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Review article

Proton Magnetic Resonance Spectroscopy in Alzheimer's disease, a review

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Abstract

Alzheimer disease (AD), a progressive neurodegenerative disorder, is the most common cause of dementia in the elderly. Current consensus statements have emphasized the need for early recognition of AD. In vivo magnetic resonance spectroscopy (MRS) has recently opened new possibilities for noninvasively assessing metabolic and functional correlates of dementia in research and clinical settings. The purpose of this article is to provide a conceptual review, covering the principles of MRS and main pathological findings related to AD. H^1 MRS has the possibility of being a neuroimaging marker because the potential clinical applications in patients with AD include a role in early diagnosis and differential diagnosis of AD, a role in prognosis of disease severity, a role in predicting future progression to AD in patients with mild cognitive impairment and tracking disease progression. MRS can also help in the evaluation of treatment effects and in the development of new therapies. In conclusion, H^1 MRS has great potential in becoming an adjunct to clinical evaluation and management of dementia in the future. Nevertheless, there is still need for further research for the implementation of this neuroimaging technique in the management of dementia.

Key words: Dementia; Alzheimer disease; proton magnetic resonance spectroscopy; brain metabolites; diagnosis; differential diagnosis.

Introduction

Proton magnetic resonance spectroscopy (H^1 MRS) is unique among imaging modalities, because it provides both qualitative and quantitative information about the biochemical composition of pathological and healthy brain tissue. This review gives an update on the current state of knowledge on spectroscopy in dementia in order to demonstrate the potential clinical applications of the technique and its limitations to the field. The intent is to focus primarily on Alzheimer's disease, and to review the potential applications of MRS in the diagnosis, in the prognosis and the differential diagnosis of Alzheimer's disease. Finally, the article will also address which future steps are required for the implementation of this advanced neuroimaging technique as a useful diagnostic tool in patients with dementia.

Proton magnetic resonance spectroscopy (H1 MRS)

Principle

In contrast to the structural information provided by MRI, with MRS a number of metabolites within the brain can be measured. This technique is based on the phenomenon of chemical shift to distinguish between various cerebral metabolites, whereby the H^1 signals from the metabolites exhibit slightly different resonant frequencies dependent on their specific chemical environment. MRS is sensitive to within-individual changes in the concentration of metabolites over time on the order of 1 mmol/L, permitting a volume of interest of between 1 to 8 cm^3 (Brooks *et al*., 1999).

MRS provides spectra in which each peak represents a metabolite or group of metabolites, its position being characteristic for the resonance frequency of its constituent nuclei (e.g. protons) and is expressed in parts per million of the resonance frequency of a reference metabolite (tetramethylsilaan). The signal intensity, represented by the peak's surface, is proportional to the metabolite concentration. Molecular groups generate specific resonance patterns on the spectrum, either as single peaks, doublets or more complex spectra. As the magnetic field strength is increased, the separation of the peaks improves. Careful selection of pulse sequence and echo time is required as each can affect the range of biochemicals measured in the MRS scan. Long echo times (120-300 ms) result in plots with a flat baseline, on which only creatine (Cr), choline (Cho),

N-acetylaspartate (NAA), lactate and lipids are visible. Short echo times (20-40 ms) result in spectra containing contributions from a large set of metabolites, which may be difficult to separate. Due to a number of confounding measurement variables, reliable absolute quantification is often difficult to achieve and requires the use of a reference signal. This reference signal is either internal, e.g. the internal water signal (Tong *et al*., 2004) in the assumption that its concentration is known and stable, or external (phantom replacement technique) (Soher *et al*., 1996). Much more often a simple but usually effective approach consists of simply looking at the metabolite profile in disease and comparing this to a known normal metabolite profile (Sibtain *et al*., 2007). In diffuse or general brain diseases a ratio is often calculated between key metabolites (e.g. NAA/Cr, Cho/Cr of NAA/Cho) and then compared to known values for these ratio's for normal brain measured in identical conditions (Di Costanzo *et al*., 2007).

Physiological function of brain metabolites measured with MRS

At 2.0 ppm, N-acetylaspartate (NAA) is an amino acid derivative synthesized in the mitochondria of neural cells, and its concentration correlates with oxygen consumption. Second, NAA is also involved in the synthesis of myelin, and is therefore a very specific marker for viable neurons, axons and dendrites. The diagnostic value of NAA lies in the ability to quantify neuronal injury or loss on a regional basis; therefore it is widely used as a marker of neuronal density and as an in vivo marker of neurometabolic fitness. Reduced concentrations have been reported for a wide spectrum of conditions involving cognitive decline and may reflect a combination of loss of neuronal cells, axonal loss, decreased neural metabolism, reduced myelination and loss of dendritic structures (Birken and Oldendorf, 1989).

