Evaluation of the Role of Magnetic Resonance Spectroscopy in Diagnosing Alzheimer's Disease at a Tertiary Care Hospital

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Hippocampus

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Alzheimers disease

ABSTRACT:

Neurodegenerative disorders encompass a wide range of neurological diseases, often of unknown origin, characterized by genetic predisposition and affecting various neurofunctional systems. These disorders frequently lead to memory disturbances and cognitive impairment, with their prevalence increasing as the population ages. Early detection and accurate classification based on underlying causes are essential for effective management. Magnetic Resonance Imaging (MRI) has become a cornerstone in diagnosing neurodegenerative diseases due to its high tissue contrast, while Magnetic Resonance Spectroscopy (MRS) has emerged as a valuable tool for assessing brain metabolism. MRS provides insights into the biochemical processes occurring in the brain, quantifying metabolites such as N-acetylaspartate (NAA), creatine (Cr), choline (Cho), and myo-inositol (MI), as well as glutamate, glutathione, and gamma-aminobutyric acid (GABA). The aim of this study is to explore the application of 1H-MRS in detecting metabolic changes in individuals with dementia and MCI, comparing them to healthy controls, and distinguishing between various neurodegenerative conditions. By providing a comprehensive view of metabolic alterations, MRS holds promise in advancing the early diagnosis, monitoring, and treatment strategies for neurodegenerative diseases.

Objectives: To evaluate metabolic irregularities in individuals presenting with dementia and neuro cognitive impairment using MRS and to evaluate utility of MRS in detecting prodromal signs of Alzheimers disease.

Methods: A total of fourty cases were included.
All patients aged above 18 years with known cases of alzheimers disease and

age matched normal patients.
MRI Procedure: Based on inclusion criteria with informed consent MRI brain along with MR spectroscopy is done.
MRI Analysis: MRI brain is used to assess the brain atrophy and diagnose the alzheimers disease. MR spectroscopy is used to assess the metabolic ratios in hippocampus.
ROC analysis is done to derive the cutoff of metabolic ratios for early detection of alzheimers disease.

Results: among 40 patients, 26 males and 16 female subjects were enrolled in this study. MRS showed that naa/cr ratio is significantly reduced (p value <0.001, sensitivity 55%, specificity 80%). ROC analysis revealed estimated cutoff values of naa/cr is <1.51 and we propose this cutoff for early detection of alzheimers disease.

Conclusions: Magnetic Resonance Spectroscopy (MRS) can serve as a valuable screening tool in the neuroimaging of neurodegenerative diseases and may also function as an adjunctive marker for detecting preclinical Alzheimer's disease in clinical practice.

1. Introduction

Neurodegenerative disorders refer to a diverse group of neurological diseases, primarily of unknown origin, characterized by genetic predisposition. These disorders can affect single or multiple neurofunctional systems, leading to memory disturbances and cognitive impairment. Early detection and later division of patient based up on underlying causes are crucial [(1)]. As society ages, the incidence of neurodegenerative disease increases, highlighting the significance of neurological imaging in their detection and treatment.
MRI has become an essential device for diagnosing neurodegenerative illnesses because of its superior tissue contrast in comparison to other diagnostic methods. In addition to morphological MRI, MRS is becoming essential for evaluating metabolite levels in both healthy and ill persons [(2)]. MRS offers comprehensive data on tissue characterisation, specifically emphasizing the structural and functional alterations in metabolic reactions happening in the brain.

Recently extensive research is being conducted to build stratification systems with the goal of decelerating the advancement of AD, which is the leading cause of neurodegenerative dementia. Structural, functional neuroimaging, along with the evaluation of neuronal biomarkers, are essential for assessing cerebral disease and enabling appropriate treatment techniques. Proton MRS is a technique that utilizes hydrogen nuclei (1H) to analyze brain chemistry. It is useful for quantifying metabolites such as Naa, mi, cho, and cr [(3)]. Additional metabolites which can be measured using MRS include glu, glutathione, glutamate, and GABA.

The process of ageing is a prominent contributing factor for the development of dementia, which is a notable health issue that becomes more prevalent as life expectancy increases.

Typical conditions linked to dementia and MCI comprise AD, cerebrovascular disease, DLB, VaD and FTLD [(4)].

