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Prognosis and diagnosis of the Alzheimer's disease in early stages by new magnetic resonance imaging techniques

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ABSTRACT

A large number of people have dementia all over the world, mainly suffering from Alzheimer's disease. The worldwide prevalence of dementia is expected to increase up to 24 million, and would to double every 20 years through to 2040, resulting in an expensive burden of disease. The overlap between clinical groups and the longitudinal stability of the technique which currently may limit its clinical application in this context. The advent of new specific treatments for dementia will doubtless stimulate further research into the use of in vivo MRS as a clinical and scientific technique. Future technological developments may allow biochemical features of the underlying pathology in neurodegenerative disease.

KEY WORDS: Alzheimer disease, magnetic resonance spectroscopy, Mild Cognitive Impairment, MCI, Neuroimaging, fMRI, MRS

1. INTRODUCTION

More than 25 million people worldwide have dementia, mainly suffering from Alzheimer's disease (Wimo, 2003). The worldwide prevalence of dementia is expected to increase up to 24 million, and would to double every 20 years through to 2040, resulting in an expensive burden of disease. Dementia is defined as a cluster of symptoms and signs characterized by difficulties in memory function, disorders in language and other functions, behavior changes, and problems in daily activities. Alzheimer's disease (AD) is the most common cause of dementia including about 75 % of all dementia cases, is known as a progressive neurodegenerative disorder. It has substantial impact on the patients, caregivers, and population (Wimo, 2003). Older age and genetic susceptibility are the main risk factors of AD. In addition, other potential risk factors and disorders would be cigarette smoking, high blood pressure and obesity, diabetes mellitus, and cerebrovascular lesions as well as psychosocial factors such as social activity, high level of education, somatic exercise, and mentally stimulating activity (Rasolabadi, 2015, Ghaffari, 2015).

The age-standardized prevalence in people aged >65 years old is about 6.4 % for dementia and 4.4 % for AD (Berr, 2005). In the US, among people aged >70 years old the prevalence of AD is around 9.7 %. The worldwide prevalence of dementia is about 3.9 % in people aged > 60 years, 1.6 % in Africa, 4.0 % in China and Western Pacific regions, 4.6 % in Latin America, 5.4 % in Western Europe, and 6.4 % in North America. The average incidence rate of AD among people aged >65 years in Europe was 19.4 per 1000 person-years. In the US was about 15.0 (male, 13.0; female, 16.9) per 1000 person-years (Berr, 2005).

There is a transitional, heterogeneous stage, mild cognitive impairment (MCI) with cognitive deficits beyond between physiological aging and dementia those expected based on the age and education of the individual, but which are not significant enough to interfere with their daily activities.

Previous studies have demonstrated better understanding of the molecular pathogenesis of the hallmarks of AD such as plaques, composed of amyloid β (Aβ), and tangles, composed of hyperphosphorylated tau (Sturchler-Pierrat, 1997). However, they have also emphasized on the pathogenic complexity of the disease. Early detection of AD and diagnosis at early stages of cognitive deficiency could result in the possibility of earlier therapeutic intervention and prevention of further progression of the disease.

One of the neuroimaging methods that could be potentially useful for identification of patients with MCI who are at increased risk of developing dementia is magnetic resonance spectroscopy (1H-MRS). This method as a noninvasive method could provide information about metabolic changes in the brain tissue. It was reported that there are many differences in brain metabolism between demented elderly adults and unimpaired ones. However, various studies are obtained from different brain regions and with the application of different data acquisition and processing methods. Apart from studies comparing metabolites in healthy and cognitively impaired patients, there are just few conflicting studies that prospectively assessed 1H-MRS as a predictor of conversion of MCI to dementia. With an aging population that is getting increasingly older, the prevalence of dementia is increasing. Unfortunately, the diagnosis of dementia is typically made at a stage in which the underlying pathology has reached an advanced and irreversible state. In the past few years, MIC has been known as an early stage on the path towards dementia due to its important for predicting the progress of dementia at early stage, which it can still be treated, thereby stopping or