The glutamine-glutamate complex (at 2.1 and 2.4 ppm) is a mixture of amino-acids, amines and derivatives. Glutamate functions as the major excitatory neurotransmitter in the brain, involved in motor, cognitive and emotional activities. Glutamine is a precursor for synthesis of glutamate and also a precursor of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), and generally plays a part in the detoxification and the regulation of glutamate within the astrocyte body (Ross, 1991).

The primary resonance of creatine (Cr) lies at 3.0 ppm, the second at 3.9 ppm. This resonance combines PCr and some Cr as the latter is partly bound to macromolecules and hence invisible in MRS. As mainly phosphocreatine (PCr) is detected, this peak reflects the central energy reserve of both neurons and astrocytes. Although studies have shown that Cr is stable over the course of months within an individual (Moats *et al*., 1994), and in the case of AD no significant change of Cr were found either in the hippocampus or cortical regions (Schuff *et al*., 1997; Pfefferbaum *et al*., 1999), it's use as an internal reference to calculate the concentration of the other metabolites is abandoned.

Choline (Cho) is used as a term for several soluble components of brain myelin and fluid-cell membranes that resonance at 3.2 ppm. The choline peak measures the total level of mobile choline. Choline is a rate limiting precursor in the synthesis of acetylcholine and a precursor to cell membrane phophatidylcholine. Therefore, it is generally used as a marker of cellular density and membrane turnover. Because most choline-containing brain constituents are not normally soluble, pathological alterations in membrane turnover result in a significant increase of the choline peak in the MRS spectrum (Miller *et al*., 1996).

Myo-inositol (mI) is a sugar-alcohol, that resonates at 3.6 ppm and at 4.0 ppm. Myo-inositol is often taken as a marker of glial cell numbers, because it contains a considerably higher concentration within glial cells.

Lipids are broad peaks that occur at 0.9 and 1.2 ppm. In healthy brain tissue, there is a small peak of lipids in the spectrum. The presence of lipids can have a diagnostic value in the assessment of brain tumors where it indicates necrosis. Lactate is generally seen as a doublet at 1;33 ppm, although healthy brain tissue does not have sufficient lactate detectable with MRS. Lactate is a product of anaerobic glycolysis and detectable in brain diseases where hypoxia is part of the differential, such as stroke and encephalopathy. It is also a nonspecific marker of intracranial masses, such as tumors and abscesses (Poptani *et al*., 2002).

Clinical applications

Alzheimer's disease is the leading cause of dementia in the developed world. The increasing incidence of AD necessitates the development of reliable and accessible tests for early diagnosis and for monitoring disease progression. The potential clinical applications of MRS in patients with AD include a role in early diagnosis and differential diagnosis of AD, a role in the prediction of dementia and tracking disease progression. MRS can also help in the evaluation of treatment effects and in the development of new therapies.

MRS AND DIAGNOSIS

Although the exact metabolism of NAA is still unclear, it is generally thought to be a marker of neuronal integrity. The NAA level decreases in case of neuronal loss or damage, and may return to normal levels during recovery from head trauma (Brooks *et al*., 2000). AD is characterized by widespread neuronal loss. The frontal regios and the medial occipital lobe are involved, with the neurofibrillary pathology, only at the later stages of the disease, while the temporal lobe and the posterior cingulate gyri are the earliest sites of neuronal loss. Therefore, a consistent finding in AD patients is a reduction of NAA levels in the temporal lobe (Doraiswamy *et al*., 1998; Jessen *et al*., 2009) and the parietal lobe (Miller *et al*., 1993), and in the later stages also in the occipital lobe (Moats *et al*., 1994) and the frontal lobe (Schuff *et al*., 1998). The NAA depletion may represent two separable processes: actual neural cell death in the brain and a decreased level of functionality or metabolic integrity in the neurons. NAA is reduced in both the cortical gray matter and the white matter of AD patients, but these reductions are to a lesser degree in the white matter, suggesting that there is not only neuronal cell death, but also axonal injury. There is a positive correlation between the magnitude of NAA decrease and the severity of neuropathologic findings, such as the counts of amyloid plaques and neurofibrillary tangles (Klunk *et al*., 1992). Therefore it is in agreement with the regional neuropathological involvement in AD. The decrease in NAA concentrations accelerates with disease progression, and these NAA changes are detectable in the early stages of AD (Schuff *et al*., 1997).

