–phenotype association in MS showed that human leukocyte antigen (HLA) DRB1*1501 allele is linked to an NAA decrease within NAWM and to an impairment of cognition as measured by the paced auditory serial addition test performance (Okuda et al., 2009). Moreover, in early stage MS MRS-derived axonal damage of the right locus ceruleus in the pons was associated with selective attention deficit, as measured by a dichotic listening paradigm (Gadea et al., 2004). ^{1}H MRS has also revealed a relation between integrity of frontal lobe and memory function in MS, by demonstrating a significant correlation of NAA/Cr in the frontal cingulate gyrus with the Wechsler Memory Scale (Staffen et al., 2005).

Recent studies demonstrated the use of MRS for monitoring therapy in MS patients, highlighting that MRS seems to be accurate and reproducible in longitudinal studies. A standardized MRS protocol has been used in a substudy of a multicenter phase III clinical trial that involved a homogeneous acquisition procedure of single-voxel MRS and a centralized analysis of the MRS data. Preliminary results of this trial, which failed to show evidence of therapeutic efficacy (Narayanan et al., 2005), showed no NAA/Cr change over time in either the treated group or the placebo group. However, the study established the feasibility of brain metabolite levels, particularly NAA, as an outcome measure in clinical trials. Because pathologic specificity of MRS measures toward MS pathology is attractive for multicenter clinical trials, guidelines suggesting simple and robust MRS protocols applicable in this setting on a wide range of commercial MR scanners have been provided (De Stefano et al., 2007).

Using MRS to Distinguish MS from Other Inflammatory Diseases

Intracranial infection, inflammation, and demyelination are pathogenic mechanisms that underlie a wide range of disorders in CNS. In this context, MRI plays a key role in the diagnostic workup and therapeutic decisions and, in recent years, advanced MR methods, in particular ^{1}H MRS, have provided a valuable contribution. For instance, ^{1}H MRS findings in conditions as different as bacterial abscesses, tuberculomas, herpes simplex encephalitis, and human immunodeficiency virus (HIV)-related infections have demonstrated specific metabolic profiles that turned out to be useful in differential diagnosis.

Overall, there is evidence that ^{1}H MRS can be employed for supporting diagnosis in individual cases of infectious, inflammatory, or demyelinating disease.

Intracranial Infections

Infections of the CNS are often life-threatening conditions that may have a rapid progression. The prognosis often depends on the prompt recognition of both the pathogen and site of inflammation. Significant morbidity or mortality occurs, especially in bacterial infections, if appropriate therapies are not started promptly.

The clinical presentation of these conditions may vary significantly. The clinical involvement of the CNS usually includes heterogeneous focal deficits (due to the focal brain lesion) as well as altered mental status and, possibly, seizures (due to the diffuse inflammation). Analysis of cerebrospinal fluid (CSF), laboratory analysis, and, in selected cases, biopsy are the foundation for identifying the infectious agent. However, brain MRI is important as it clearly shows the inflammatory brain lesions, thus allowing a rapid diagnosis and subsequent therapeutic decisions.

In this context, ^{1}H MRS has been shown to be useful, since some brain lesions are difficult to interpret on conventional MRI and, in some cases, the infected brain tissue is characterized by specific spectroscopic patterns (Cecil & Lenkinski, 1998; Foerster et al., 2007).

Brain Abscess

Brain abscess is a focal suppurative process within the brain parenchyma, which is usually secondary to local extension from a contiguous source of infection (e.g., otitis, sinusitis, or mastoiditis) or to hematogenous dissemination of an extracranial infection. The clinical manifestations are usually fever and signs of raised intracranial pressure. However, in some cases, these signs of infection may be subtle or absent, with serious difficulties in interpreting the clinical picture. Conventional MRI is the main noninvasive tool for a diagnosis of brain abscess, revealing a ring-enhancing lesion with perifocal edema, although this also occurs in other necrotic masses (i.e., glioblastoma and metastasis; Haimes et al., 1989; Kastrup et al., 2005). In the case of hematogenous abscess, the MRI lesions are usually multiple and almost all pyogenic abscesses have markedly hyperintense signal on diffusion-weighted imaging, secondary to restricted water diffusion (Kastrup et al., 2005; Kingsley et al., 2006). However, diagnosis of pyogenic brain abscess remains difficult and, in many cases, the biopsy is inevitable. In uncertain cases, additional information can be gleaned from ^{1}H MRS, which enables a better lesion characterization (Poptani et al., 1995b, 1999). Several *in vivo* ^{1}H MRS studies have demonstrated the presence, in the center of the pyogenic lesion, of specific resonances such as succinate (2.40 ppm), acetate (1.92 ppm), alanine (a doublet centered at 1.47 ppm), and amino acids (valine, leucine, and isoleucine resonating together at 0.90 ppm) as well as lipids and lactate. This metabolic pattern has been confirmed in several *in vitro* studies and might show small differences in case of aerobic or anaerobic infections (Garg et al., 2004).