1H- MRS is highly useful in evaluating the metabolic status of various situations like cerebral lesions, post-radiotherapy monitoring, de-myelinating diseases like MS and leukodystrophy, hepatic encephalopathy, ischemic, traumatic brain injuries, and epilepsy evaluation [(5)]. The present study is centered on the basic principles of 1H-MRS, including its many methodologies, the typical spectrum found in adults, and its therapeutic applications. The primary goal is to identify metabolic changes in MRS (Magnetic Resonance Spectroscopy) in individuals with dementia and MCI compared to normal settings. Additionally, the aim is to differentiate the distinctions among these common neurological illnesses.

2. Objectives

1. To evaluate metabolic irregularities in individuals presenting with dementia and neuro cognitive impairment using MRS
2. To evaluate utility of MRS in detecting prodromal signs of Alzheimer's disease.
3. To establish correlations between findings of current study and other MRI sequences for identifying initial degenerative brain changes.
4. To enhance diagnostic precision for neurodegenerative conditions.

3. Methods

Inclusion criteria:

Patients who are suspected clinically of having a neurodegenerative disease, but the disease state is ambiguous.

Patients who have a h/o neurodegenerative disease

Patient aged 35 years or older, regardless of gender.

The subjects consist of age matched individuals who underwent MRIs for other purposes and exhibit normal findings.

Exclusion criteria:

Patients who exhibit signs of neuro cerebral illness that impair neurological function (e.g., cerebral infection, head trauma, substance misuse or psychiatric disorders)

Patients who have underwent neurological surgery

Patients who have implants or cardiac pacemakers

Following the acquisition of signed informed consent, the investigator used a pre-structured proforma to study each participant's clinical presentation and demographics. Also, all the group 1 were subjected to MRI scan. The lead investigator recorded the clinical presentation on the same proforma in which all the findings were submitted.

patients with clinical suspicion of neuro degenerative disease

↓

consent will be taken from the patient

↓

Group 1 subjects will be dementia and cognitively disabled individuals diagnosed with Alzheimer's disease, based on clinical and imaging diagnosis. Group 2 subjects will be cognitively well patients who were referred for imaging for other indications and showed normal brain neuroimaging.

↓

MRI along with MR spectroscopy will be performed

↓

The metabolites naa, cr, mi and cho will be measured and the metabolic ratios naa/cr, cho/cr, mi/cr and naa/mi will be calculated for group 1 and group 2.

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The metabolic ratios of group 1 will be compared to those of group 2 and their clinical diagnosis.

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ROC analysis will be used to get cut off values with appropriate senstivity and specficity.

4. Results

The study consisted of 40 participants, with an equal distribution of 20 participants in group 1 and 2. The MR images assisted in the evaluation of occurrence and specific location of atrophy of brain in group 1. Out of these group 1, all 20 patients displayed brain atrophy.

The assessment of ratios in the hippocampus involved calculating the average values, measuring the variability with standard deviations, determining the confidence intervals, evaluating the statistical significance with p-values, and creating receiver operating characteristic curves.

the case subjects showed a reduction in Naa/cr in comparison with the group 2 (p = 0.010, sensitivity 55%, specificity 80%).

The group 1 also showed reduced cho/cr, mi/cr and naa/mi, Nevertheless, it is crucial to emphasize that these disparities were not statistically significant in our investigation (cho/cr p - 0.445, mi/cr p - 0.811, naa/mi p - 0.540).

Table 1: Age distribution of patients

Age	Frequency	percentage
30 – 40	4	10
41 – 50	9	23
51 – 60	10	25
61 – 70	11	27
>70	6	15
Total	40	100