Although some studies found elevated creatine levels in AD (Huang *et al*., 2001), many have shown that the Cr peak is stable (Schuff *et al*., 1997; Pfefferbaum *et al*., 1999). Therefore, in a clinical setting Cr was often used as a concentration reference. However measuring the absolute concentration of Cr may increase the sensitivity and the specificity of MRS (Soares and Law, 2009).

The level of mI is generally elevated in the gray matter of AD patients, although mI levels may be confounded by a number of coexisting disease processes, such as chronic hepatic encephalopathy and diabetes mellitus (Kreis *et al*., 1992). Most of mI in the brain is present in glial cells, and there is a possible association between the increased level of mI and gliosis in AD (Ross *et al*., 1998). Abnormal concentrations of mI are found in the earliest stages of AD, even before there are alternations in the NAA levels. Therefore abnormalities of mI in AD patients are prior to alternations of NAA in the neocortex and can play a role in the early diagnosis of AD (Huang *et al*., 2001). There is a higher concentration of mI in astrocytes compared to neurons, which implies that glial proliferation may be an early pathological change in AD, preceding significant neuronal loss or mitochondrial dysfunction (Glanville *et al*., 1989).

There are conflicting reports about the alternations of the Cho level in AD patients. Some studies identified elevated Cho levels in AD (Kantarci *et al*., 2004), and others did not (Valenzuela and Sachdev, 2001). An increased membrane turnover due to neuronal degeneration leads to an elevation of the Cho level in patients with AD. It is also postulated that the elevation of choline is a consequence of membrane catabolism in order to provide free choline for the chronically deficient acetylcholine production in AD (Wurtman and Marie, 1985; MacKay *et al*., 1996).

Whereas the clinical specificity of one metabolite alteration in AD is poor, the addition of another metabolite, forming a ratio of two metabolites, increases the accuracy of the diagnostic function. The proton spectrum in AD patients is different from normal elderly with reduced NAA/Cr and elevated mI/Cr. The ratios of NAA/Cho and NAA/mI are consistently decreased in the posterior cingulate gyri, especially in the hippocampus, compared with normal elderly (Shonk *et al*., 1995; Ross *et al*., 1998; Jessen *et al*., 2000; Kantarci *et al*., 2000). Furthermore, the NAA/mI ratio is decreased more in the parietal lobe than in the frontal lobe, in agreement with the regional distribution of the neurofibrillary pathology of AD. The ratio of NAA/mI is the most accurate MRS measurement to differentiate AD from normal elderly. NAA/mI ratios distinguish clinically diagnosed patients with AD from non-demented elderly with a specificity of 73 to 95% and a sensitivity of 57-90% (Shonk *et al*., 1995; Kantarci *et al*., 2002; Zhu *et al*., 2006). The reduction in NAA concentration in the gray matter is also more sensitive in detecting cognitive decline in AD than structural volume measured with MR (Adalsteinsson *et al*., 2000; Dixon *et al*., 2002, Jessen *et al*., 2009). Therefore, it is possible to detect alternations in brain metabolic activity before changes in the brain volume. In keeping with that, MRS may have a possible role in early diagnosis of AD, in a preclinical stage. In conclusion, all these pathological alterations in AD measured with MRS can help in the diagnostic assessment of AD and in the early, preclinical diagnosis.

MRS AND DISEASE PROGRESSION

Regional evaluation of mI/Cr levels in prodromal AD suggest that MRS is sensitive to the metabolic

changes during the early pathologic progression of AD, before there is an irreversible loss of neuronal integrity. There is also a correlation between the decrease of the NAA/Cr ratio, the increase of the mI/Cr ratio and neuropsychological measures of cognitive function in patients with AD (Doraiswamy *et al*., 1998; Schuff *et al*., 1998; Huang *et al*., 2001). Therefore, mI/Cr and NAA/Cr can predict and monitor prodromal AD in risk patients (Schuff *et al*., 1997; Huang *et al*., 2001). There is a significant decrease of NAA with disease progression and indicates that a lower NAA is related with a poorer cognitive function in AD, reflective of progressive loss of neuronal activity with greater dementia severity (Huang *et al*., 2001).

MRS AND COGNITION

There is an association between neuropsychological assessments and metabolite ratios in AD, mostly marked in the NAA/mI ratio. Both decreased NAA/Cr and elevated mI/Cr appear to contribute to this correlation, but individually they show weaker associations with the neuropsychological tests. Furthermore, the correlation with cognitive impairment implies that NAA/Cr decreases and mI/Cr increases progressively as part of the disease process (Waldman and Rai, 2003). The NAA/Cr ratio predicts cognitive decline and monitors disease activity in patients with clinically established AD. Therefore it has a useful role in predicting the prognosis of cognitive function (Jessen *et al*., 2001; Kantarci *et al*., 2007).