In particular, ^{1}H MRS has shown to be beneficial in differentiating a brain abscess from other cystic lesions (Poptani et al., 1995a). In these cases, the resonances of succinate, acetate, alanine, and amino acids can be found in untreated bacterial abscesses or soon after the initiation of treatment, but are not detected in normal or sterile pathologic human tissue (Gupta et al., 2001; Kingsley et al., 2006; Foerster et al., 2007; Lai et al., 2007). Spectra of arachnoid cysts, for example, typically show lactate signal and no other metabolites, easily allowing a differential diagnosis with a pyogenic mass (Kingsley et al., 2006). In the latter, the presence of succinate and acetate resonance intensity is probably the result of increased glycolysis (Garg et al., 2004). The detection of valine, leucine, and isoleucine signals should be related to the massive necrosis of neutrophils within the lesion producing a massive release of proteolytic enzymes that hydrolyze the proteins into amino acids (Mendz et al., 1989). In a brain mass, the resonance intensities of acetate, succinate, and amino acids can be considered as markers of infection, since they are not usually found in spectra from intracranial tumors (Grand et al., 1996; Dev et al., 1998; Poptani et al., 1999; Lai et al., 2002). Moreover, while lactate, alanine, and lipid resonance intensities can be often found in both meningiomas and brain abscesses, a raised Cho peak can be found only in conditions of increased cell proliferation and density, as occurs in a neoplastic tissue (Tedeschi et al., 1997; Foerster et al., 2007; McKnight et al., 2007). Overall, these data suggest that ^{1}H MRS provides useful information for differentiating an abscess from brain masses. However, it should be taken into account that the distinctive ^{1}H MRS pattern of a brain abscess changes a few days after starting the antibiotic treatment, which leads to a loss of the resonances related to the infectious process (i.e., acetate, succinate, and amino acids; Burtscher & Holtas, 1999).

Herpes Simplex and Other Viral Encephalitides

The most common cause of encephalitis is herpes simplex virus (HSV) infection. Brain invasion occurs after reactivation of a latent virus in the ganglia of cranial nerves. Patients present often with hyperpyrexia, altered mental status, focal neurological deficits, and seizures. The clinical course and prognosis are usually severe. The gold standard for diagnosis of HSV encephalitis is the detection of HSV DNA in the CSF. However, as treatment with antiviral therapy should be initiated as early as possible, MRI (or CT) can be important to support diagnosis. High signal is usually found on T_2-weighted and fluid attenuated inversion recovery (FLAIR) images, especially in temporal and inferior frontal lobes (Schroth et al., 1987; Tien et al., 1993). Mass effect on the lateral ventricles can sometimes be present. ^{1}H MRS studies have shown metabolic alterations of the HSV lesion, which is characterized by reduced NAA/Cr, elevated Cho/Cr, and the presence of lactate. There is a marked

reduction of NAA/Cr, probably in relation to the severe neuronal loss caused by the infection (Salvan et al., 1999). An increase of the Cr signal due to astrocytosis is also probable (Salvan et al., 1999). The lactate signal, not always present, is probably due to the activity of macrophages and other inflammatory cells (Menon et al., 1990b; Takanashi et al., 1997). The Cho/Cr ratio is usually lower than in malignant tumors (Kingsley et al., 2006). However, the spectroscopic pattern of HSV infection is nonspecific and the use of ^{1}H MRS in this context is limited. The use of ^{1}H MRS to chart disease evolution could be more useful.

HIV Encephalopathy

This HIV-induced encephalopathy has been well characterized. It generally occurs in the late disease stage, when immunodepression becomes more severe, leading to the HIV-related dementia. This is a subcortical dementia characterized by progressive loss of cognitive functions, often later accompanied by motor impairment (Nath et al., 2008). Cortical/subcortical atrophy is usually present on conventional MRI. The primary infection from HIV may lead also to variable focal abnormalities of the deep WM (Trotot & Gray, 1997; Offiah &Turnbull, 2006). In severe cases, diffuse symmetric hyperintensity is present in the supratentorial WM, predominantly in the frontal and parietal lobes. There have been several ^{1}H MRS studies showing metabolic abnormalities in the brain of patients with HIV (Menon et al., 1990a; Jarvik et al., 1993; Meyerhoff et al., 1993; Chong et al., 1994; Wilkinson et al., 1997; Salvan et al., 1999; Tarasow et al., 2003; Yiannoutsos et al., 2004) such as reduction in NAA and increase in Cho and mI in both lesions and normal-appearing brain. Decreased NAA is present in virtually all cases. The Cho signal likely increases when the immunodepression becomes more important. The increase of mI should be related to the glial reaction observed in the brain parenchyma (Meyerhoff et al., 1999; Moller et al., 1999; Salvan et al., 1999). The brain metabolic pattern provided by ^{1}H MRS is not disease specific and does not help significantly in the diagnostic workup. However, there is compelling evidence that ^{1}H MRS reveals abnormalities in neurologically asymptomatic subjects and therefore it may be of particular value in documenting early CNS involvement when both neurological examination and conventional MRI are normal. Several other studies have shown that the ^{1}H MRS patterns have a good correlation with clinical status (Chong et al., 1993; Meyerhoff et al., 1999; Salvan et al., 1997; Chang et al., 2002; Paul et al., 2007). Furthermore, ^{1}H MRS has been successfully used in HIV multicenter trials to monitor brain changes after therapy (Salvan et al., 1997). This has become particularly important given the availability of highly active antiretroviral therapy in HIV.

