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REVIEW

Magnetic Resonance Imaging of Alzheimer's Disease: from Diagnosis to Therapeutic Evaluation*

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ABSTRACT Alzheimer's disease (AD) is a devastating late-life dementia that produces progressive loss of memory and mental faculties in elderly people. It is important to identify the earliest evidence of AD and to monitor the development of this disease for us to make positive response to its management. Magnetic resonance imaging (MRI) is powerful to image the tissue or organ without damnification. MRI can be employed to diagnose the early AD development and monitor the key biomarker development in AD. MRI may be helpful not only in diagnosing early AD, but also in evaluating its development. This article reviews the progress of MRI on the diagnosis and detection of AD, and makes comments on its therapeutic application.

KEYWORDS *Alzheimer's disease, diagnosis, magnetic resonance imaging*

Alzheimer's disease (AD) is a devastating late-life dementia that produces a progressive loss of memory and mental faculties in elderly people[1]. More than 5 million people in the United States have suffered from AD[2], while the number has even reached more than 5 million in China. There is significant interest in biomarkers and typically pathological changes that can identify the earliest evidence of AD to allow quantitatively evaluating new interventions, and tracking a patient's response to treatment. Many approaches or techniques have been proposed to investigate the AD pathology research, such as positron emission tomography (PET)[3-5] and magnetic resonance imaging (MRI)[6-8]. MRI, or so called nuclear magnetic resonance imaging (NMRI), was introduced in the mid-1970s based on the properties of nuclear magnetic resonance[9,10]. The first studies performed on humans employing MRI were published in 1977[11]. In Contrast to the traditional radiological medical imaging technique to visualize the detailed internal structure and limited function of the body, MRI provides much greater contrast between the different soft tissues of the body than computed tomography (CT) does, making it especially useful in neurological (brain), musculoskeletal, cardiovascular, and oncological (cancer) imaging. MRI technique has introduced a new set of tools for capturing features of brain development in humans. With the assistance of MRI, we revolutionize our expectations for diagnostic and investigative work with the developing brain. In this review, we will discuss the progress of MRI techniques in the diagnosis and determination of the biomarkers of the disease.

Basic Principles of MRI

Brain scans which include CT, MRI and PET can be commonly used in the diagnosis of dementia[12,13]. Both CT and MRI scans generate excellent images of the internal structure and brain condition, while MRI scans provide more clear and detailed images of the brain or other internal organs by using magnetic and radio waves instead of X-rays used in CT. However, PET scans, which can only be used in monitoring brain activity, are not typical to diagnose AD.

MRI is based on the principles of nuclear magnetic resonance, and its basis is the directional magnetic field, or moment, associated with charged particles in motion. Nuclei containing an odd number of protons and/or neutrons have a characteristic motion or precession. Because nuclei are charged particles, this precession produces a small magnetic moment. When a human body is placed in a large magnetic field, many of the free hydrogen nuclei align themselves with the direction of the magnetic field.

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The nuclei process about the magnetic field direction like gyroscopes. This behavior is termed Larmor precession. The Larmor equation (γ B0=F) expresses the relationship between the strength of an applied magnetic field, B0, and the processional frequency, F, of an individual spin, where γ is the gyromagnetic ratio. For more information about the basic knowledge, it is available from the reviewed work[14-16]. The strength and duration of the MRI signal depend on three quantities: ρ (proton density), spin-lattice relaxation time [the time which describes how fast the net magnetization is and how fast it takes to relax back to its equilibrium (T1)], and spin-spin relaxation time [with this time, magnetization components decrease to zero (T2)]. By using different parameter settings, it is possible to obtain three different images of the same body: T1-weighted, T2-weighted, and ρ-weighted. MRI acquisitions that are useful in AD include high resolution T1-weighted images perpendicular to the long axis of the hippocampus to evaluate medial temporal lobe atrophy, axial or coronal T2-weighted to evaluate cerebrovascular pathology and white matter hyperintensities, and axial gradient echo T2-weighted images to detect micro-bleeds in vascular dementia[17]. Brain images of magnetic resonance mostly contain noise, inhomogeneity and sometimes deviation. Therefore, brain image segmentation is one of the most important parts of clinical diagnostic tools, and it is a very difficult task to get perfect and accurate MRI-results. Segmentation is the partitioning of an image to several segments. The main difficulties in segmentation are: (1) signal noise; (2) the bias field (the presence of smoothly varying intensities inside tissues) and (3) the partial-volume effect (a voxel contributes in multiple tissue types). Balafar MA, et al[18] reviewed the available segmentation algorithms and methods of MRI segmentation in their review work.