Chart 1: age wise distribution of patients

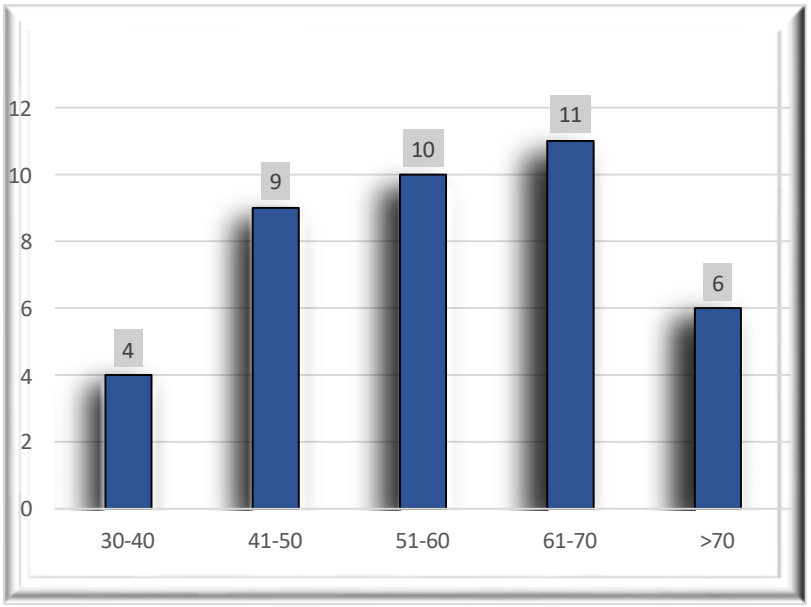


Table 2: Gender distribution of patients

Gender	Frequency	Percent
Male	26	65
Female	14	35
Total	40	100

Chart 2: gender wise distribution of patients

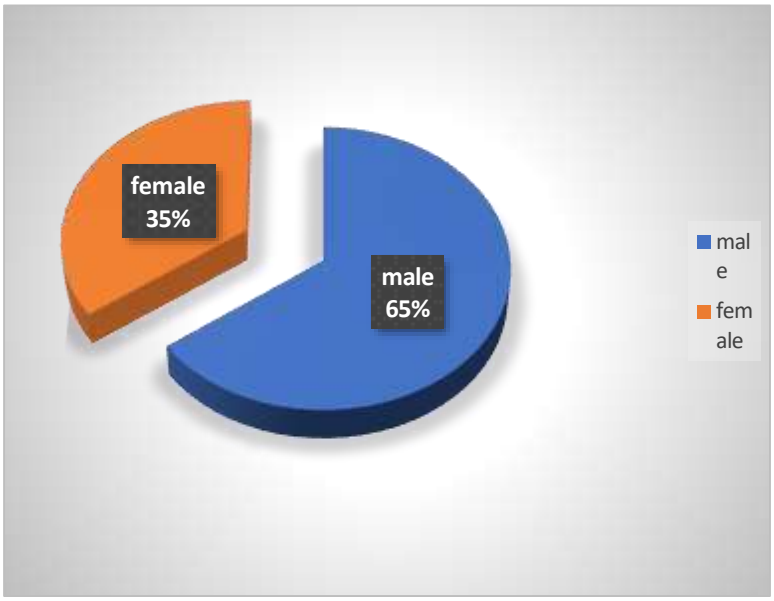


Table 3: group 1 subjects' distribution according to the clinical and imaging diagnosis

Diagnosis	Frequency	percentage
Alzheimers disease	18	90
Parkinsins disease	2	10
Total	20	100

Table 4: mean values of metabolic ratios in hippocampus

Metabolic ratios		N	Mean	SD
Naa/cr	Group 1	20	1.532	0.228
	Group 2	20	1.814	0.376
Cho/cr	Group 1	20	0.731	0.128
	Group 2	20	0.768	0.083
Mi/cr	Group 1	20	0.439	0.087
	Group 2	20	0.449	0.069
Naa/mi	Group 1	20	2.909	0.318
	Group 2	20	3.196	1.313

Table 5: confidence interval and p-value in hippocampus

Metabolic ratios	95% CI of differences		p-value	significance
naa/cr	1.432	1.632	0.010	SIG
	1.649	1.979		
cho/cr	0.675	0.787	0.445	NOT SIG
	0.732	0.804		
mi/cr	0.401	0.477	0.811	NOT SIG
	0.419	0.479		
Naa/mi	2.770	3.048	0.540	NOT SIG
	2.621	3.771		

Table7: Area under curve

Type	Variable of test result	AUC	95% CI	
			Lower bound	Upper bound
Hippocampus	Naa/cr	0.713	0.548	0.844
	Naa/mi	0.563	0.397	0.719
	Cho/cr	0.571	0.405	0.726
	Mi/cr	0.523	0.359	0.683