Memory impairment is the earliest symptom of AD. The syndrome of mild cognitive impairment (MCI) is defined on clinical grounds to identify those people with memory impairment who are not clinically demented. It is becoming increasingly evident that MCI is a heterogeneous group. People with amnestic MCI have a higher risk of developing AD compared to normal elderly and most people with amnestic MCI will progress to AD in their lifetime. The conversion rate from amnestic MCI to AD is approximately 10% per year, regardless the age (Yesavage *et al*., 2002). Therefore MCI patients are an important clinical group for preventive therapy and for monitoring disease progression in the early stages. Similar to people with AD, MRS measurements of the posterior cingulate gyri in patients with amnestic MCI show an elevated mI/Cr ratio and a mildly decreased NAA/Cr ratio (Kantarci *et al*., 2000, Kantarci *et al*., 2009). The strongest association between MRS and pathologic measurements was observed in the NAA/mI ratio; this finding suggests that NAA and mI have complementary roles in predicting the AD pathology (Kantarci *et al*., 2002; Zhu *et al*., 2006). There is a suggestion that the mI/Cr ratio alternation occurs earlier than the NAA/Cr decrease during the progression of AD. For this reason there is a hypothesis that the increase in mI/Cr precedes the decrease in NAA/Cr and that mI/Cr ratio is more sensitive to early pathologic changes in AD (Kantarci *et al*., 2008,). Studies show that the Cho/Cr ratio is increased in patients with amnestic MCI who progress to AD, and is decreased in patients with amnestic MCI who remain stable (Kantarci *et al*., 2007). This finding suggests that there is a possible relationship between the decreased Cho/Cr ratios and the compensatory cholinergic mechanisms of amnestic MCI (DeKosky *et al*., 2002). It is also shown that a higher Cho/Cr ratio in the white matter above the ventricles is associated with an increased risk to develop AD within four years, yet not after this period (DeKosky *et al*., 2002).

In conclusion, use of H^1 MRS might represent a useful tool in detecting patients with amnestic MCI who are more at risk of developing AD in the future.

MRS AND DIFFERENTIAL DIAGNOSIS

Although AD is the most common form of dementia, there is still an important group of elderly with other forms of dementia. The differentiation of these dementing conditions is not always easy, because neurological diseases display a limited repertoire of cognitive, behavioral and neurological symptoms. This differential diagnosis becomes even more complex when patients have more than one condition which might contribute to dementia, for example mixed dementia in which vascular and AD lesions co-exist. MRS can be a useful tool to distinguish AD patients from those suffering from other forms of dementia. This might be of special importance in the early course of the disease when the clinical assessment does not indicate unequivocally that the patient suffers from a specific form of dementia.

Consensus criteria for vascular dementia require a link between the demonstration of cerebrovascular disease and the onset of dementia. One of the problems with these diagnostic criteria is that white matter lesions can be present in a variety of situations, including normal aging and frontotemporal dementia. MRS studies indicate that NAA and NAA/Cr levels are reduced in patients with vascular dementia and are even lower in the white matter of vascular dementia compared to in AD, reflecting the white ischemic damage in vascular dementia with respect to the cortical degenerative pathology in AD (MacKay

et al., 1996; Kattapong *et al*., 1996; Schuff *et al*., 2003). In contrast, the Cho/Cr and mI/Cr ratios are elevated in patients with degenerative dementias, but not in patients with vascular dementia (Kantarci *et al*., 2004). Therefore, NAA/Cr, mI/Cr and Cho/Cr may help to identify the presence of AD in demented elderly with cerebrovascular disease (Kantarci, 2007).

Frontotemporal dementia (FTD) is often mistaken for AD or psychiatric disorders. Frontal and temporal atrophy are listed as supportive diagnostic features for FTD. MRS metabolite changes in the frontal and the temporal areas are similar to the changes in AD, including a lower NAA/Cr and a higher mI/Cr (Shonk *et al*., 1995; Kantarci *et al*., 2004). One study identified lower NAA/Cr and higher mI/Cr in the frontal cortex of patients with FTD comparing to AD, indicating that MRS can help differentiate dementias that display regionally specific involvement. It should be noted that these regional differences are prominent during the early stages and are lost as neurodegenerative pathology progresses. Therefore, all these changes are lost when the pathology involves the majority of the cerebral cortex in the later stages (Ernst *et al*., 1997).