Diagnosis of the Clinically Atrophied Characteristics

In AD, nerve cell death and tissue loss cause all areas of the brain, especially the hippocampus region, to shrink. Besides the whole brain imaging, MRI can also image the internal organs of the brain. Seab JP, et al[19] studied 10 patients with AD and seven healthy elderly control subjects with MRI, and found that the hippocampal volume (normalized relative to the size of the lenticular nucleus) was reduced by 40% in the AD group compared with the controls, with no overlap between the two groups. Hippocampal atrophy did not correlate with either overall brain atrophy or dementia severity, although the degree of brain atrophy was correlated with dementia severity. MRI with high spatial resolution allows radiologists to visualize subtle anatomic changes in the brain that signal atrophy, or shrinkage. Colliot, O[20] investigated 25 patients with AD [11 men and 14 women, 73 ± 6 years; Mini-Mental State Examination (MMSE) score: 24.4 ± 2.7], 24 patients with amnestic mild Cognitive impairment (MCI, 10 men, 14 women, 74 ± 8 years; MMSE score: 27.2 ± 1.4) and 25 elderly healthy controls (13 men, 12 women, 64 ± 8 years). For each participant, the hippocampus was automatically segmented on three-dimensional T1-weighted MRI with high spatial resolution. The results showed that significant hippocampal volume reductions were detected in all groups of AD patients (-32% in AD patients *vs* controls, $P<0.001$; -19% in MCI patients *vs* controls, $P<0.001$; and -15% in AD patients *vs* MCI patients, $P<0.01$). Individual classification on

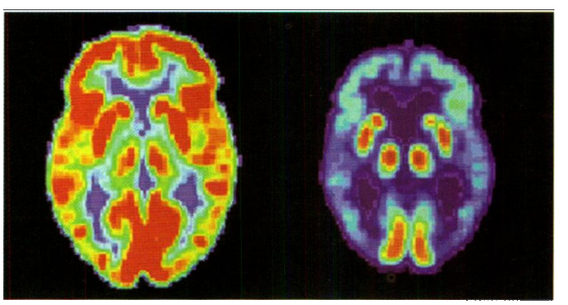
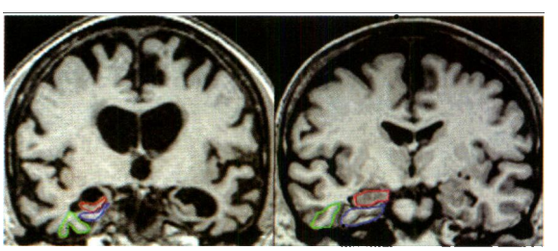


Figure1. Brain Scan of PET of Identify Brain Atrophy

Notes: left: Normal brain; rihgt: AD brain. Source: The Aheimer's Disease Education and Referral (ADEAR) Center of American National Institue on Aging



Normal AD

Figure 2. MRI Brain Scans in Early Diagnosis of AD

Notes: a normal MRI brain, showing no atrophy, depicts the three areas of interest in the brain's medial temporal lobe: hippocampus (outlined in red); entorhinal cortex (blue) and perirhinal cortex (green). The MRI brain with AD shows severe atrophy indicative of Alzheimer's pathology in all three areas, except the right perirhinal cortex, which has moderate atrophy

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the basis of the hippocampal volume resulted in 84% correct classification (sensitivity, 84%; specificity, 84%) between AD patients and controls and 73% correct classification (sensitivity, 75%; specificity, 70%) between MCI patients and controls. From the neuro-image MRI gives more details of AD than PET (contrast in Figures 1 and 2).

Overall, from the MRI analytic results, the annual rate of hippocampal atrophy in AD was calculated up to 3.6%-5.9%, compared with 1.4%-1.73% in age-matched control subjects[21,22]. The annual rate of entorhinal cortex atrophy in AD was about 7% to 8%[22]. Dynamic maps of disease progression in AD show a spreading wave of grey matter loss extending from the limbic to frontal cortices, whereas the sensorimotor cortex is relatively spared[23], in agreement with postmortem observations[24].