Chart 1: ROC curve analysis of naa/cr in hippocampus

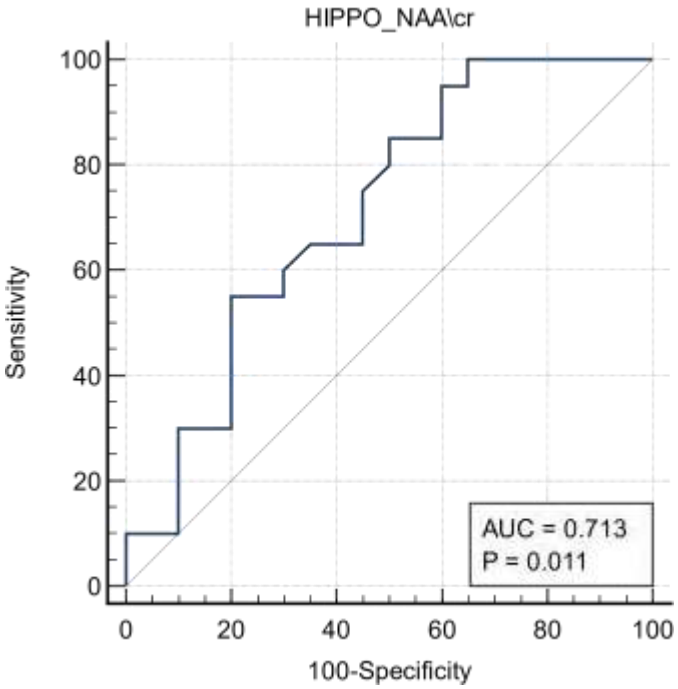


Table 8: proposed threshold values for significant ratios

Metabolic ratios	Positive if < or =	Sensitivity	Specificity
Naa/cr	1.51	55%	80%

CASE 1

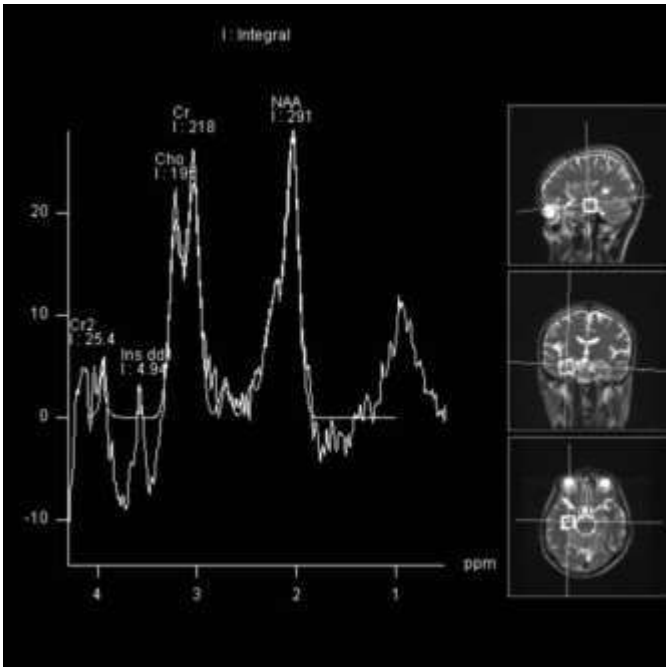
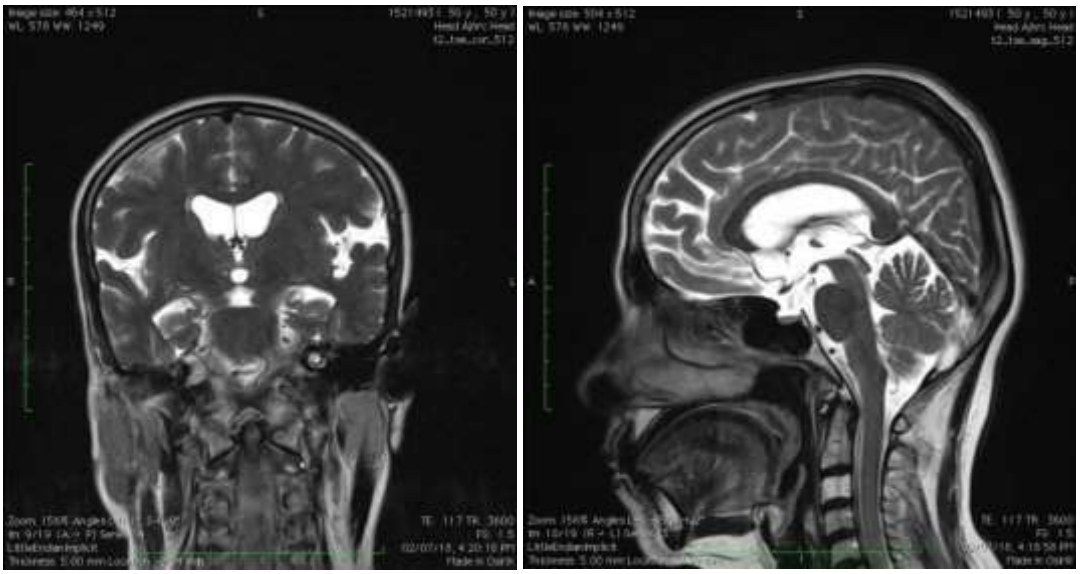