Dementia with Lewy bodies (DLB) is characterized by a clinical triad of fluctuating cognitive decline, parkinsonism and visual hallucinations. On MRS, DLB patients have also decreased NAA/Cr ratios in the hippocampus, which suggests damage of neurons in the hippocampus of patients with DLB (Xuan *et al*., 2008). The Cho/Cr ratio is higher in DLB compared to normal controls (McKeith *et al*., 2000).

Overall, studies show a decreased NAA/Cr in dementia characterized by loss of neurons, such as AD, FTD, DLB and vascular dementia (Ernst *et al*., 1997; Schuff *et al*. 2003). On the other hand the mI/Cr levels are increased in dementia associated with gliosis, including AD and FTD. In contrast, this mI/Cr ratio appears to be normal in vascular dementia and in DLB. Dementia with cholinergic dysfunction, such as AD and DLB, is characterized by an elevation of the Cho/Cr level (Kantarci *et al*., 2004). Therefore, MRS and the changes of the metabolite ratios may have a potential role in differentiating dementias at an early stage.

MRS AND THERAPY

Because MR scanners are widely available and MRS allows a non-invasive detection of changes in brain structure and metabolism, there is an increasing interest in the use of MRS to monitor treatment effect in clinical trials of neurodegenerative disease. Recent trials of disease-modifying drugs and advances in understanding the molecular mechanisms of AD offer the promise of creating useful therapeutic interventions in the near future. Disease modifying therapies in AD will be most useful before any irreversible neuron loss takes place, prior to the onset of dementia. For this reason, there is a need for improved methods for detecting these early pathologic changes. Important information about the mechanisms of action of drugs, about the influence of drugs on the brain tissue and the pathological process, as well as therapeutic dose ranges, can be obtained with MRS. This technique has also a potential role as a biomarker for the evaluation of therapy efficacy, because depressed NAA levels in AD normalize within the first six weeks of treatment with cholinesterase inhibitors and Cho levels decrease with cholinergic agonist treatment in AD (Satlin *et al*., 1997; Modrego *et al*., 2006). The findings that Cho/Cr levels decrease and the NAA/Cr ratio increases with cholinergic agonist treatment in AD, raise the possibility that these ratios may also be a biomarker of therapeutic efficacy in drug trials (Satlin *et al*., 1997; Modrego, 2006).

MRS IN THE FUTURE

This discussion demonstrates that MRS has great potential, but currently the question of the practical feasibility of MRS in the diagnostic and therapeutic management of dementia and AD remains unanswered. Nowadays, MRI scanners are widely available. Routine MR and MRS share the same radio-frequency range and there is a ready-made method of MRS, so there is no need for expensive upgrades to the MR scanner. Therefore, it is cost-effective and expeditious. MRS has also other advantages compared to other functional imaging techniques. MRS is completely non-invasive, without the use of radioactive agents and therefore it is safe, without any risk for the patient. Studies show that the exposure to magnetic field have no measurable effects on nerve bioelectric activity, on vision, on immune system competence, thermoregulatory capacity and physiological regulation, nor on cardian rhytmes (Tenforde, 2003). A good and extensive review of safety issues is given by Hartwig *et al*. These authors conclude that *"While the whole data does not confirm a risk hypothesis, it suggests a need for further studies and prudent use in order to avoid unnecessary examinations, according to the precautionary principle"* (Hartwig *et al*., 2009).

Due to the growing interest in the potential of MRS in the field of dementia, further research is on the way. Nevertheless, it should be noted that there

are still some points that need further research for the practical implementation of MRS. The techniques for acquiring and interpreting MR spectra are not well standardized. There is a need for automation, standardization and systematic reporting of MR spectra. Therefore, further research and evidence based literature is warranted.

Conclusion

In conclusion, MRS has great potential in becoming an adjunct to the clinical evaluation and management of dementia in the future. MRS can add precision to existing pathological knowledge, make a diagnosis or help in the differential diagnosis and predict future disease progression. Furthermore, the noninvasive nature and the cost-effectiveness of this technique are arguments to further develop it as a tool for neurological therapeutic decision making and therapeutic monitoring of dementia. According to the diagnostic guidelines by the American Academy of Neurology, this MR technique is not recommended for routine use of dementia evaluating because the superiority to clinical criteria has not been demonstrated (Knopman *et al*., 2001). Therefore, an important missing factor is available literature on efficacy of MRS in clinical decision making and therapeutic choice.

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