Detection of Metabolic Networks

AD is a complex disease involving many nosogenetic factors, and it is difficult to define a detectable biomarker for diagnosis in clinics. This also represents a major problem for diagnosis and the advance of efficient drug discovery programs of AD. A successful approach towards the understanding and treatment of AD should be taken into consideration. In this sense, metabolic networks of the brain are subjected to severe stoichiometric restrictions. Metabolomics amplifies changes both in the proteome and the genome, and represents a more accurate approximation to the phenotype of an organism in health and disease. MRI techniques can be employed to monitor the metabolic network changes on the brain AD pathological progress[25].

Mellon EA, et al[26] presented the idea that alterations of sodium levels in the brain of patients with AD would relate to AD cell death from the fact that sodium levels correlate with cell death in stroke. They detected MR Ⅰ with a scan of a 20-min sodium (^{23}Na) MRI protocol on a 3T clinical scanner in 10 volunteers (5 with mild AD and 5 healthy control subjects), and found that sodium MRI may be a clinically useful tool to detect the neuropathologic changes associated with AD. Since sodium metabolism is important for the brain, (^{23}Na) MRI is helpful to diagnose the early AD (Figure 3).

Hippocampal atrophy is not specific to AD,

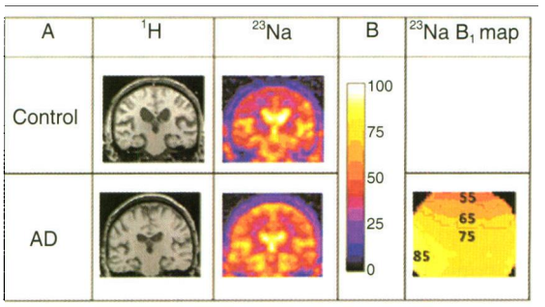

Figure 3. Metabolism of Na^+ in AD Brain

Notes: A: representative coronal control (control C2) and AD (patient AD4) images are shown from the sections for region-of-interest analysis. The proton images demonstrate the anatomy of the brain in the corresponding sodium sections and were part of the dataset used for hippocampal volume determination. The sodium images are normalized to the ventricular signal intensity, scaled as shown with the color bar on the right, which is also used for B. The images were normalized to the brightest areas of intensity in the center of the image, seen clearly in these images as the lateral ventricles. The hippocampal volumes from the proton sets were coregistered to the sodium images and used to mask the hippocampuses as described in the methods. B: Shown is the corresponding section from a B1 map calculated from a spherical sodium phantom with contour lines added for each 10th percentile. This indicates excellent homogeneity over the areas of interest. The units are in B1 relative to the maximum in that section scaled to the same color bar. The maximum is found at the edges of the phantom near the struts of the birdcage

and the structure is also highly atrophied in some other disorders, such as frontotemporal dementia and hippocampal sclerosis. So combining different measures will improve the accuracy of the clinical diagnosis. Magnetic resonance spectroscopy (MRS) is shown as a powerful tool to co-diagnose early AD[27]. MRS is a noninvasive technique that can be used to measure the concentrations of different chemical components within tissues. The technique is based on the same physical principles as magnetic resonance MRI. Brain metabolic levels of some critical biomass might be a sensitive early AD development. N-acetylaspartate (NAA) intensity is thought to be a marker of neuronal integrity and is the most important proton signal in studying CNS pathology. Decrease in the NAA signal is associated with neuronal loss. In the brain, creatinine is a relatively constant element of cellular energetic metabolism and thus is sometimes used as an internal standard. Myolnositol (Myo) is a simple sugar. It is absent from neurons. In the brain, it is synthesized primarily in glial cells and can not cross the blood brain barrier[28]. It is considered a glial marker[29]. An increase in Myo content is believed to represent glial proliferation or an increase in glial cell size, both of which may occur in inflammation. It is

elevated in the setting of gliosis, astrocytosis, and in disorders such as Alzheimer's dementia.