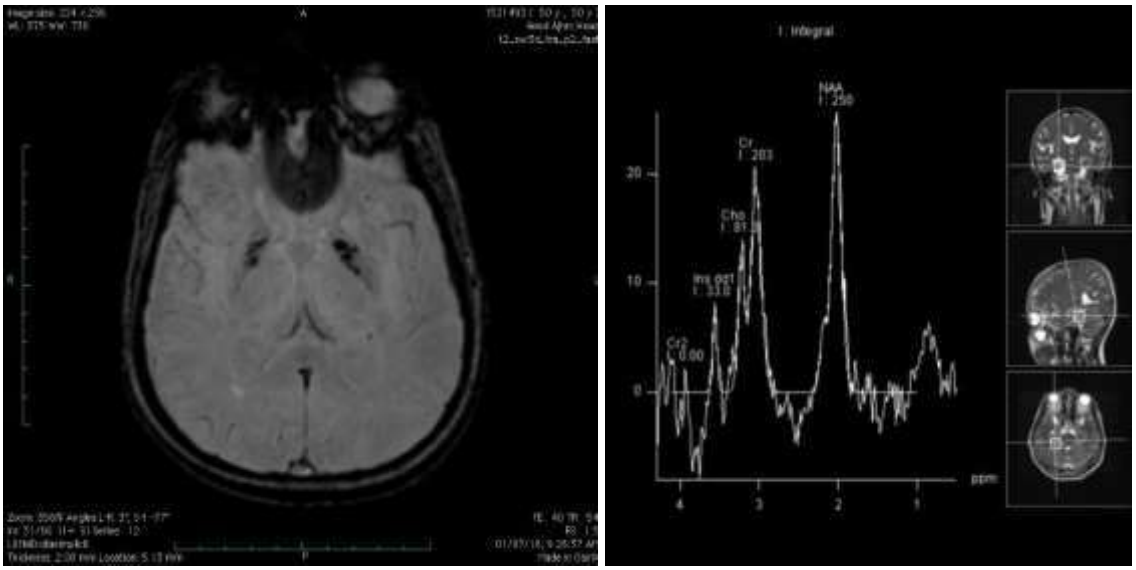
Fig.1 showing MR spectra obtained from right hippocampus in a case of alzheimer's disease

CASE 2



A **B**

Fig A & B – Shows T2 W coronal and sagittal images of 55-year-old patient with Alzheimer's disease showing atrophy of bilateral frontal and temporal lobes.



C **D**

C – axial SWI shows blooming in bilateral basal ganglia

D – MR spectra obtained from hippocampus

5. Discussion

Alzheimers disease is commonest type of neurodegenerative dementia, which led to substantial study on treatments that could potentially slow down its course. It is essential to create a system that can identify individuals susceptible to development of prodromal Alzheimers disease. This is important because it allows for the implementation of preventative medicines during the initial stages of disease. MRS has showed its efficacy in repeatedly assessing metabolites of brain in a non-invasive manner. MRS, when used alongside conventional MRI, functions as a diagnostic and monitoring technique for identifying early biochemical brain anomalies related to Alzheimers disease-associated dementia [(6)]. The priority objective of our investigation was to confirm effectiveness of traditional MRS as a screening technique for prodromal Alzheimer's disease. Our research shows that specific ratios of metabolites, specifically Naa/cr ratio can be used as reliable benchmarks to predict an elevated risk of alzheimers disease in patients.