at least delaying the progression to dementia. The criteria for the diagnosis of MCI, however, are still under active development. Neuroimaging studies are necessary for understanding the pathophysiology of this early stage of cognitive deterioration, as well as besides volumetric analyses of grey and white matter, based on Magnetic Resonance Imaging (MRI) scans, and functional MRI of brain activation differences, neuroimaging using proton magnetic resonance spectroscopy (MRS) can yield information regarding metabolite changes in the brain representing early degeneration (Fatehi, 2016c). The first time in 2009, Petersen et al reported the criteria for the diagnosis of MCI with aim of capturing the prodromal state of AD. These criteria include a memory complaint that is confirmed by an informant and is documented by appropriate testing. In addition, the subject should be normal in other cognitive domains, be unimpaired in daily living and not demented. However, observations showed that subjects that had memory complaints not only may attributed to AD but also can associated with other types of dementia or psychiatric ailments. In 2004, amnestic MCI (aMCI) and non-amnestic MCI (naMCI) were added to the criteria, which memory impairments can be determined by impairments in either a single domain or multiple domains accounting for diverse etiologies. Reports of prevalence of MCI is highly variable, which can be in the range 3 to 42%, with an increasing frequency observed from the age of 65 to 85 years (Mariani, 2007). The majority of the cases are of the amnestic type. This cohort of individuals has an annual conversion rate to AD of 3–17%, which is much higher than that for the general population (1–2%). However, the outcomes of MCI are not consistent. Although, most MCI patients progress to dementia, but some of them remain stable. So, these patients have impairments, but their disease does not progress to dementia. A small fraction may even improve to be categorized as no longer being impaired. Being a relatively new disorder, MCI continues to be characterized, with the diagnostic criteria being regularly updated to reflect the improved understanding of the disease. An important drawback of the current criteria is that they capture a clinical syndrome and not the disease. Therefore, various definitions are generally used in the diagnosis of MCI individual studies. These results are in line with the use of MCI definition in turn affects meaningful interpretation of the outcomes from various studies (Mariani, 2007). This different may be considered as an important reason for the variable results in epidemiological studies. So, standard criteria are necessary for diagnosing MCI (Ward, 2012). As the burden of AD is projected to increase in the near future, the interest in MCI as a predictor has also increased manifold. Research on biomarkers, such as brain abnormalities, can ultimately benefit reliability and early identification of the condition (Rahmani Tanha, 2016, Fatehi, 2016a). In addition, MCIneural basis studies can be useful in the necessary knowledge for developing evidence-based. In order to study the existence a consistent pattern or consolidate and highlight changes in MCI (Ward, 2012), we performed a meta-analysis. A main objective was to determine the changes of the most common metabolite as well as typical regional differences in MCI.

Neuroimaging modalities: In studies with preclinical models, there are some limitations due to the inability to longitudinally collect anatomic and functional information. Some semi-invasive imaging methods can provide details with high spatial resolution such 2-photon microscopy. In contrast they are limited by a depth resolution of several hundred microns. Despite the high sensitivity in bioluminescent imaging, it is accompanied by a very poor spatial resolution. MRI is a very attractive noninvasive imaging modality that offers a spatial resolution of tens of microns, can be conducted longitudinally within the same subject, does not rely on ionizing radiation and exhibits clear advantages over other imaging methodologies such as PET or x-rays. Images are obtained in a short time and could provide outstanding anatomic and functional insights into pathologic processes. MRI was known as an important method in diagnose, monitor progression and responses to therapeutic regimes in individuals afflicted with AD (Mizuno, 2005). In MRI in AD, the main goals include developing novel imaging strategies and using existing strategies to monitor responses to therapies. There are 3 main areas where MRI is an invaluable tool in imaging AD models and patients. These include: (1) anatomic imaging, (2) imaging function/physiological processes, and (3) molecular imaging. Due the capability of MRI in exhibiting outstanding soft tissue contrast, it are generally applied for monitoring changes in brain anatomy during the development of AD and during responses to treatments. Through MRI, it is possible to detect and score gross anatomic changes in brain matter over time. For example Ferreira et al. studied assessing brain shrinkage over time in 6 individuals with AD treated with encapsulated nerve growth factor. In this study, the group used imaging data from the ADNI database that were age-matched and also Mini Mental Status (Mizuno, 2005).