Alzheimer's dementia can only be easily diagnosed at autopsy under an arbitrary decision, while it can sometimes be positively identified with the aid of MRI and MRS (Figure 4)[27,30]. MRI can sometimes demonstrate cerebral atrophy more marked in the temporal lobes of these patients. At MRS, there is a decrease in NAA levels, as well as an increase in Myo, in the occipital, temporal, parietal, and frontal regions of patients with Alzheimer's dementia[31]. Detecting these early changes is becoming more important as the pharmacological intervention for Alzheimer's becomes increasingly effective. Although at times it may be difficult to confirm the diagnosis, serial scans may be useful to monitor changes in metabolite levels.

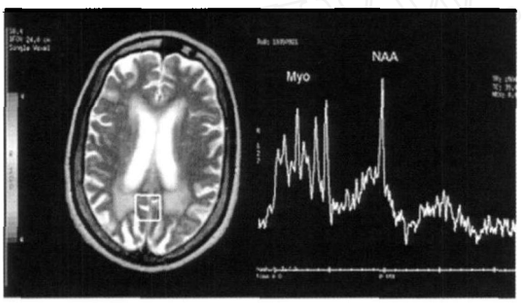

Figure 4. An Elderly AD Patient with Increasing Memory Loss

Notes: (a) Axial T2-weighted image showing cerebral atrophy, as well as some periventricular T2 signal change, in keeping with some microvascular disease. (b) Short echo (TE 35 ms) MRS of the parietal grey matter demonstrating decreased NAA and increased Myo in keeping with Alzheimer's dementia

It is important to monitor the recovery of patients with AD in order to adopt different therapeutic strategies. Memantine, a NMDA receptor antagonist, has demonstrated neuroprotective effects on AD in preclinical studies. To more accurately evaluate the effects of memantine, Schmidt R, et al[32] determined and analyzed the neuroimaging of MR in patients with AD over 1 year. Randomized patients were treated with either placebo or memantine 20 mg/day for 52 weeks. The reduction in total brain volume was similar between memantine and placebo groups, but the reduction in hippocampal volume was markedly less for memantine-treated patients. However, from the regional cerebral NAA and myoinositol MRS, there was no clear trend in NAA and MI concentrations over time in either patient group, but intra-individual variability was large. In clinical measures, memantine-treated patients showed a slower rate of decline than placebo-treated patients. The hippocampal volume may be an available marker in the determination of the AD recovery.

Monitoring the Biomarker of AD

As a progressive neurodegenerative dementia, which results in shrinkage of brain regions, AD is clinically associated with cognitive impairment, loss of language, motor skills and changes in behavior. Early diagnosis of AD is of great importance since only a sufficient treatment in early stages of this disease helps to keep patients in an autonomous state as long as possible. It has been found that AD is pathologically characterized by the presence of extracellularly senile plaques (SPs) which consist of a core of amyloid-β peptide (Aβ), and intracellularly neurofibrillary tangles (NFTs), which are composed of paired helical filaments (PHFs) that consist of aggregation of hyperphosphorylated tau protein, and the selective loss of neurons and synaptic connections. It is difficult to single out a diagnostic biomarker for AD derived from materials routinely obtained.

Besides the whole brain imaging, MRI can also image the correlative SPs in the AD brain. SPs are important pathologic markers for the diagnosis of AD, but SPs are not easily pathognomonic for AD, due to SPs' small size (5-200 mm) and unknown magnetic resonance parameters. Imaging of senile plaques may be possible without contrast reagents, that is, by taking advantage of the intrinsic properties of the Aβ deposit, or the local microenvironment of the plaque. Benveniste H, et al[33] first imaged the SPs when three-dimensional T2 and diffusion MR images with voxel sizes ranging from 3×10^{-3} mm^3 to 5.9×10^{-5} mm^3 were acquired. Their work greatly aids and simplifies the many possibilities to research the SPs pathology in the range of SPs. Pettegrew JW, et al[34] employed phosphorus-31 magnetic resonance spectroscopy to investigate the correlation between SPs and AD, and found that elevations in levels of phosphomonoesters had a negative correlation with the numbers of SPs. Aberrations in the synthesis of membrane phospholipids are early metabolic events in the pathogenesis of AD.