Our study involved the evaluation of 40 patients, with 20 of them having cognitive impairment and the other 20 being cognitively normal group 2. The mean age of patients, ranging from 61 to 70 yrs old, corresponds to the results of Katz et al., who showed a rapid rise in the occurrence of dementia as age increases, reaching its highest point between 60 and 80 years old. Our study also confirmed Peterson et al.'s finding that the occurrence of dementia and MCI is more in males compared to females.

The subjects exhibited diverse clinical manifestations. Most of the individuals in the group 1 reported experiencing overall weakness (60%) and dementia (30%), while the group 2, who had normal cognitive function, commonly complained of dizziness and headaches. Out of the 20 individuals being studied, 18 (90%) were determined to have Alzheimer's disease using clinical and imaging criteria. Among these, 5 (28%) exhibited significant atrophy in the temporal lobe as observed on MRI scans. 10% of the remaining group 1 are diagnosed with Parkinsons disease.

The experiment revealed a significant reduction in the Naa/cr ratio in the hippocampus of persons with the disorder, in comparison to individuals with normal cognitive function. The observed difference was statistically significant (p-value < 0.001), with a sensitivity of 55.0% and specificity of 80.0%. However, the ratios of Cho/Cr, mI/Cr and naa/mi did not show any statistically significant differences in the hippocampus. - and The p-value for cho/cr in the hippocampus is 0.445, p-value for mi/cr in the hippocampus is 0.811, while the p-value for naa/mi is 0.540 The low Naa/cr ratios in the hippocampus is regarded as the most dependable sign of an elevated likelihood of clinical progression to Alzheimer's disease in cognitively normal persons.

Kantarci et al conducted research that showed a reduction in Naa/cr ratio in hippocampal region in individuals with Alzheimers disease. Additionally, they observed a reduction in the Naa/cr ratio in various types of dementia, such as vascular and frontotemporal

dementia [4-6]. Hence, it is imperative to distinguish between typical types of dementia by employing traditional MRI and MRS techniques. The results of our study have verified that the case individuals have lower Naa/cr ratios in the hippocampus. This indicates that these patients are more likely to acquire neurodegenerative disorders, and therefore, additional research is required.

Our work revealed a noteworthy discovery of a substantial decrease in the Naa/cr ratio in the hippocampus. This finding aligns with previous studies conducted by Waragai et al and Schott et al Both studies have found the Naa/mi ratio as most accurate indicator for differentiating between patients and group 2, highlighting its potential as a marker for predicting an elevated risk of clinical progression to Alzheimers disease. Our study has also identified lower Cho/Cr and mi/Cr ratios in the hippocampus, which is consistent to the findings from previous studies. However, the inability to establish statistical significance prevented the determination of sensitivity and specificity.

Our study encountered many constraints. The presence of motion and susceptibility artifacts presented significant technical obstacles. Our study group found that older individuals, especially those with cognitive impairment, encountered motion abnormalities that prevented the recording of MR spectra. Occasionally, while placing VOIs in the hippocampus region, susceptibility artifacts may arise, which might complicate the interpretation of metabolic ratios. Inadequate field uniformity led to decreased signal-to-noise ratios and the widening of peaks. While obtaining single voxel data from many brain regions would have been advantageous, it would have lengthened the acquisition technique, resulting in a longer scan time. Another constraint was the lack of neuropath verification of diagnosis, as it is still challenging to distinguish between common dementias merely based on clinical observations.

Ultimately, MRS shows potential as a diagnostic tool for neurodegenerative disorders. Nevertheless, additional investigation is necessary to fully understand its function in differentiating various types of dementia. The use of naa/cr ratio, determined using MRS, in the hippocampus, should be reevaluated as potential additional screening indicators for early-stage Alzheimers disease in clinical settings.

Conclusion: Magnetic Resonance Spectroscopy (MRS) can serve as a valuable screening tool in the neuroimaging of neurodegenerative diseases and may also function as an adjunctive marker for detecting preclinical Alzheimer's disease in clinical practice.

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