Progressive Multifocal Leukoencephalopathy

Patients with depletion of the immune system may develop progressive multifocal leukoencephalopathy (PML). This is a potentially life-threatening demyelinating disease caused by the JC virus, a polyomavirus. Primary infection is usually not associated with clinical symptoms and the virus resides quiescently in the kidney, CNS, and peripheral lymphocytes (Ferrante et al., 1995). The immune deficiency presumably leads to the reactivation of JC virus. The use of the monoclonal antibody natalizumab (an $\alpha 4\beta 1$ integrin inhibitor) to treat rapidly evolving severe RRMS has been associated with development of PML, especially in patients with high anti-JCV antibody titer, long exposure to the drug, and prior use of immunosuppressive therapies (Kleinschmidt-DeMasters et al., 2012).

Definitive diagnosis of PML is based on pathologic examination of brain tissue, but less invasive diagnostic methods are more often utilized in clinical practice. Conventional MRI shows multiple, asymmetric foci of hyperintense signal on T_2-weighted and FLAIR images. They are mainly subcortical (with involvement of the U-fibers) and located almost exclusively in the WM (Yousry et al., 2006). The JC virus predominantly infects oligodendrocytes and astrocytes, resulting in severe demyelination and cell loss whereas the inflammatory reaction is usually moderate (von Einsiedel et al., 1993). The spectra pattern of PML lesions is characterized by increase of Cho (due to demyelination) and sometimes of Cr (due to astrocytosis). The lactate signal may be present, probably reflecting necrosis or macrophagic infiltration. The NAA resonance is often diminished, especially in the lesion center, where neuronal damage/loss secondary to demyelination is more evident. At short TE, large increase of the lipid signal may add to the lactate and, possibly, amino acid signals. The resonance of mI may be increased as well (Chang et al., 1997; Simone et al., 1998; Iranzo et al., 1999). Although these metabolic alterations are nonspecific, this pattern could be useful to differentiate this type of lesion (i.e., demyelinating) from other brain lesions (i.e., cystic, tumoral, etc.) occurring in immunodepleted individuals.

Acute Disseminated Encephalomyelitis

Acute disseminated encephalomyelitis (ADEM) is an acute, autoimmune, demyelinating disorder of the CNS. Common symptoms include altered consciousness and multiple focal neurological deficits. Diagnosis generally relies on the clinical features, CSF analysis, and neuroimaging. A differential diagnosis should be made with MS and, sometimes, with other less

frequent conditions such as vasculitides and leukoencephalopathies. Clinical symptoms may guide diagnosis, as ADEM usually is monophasic and presents days after a viral illness or vaccination. On conventional MRI, lesions of ADEM are strikingly similar to other demyelinating conditions such as MS. Lesions include foci with variable T_1-weighted hypointensity, T_2-weighted hyperintensity, and contrast enhancement after gadolinium administration. The WM is primarily affected, but deep GM structures and brainstem may be affected as well. Early diagnosis might have implications for treatment, particularly in differentiating ADEM from MS (Kesselring et al., 1990). ^{1}H MRS can be useful for diagnosis and monitoring clinical outcome. Similarly to other demyelinating conditions, spectra of ADEM lesions show reduction in NAA, variable changes in Cho, and the presence of lactate during the acute phase (Gabis et al., 2004). Marked decrease in NAA can be the only abnormality in the acute or chronic phase. In a few cases, a partial recovery of NAA has been reported (Bizzi et al., 2001). The lack of Cho elevation may support the diagnosis of ADEM versus MS. Interestingly the metabolic pattern of the normal-appearing brain is usually normal (Bizzi et al., 2001), further assisting in the differential diagnosis between ADEM and MS.

CONCLUSIONS

^{1}H MRS can be used in clinical practice to characterize in individual patients the metabolic pattern of infectious, inflammatory, and demyelinating diseases, thus contributing to disentangling the diagnostic workup of these conditions.

The information provided by ^{1}H MRS enables a better knowledge of the pathological underpinnings of these disorders. In MS, ^{1}H MRS has been applied to chart progress over time, and in some cases to monitor treatment response.

Despite limitations, ^{1}H MRS can also be potentially implemented in large, multicenter MS clinical trials.

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