MRI biomarkers for AD may enable earlier clinical diagnosis and the monitoring of therapeutic effectiveness. Cerebrospinal fluid (CSF) is a clear

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Table 1. Herbal Agents for AD Therapy

Herbal agent	Derivation	Effection
Galantamine[37]	European daffodils or common snowdrops	Selective acetylcholinesterase inhibitor
Ginkgo biloba extract[38]	Ginkgo biloba	Effective in the early stages of AD
Huperzine A[39]	A chemical derived from a particular type of club moss (*Huperzia serrata*)	Recovery of memory loss and mental impairment
Vinpocetine[40]	Common periwinkle (*Vinca minor*)	Treatment for memory loss and mental impairment
Curcumin[41, 42]	*Curcuma longa L.*	Anti-Aβ deposition, anti-oxidation

body fluid that occupies the subarachnoid space and the ventricular system around and inside the brain. It acts as a "cushion" or buffer for the cortex, providing a basic mechanical and immunological protection to the brain inside the skull. The combination of nuclear magnetic technique and CSF modalities can improve preclinical diagnostic accuracy of AD.

Kork F, et al[35] measured CSF of AD patients by ^{1}H of NMR and found that specific multipletts at 2.15 ppm and 2.45 ppm, which could not be detected in the majority of healthy control subjects. Moreover, CSF ^{1}H-NMR spectra of AD patients showed specific resonances at 7.03 ppm, 7.19 ppm, 7.43 ppm and at 7.91 ppm. The specific NMR biomarker may be a capable method for detection and quantification of substances in the CSF of early AD patients even without the knowledge of molecular structures. Brys M, et al[36] examined CSF biomarkers: P-tau/total tau (T-tau), Aβ 1-42/Aβ 1-40, isoprostanes (IP) and grey matter concentration (GMC) and medial temporal lobe (MTL) atrophy level in incipient AD by MRI. Forty-five subjects [21 controls normal (NL-NL), 16 stable mild cognitive impairment (MCI) (MCI-MCI), 8 MCI who declined to AD (MCI-AD)] received MRI and lumbar puncture at baseline and after 2 years. At baseline, they found that in the MCI-AD brain the CSF T-tau, P-tau231 and IP were higher as compared with the MCI-MCI or normal brain, while Aβ 1-42/Aβ 1-40 ratio was lower. Also the GMC was low and MTL atrophy was higher in AD brain. Combining baseline CSF-P-tau231 and GMC-MTL significantly increased overall prediction of AD from 74% to 84%. The combination of MRI and CSF modalities can improve preclinical diagnostic accuracy of early AD.

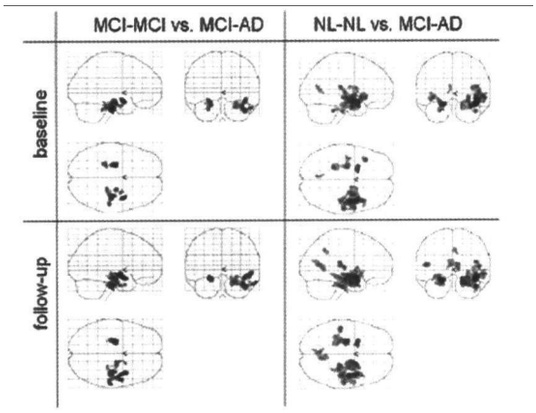

Figure 5. Voxel-based Morphometry Results

Notes: clusters with significantly different GMC in MCI-MCI subjects *vs.* MCI-AD subjects and NL-NL subjects *vs.* MCI-AD subjects at baseline and at follow-up

Prospect

Although AD has been found to be the most common cause of severe mental deterioration (dementia) in the elderly since Dr. Alzheimer first described the disease in 1907, there are no specific drugs to block and recover the disease despite that various agents have been used in an attempt to modify the course or improve the symptoms of AD, while acetylcholinesterase/cholinesterase inhibitors and memantine are the only agents approved by the Food and Drug Administration of the United States for the treatment of AD. Herbal medicine has been used in many diseases, including neurological disorders, and it would play a key role in the AD therapy. There are several herbal medicines that are suggested to be employed for the treatment of AD (Table 1). However, there are questions on how to evaluate the therapeutic effect of the candidate medicine, and how to inspect the development or recovery state of AD to further make more positive therapy strategies. Since the MRI technique provides vivid and accurate neuro-imaging, can detect the brain metabolism and monitor the AD biomarkers changes, it would be helpful and convenient to evaluate the herbal agents and other medicines on the AD treatment.

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