DTI: A complementary type of MRI for general anatomic MRI is that of DTI. DTI is an elegant MRI methodology that allows for the mapping of water diffusion in biological tissues and can be used to assess changes in white matter integrity. Subcellular constituents that can alter water diffusion patterns typically hinder the molecular diffusion of water. DTI builds on the basic principles of diffusion imaging and in this method, case each voxel indicates the rate of diffusion and the directionality of the diffusion in 3-dimensional space. The multiple diffusion-weighted acquisitions (giving directionality) and integrity of the associated white matter tracts (in the central nervous system) can be used in the calculation of a tensor (Gharib Salehi, 2016). DTI is a promising very powerful method in as sessing not only overt but also subtle perturbations in neuronal circuitry. One of the major readouts in DTI imaging

is that of fractional anisotropy (FA). Typically, FA is represented in a map of the brain but can also be quantified. The values of FA varies in the range 0 to 1, which the values close to 0 indicates a state of unrestricted diffusion of water (disordered system). While, the values close to 1 indicates restricted diffusion of water that is indicative of a very ordered system (such as along an intact axon). There are contradictory reports about white matter tractography perturbations in AD. It was reported that DTI can be applied to discriminate dementia Lewy bodies from AD, as with Firbank, 2007, finding greater mean diffusivity in AD than dementia with Lewy bodies in small regions in the left parietal and temporal lobe. Other groups have reported widespread perturbations in white matter connectivity. Recently, according to previous literature, certain areas of the white matter are affected in early onset AD including the parietal sector of the corpus callosum and the parahipoccampal cingulum (Wozniak, 2007).

fMRI: Another type of MRI known as functional MRI (fMRI) typically refers to the monitoring of changes in blood flow in response to changes in neuronal activity. Quite commonly, blood oxygen level detection (BOLD) imaging is used in fMRI studies. Increased blood flow has been correlated with increases in neuronal activation, reflective of local field potentials. BOLD relies on changes in blood flow, blood volume, and the oxygenation state of blood to alter the MRI signal. Fast imaging sequences such as echoplanar imaging or fast gradient echo imaging sequences is used in BOLD fMRI studies. Resting state fMRI reflects not only functional information but also connectivity duringa ‘‘resting state,’’ which is when the subject is not asked to perform a specific task during the collection of the fMRI data. Brain regions that exhibit synchronous activity allow for the creation of functional maps and deviations from these functional networks can be evaluated in different disease states. For example, some resting state fMRI studies have recently shown that there are impairments in functional connectivity in the parahippocampal gyrus and that disruptions in the functional connectivity in the parahippocampal gyrus appeared to be associated with the severity of AD. Furthermore, some studies on resting state fMRI reported that there are many differences in distinct functional brain connectivity between AD and frontotemporal dementia. In term of analytical, brain network maps were used for evaluating changes in brain connectivity in AD patients through fMRI. They were able to discriminate between different stages of dementia those eventually lead to different impairments in brain connectivity. Its potential in the detection of changes in early stages of dementia in patients without severe or even mild clinical symptoms is noteworthy. It should also be noted that perturbations in blood flow have been reported in AD. Because of this, fMRI studies on blood flow changes as part of the readout should be carefully interpreted as well as studies with animal models. For not only concerns regarding blood flow deficits but with the additional compounding factors that are introduced by anesthesia used during small animal imaging. Anesthesia is attributed to the additional factors of depressing neuronal activity and hemodynamic response affected by blood gas levels and hence the fMRI readout (Vernooij, 2007; Friston, 1998).

MRS: MRS is a novel technique that provides a detailed picture of the in vivo biochemistry of the brain. Standard MRI scanner is used to present the spectrum reflecting the concentration of metabolites in the brain. Unfortunately, there are only a few metabolites in sufficient concentrations in the brain that be detected by MRI scanners, which was approved for safe use in humans. The detection of the metabolites is partly dependent on the strength of the field, with higher field strengths required to detect metabolites present in low concentrations. The metabolites that are present in high concentrations and thus most commonly studied are N-Acetyl Aspartate (NAA), choline (Cho), creatine (Cr), myo-inositol (mI), and glutamate and glutamine (Glx). Each of these metabolites is sensitive to a different pathological process in the brain. NAA is produced only within neurons and its concentration represents the neuronal density and viability. The peak on the spectra at 2.0 ppm is associated to the NAA. The presence of free glycerol phosphocholine and phosphocholin contribute to the choline signal. When these compounds constitute the cellular membrane are immobile. While, they become mobile, when the cell membrane has broken down and contribute to the Cho signal. A peak at 3.2 ppm is attributed to the Cho signal that is a marker for membrane integrity. Creatine and phosphocreatine were known as markers for energy metabolism which they have a peak at 3.03 ppm. It is supposed that Cr concentrations are fairly constant and is used as a reference value. Though, there are various reports disputing this claim. Myo-inositol as an osmolyte has a key role in the second messenger system. Its peak are appeared at 3.55 ppm, which can considered as a marker for glial activation. Glutamate and glutamine (Glx), key amino acids in the brain, appear as a single peak at 2.1–2.3 ppm in the spectrum. The peak can be resolved into individual wavelets in high-field MRI or less accurately by post-processing methods. A second smaller peak is also seen at 3.75 ppm provide a recent review on MRS. Magnetic resonance spectroscopy has many advantages. The MRS spectrum is easily obtained from a conventional MRI machine requiring relatively little time. It is possible to obtain spectrum either from a single voxel (SV) of interest or from multiple areas (Multivoxel Spectroscopy (MVS)) simultaneously making it sensitive to regional changes in metabolites. It is non-invasive and free from radiation which allows for monitoring the disease progression in patients. A number of studies have also studied the efficacy of pharmacological interventions using MRS. When combined with MRI it enhances the sensitivity and specificity of differentiating MCI from healthy subjects and from AD patients. In recent years, several studies on MCI conducted using different methods have shown metabolite profiles, which their profiles are similar to those typically found in

AD. Diverse regions of the brain have been studied with the posterior cingulate and the hippocampal regions receiving the most interest. Also the posterior white matter and gray matter, temporo-parietal region, prefrontal, medial temporal lobe, as well as the whole brain have been investigated. In comparison to control group, MCI patients have shown decreased NAA/Cr and Glx/Cr levels, and elevated mI/Cr and Cho/Cr levels, although some studies failed to find any differences between the groups. Only a few studies examined longitudinal changes in MCI subjects. Despite the difference in aims and methods used by the mentioned studies, their results conclude the potential of MRS as a diagnostic tool. Additional approaches have been used that incorporate the use of MRI contrast agents to target plaques. Reduced levels of N-acetyl aspartate (NAA) and elevated myo-inositol (mI) in the posterior cingulate region of subjects with probable AD were first reported from short echo time (TE) single voxel studies in the early 1990s. Since There so many MRS studies in AD using single voxel and CSI methods, the latter predominantly at long TE. These have allowed regional metabolite abnormalities in AD to be investigated. The most consistent finding is of reduced NAA and elevated mI, reflected in both metabolite ratios to Cr and absolute concentrations. MRS studies provide valuable information about regional distribution of changes in metabolite levels and as a result can avoid the potential problems with sampling errors that may occur with single voxel techniques. NAA, Cho and Cr are the metabolites most commonly mapped by MRS. Schuff et al. demonstrated decreased levels of NAA in the mesial temporal lobes, including the hippocampus and parietal grey matter but not in the frontal lobes or white matter, which agreed with the known distribution of the pathological changes in AD (Ferreira, 2011, Rumsey and Ernst, 2000).

2. CONCLUSION

Currently, AD diagnosis is a key factor in the treatment of disease which by improving medical imaging technology, new possibilities will be present for the evaluation of this disease at the structural, functional and cellular levels. New advanced MRI techniques such as DTI, fMRI, and MRS could have the ability of the assessment of cellular and functional, considering the fact that MRS has a more practical and validity role than the other techniques for clinicians. MRS may reveal quantitative abnormalities in normally occurring brain metabolites in patients with dementia. Of those which are currently accessible to clinical MRS, NAA and mI seem to be the most robust discriminators for the diagnosis and characterization of dementias. The combination of decreased NAA and elevated mI in the posterior cingulate region may be helpful in the diagnosis of AD, and may be used as an adjunct to structural imaging in a clinical environment.

These metabolite abnormalities are likely to reflect the final common pathways of neuronal loss or dysfunction and gliosis, respectively. In addition, the anatomical and temporal patterns of metabolite abnormalities could help to distinguish different forms of dementing illness. Furthermore, metabolite abnormalities in those with mild cognitive impairment suggest a role for identifying those at risk of developing AD, and serial metabolite measurements may provide potential surrogates of disease progression and therapeutic response.

The overlap between clinical groups and the longitudinal stability of the technique which currently may limit its clinical application in this context. The advent of new specific treatments for dementia will doubtless stimulate further research into the use of in vivo MRS as a clinical and scientific technique. Future technological developments may allow biochemical features of the underlying pathology in neurodegenerative disease.

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