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Review Article

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Diagnostic Tools for Alzheimer's Disease: A Narrative Review Based on Our Own Research Experience

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ABSTRACT

Alzheimer's disease (AD), one of the most representative neurodegenerative diseases, has diverse neurobiological and pathophysiological mechanisms. Treatment strategies targeting a single mechanism have repeated faced failures because the mechanism of neuronal cell death is very complex that is not fully understood yet. Since complex mechanisms exist to explain AD, a variety of diagnostic biomarkers for diagnosing AD are required. Moreover, standardized evaluations for comprehensive diagnosis using neuropsychological, imaging, and laboratory tools are needed. In this review, we summarize the latest clinical, neuropsychological, imaging, and laboratory evaluations to diagnose patients with AD based on our own experience in conducting a prospective study.

Keywords: Dementia; Biomarkers; Diagnosis

INTRODUCTION

The World Health Organization has estimated that by 2050, the world's population of those aged more than 60 years will reach 20 billion. Population aging is expected to progress rapidly. The prevalence of neurodegenerative diseases and dementia commonly found in the elderly is also expected to increase. The prevalence of dementia is increasing worldwide. Related medical expenditures by country are also rapidly increasing. Dementia has become one of the highest priorities among public health policy issues.

The National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria established in 1984 were the earliest diagnostic criteria for Alzheimer's dementia. These criteria were based on the concept considering Alzheimer's dementia as a clinicopathological entity. The NINCDS-ADRDA criteria were designed with the expectation that if patients

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Conflict of Interest

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had real Alzheimer's disease (AD) pathology (amyloid and hyperphosphorylated tau), their clinical presentation would meet the criteria (dominant memory decline) in most cases. However, over the next 30 years, it became clear that this clinicopathological relationship was inconsistent. AD pathology might present with clinically atypical symptoms, marked language, and visuospatial or frontal impairments. Therefore, the National Institute of Aging and the Alzheimer Association (NIA-AA) has recently revised the criteria for AD and a conceptual distinction has been established between the pathophysiological process of AD and various clinical syndromes resulting from it. Among them, the most important point is that biomarkers related to AD pathology are integrated into the A (amyloidopathy)/T (tauopathy)/N (neuronal injury) (ATN) system and various stages of the disease are distinguished in the diagnostic criteria.

However, AD is not simply described by the ATN system. It is considered to have multiple neurobiological and pathophysiological mechanisms. Because mechanisms of neuronal death are complex, single-mechanism targeting amyloidopathy strategies have often failed spectacularly in late-stage clinical trials.[1]

Recently, many new diagnostic techniques have been proposed to evaluate diverse clinical phenotypes, neuropathology, and pathophysiological mechanisms. This paper provides a narrative review of diagnostic tools for AD, based on our own experience in a prospective study.

CLINICAL DIAGNOSIS AND BIOLOGICAL DEFINITION OF AD

The NINCDS-ADRDA diagnostic criteria of 1984 established that AD diagnosis should be confirmed with post-mortem pathology. This guideline was used as a de facto clinical diagnostic criterion. However, owing to the development of various biomarkers, the 2007 International Working Group (IWG) and 2011 NIA-AA criteria approached AD with a combination of clinical diagnosis and biomarkers. The 2018 NIA-AA research criteria first tried to define AD only with biomarkers.[2] However, recently, the 2021 IWG criteria have reverted to a combination of clinical diagnosis and biomarkers. Here, we will cover the 2018 NIA-AA research framework and the 2021 IWG criteria.[3] Unlike existing diagnostic criteria, the 2018 research criteria biologically defined AD using updated biomarkers, and treated clinical symptoms separately as symptoms/signs caused by this disease. Thus, compared to existing diagnostic criteria based on clinical symptoms, the separation of clinical symptoms-biomarkers and AD as changes in biomarkers is a significant shift in thinking. The categorical cognitive stage for an observational study was divided into 3 stages independent of biomarker classification: cognitively unimpaired, mild cognitive impairment, and dementia. This classification included all combinations (**Tables 1** and **2**).[2]

In 2021, the IWG presented recommendations based on the clinical phenotypes and biomarkers for clinical diagnosis of AD (**Table 3**).[3] In addition, in the 2018 NIA-AA research criteria, a critical position was presented on the section defined as preclinical AD, emphasizing that patients with cognitive impairment who were positive for amyloid and tau on biomarkers did not show clinical symptoms throughout their lifetime and that the corresponding Alzheimer's pathology findings could be seen as comorbidities in other brain diseases as well. Furthermore, it has been suggested that biomarker positivity in the asymptomatic stage is not a disease state, but a risk state for disease progression.[3]

Table 1. ATN biomarker classification[2]

Biomarker	Description
A	Aβ aggregation or related pathological conditions Decreased CSF Aβ42, or Aβ42/Aβ40 ratio Amyloid PET positive
T	Aggregation of tau (neurofibrillary tangles) or associated pathological conditions Increased CSF phosphorylation of tau Tau PET positive
(N)	Neurodegeneration or neuronal injury MRI brain atrophy FDG PET brain metabolism increased Increased CSF Total-tau

As biomarkers of neurodegeneration can show abnormalities because of causes other than Alzheimer's disease, parentheses are used to distinguish them from amyloidosis or pathological tau, which are specific indicators of Alzheimer's disease.
A: amyloidopathy, T: tauopathy, N: neuronal injury, Aβ: β-amyloid, PET: positron emission tomography, MRI: magnetic resonance imaging, CSF: cerebrospinal fluid, MRI: magnetic resonance imaging, FDG: fluorodeoxyglucose.

Table 2. Descriptive nomenclature by combining biomarkers and cognitive stages by the National Institute of Aging and the Alzheimer Association Research Framework, 2018[2]

Biomarker	Cognitive stage		
	Cognitively unimpaired	MCI	Dementia
A-T–(N)–	Normal AD biomarkers, cognitively unimpaired	Normal AD biomarkers with MCI	Normal AD biomarkers with dementia
A+T–(N)–	Preclinical Alzheimer's pathologic change	Alzheimer's pathologic change with MCI	Alzheimer's pathologic change with dementia
A+T+(N)– A+T+(N)+	Preclinical Alzheimer's disease	AD with MCI (prodromal AD)	AD with dementia
A+T–(N)+	Alzheimer's and concomitant suspected non-Alzheimer's pathologic change, cognitively unimpaired	Alzheimer's and concomitant suspected non-Alzheimer's pathologic change with MCI	Alzheimer's and concomitant suspected non-Alzheimer's pathologic change with dementia
A–T+(N)– A–T–(N)+ A–T+(N)+	Non-Alzheimer's pathologic change, cognitively unimpaired	Non-Alzheimer's pathologic change with MCI	Non-Alzheimer's pathologic change with dementia

A: amyloidopathy, T: tauopathy, N: neuronal injury, AD: Alzheimer's disease, MCI: mild cognitive impairment.

As such, the NIA-AA and IWG have different views on whether to analyze biomarkers separately from clinical diagnosis or to approach them in combination. Longitudinal studies can establish the role of each biomarker and its associated AD stage with more clarity. Moreover, target identification for new disease-modifying treatments can provide an answer to the question of how best to use both clinical diagnosis and biomarkers to diagnose AD.

In this review, we will summarize different tests and imaging techniques used to evaluate and diagnose patients with AD.

NEUROPSYCHOLOGICAL TEST

The primary goal of neuropsychological evaluation in clinical research involving patients with dementia is to objectively evaluate patient cognitive function, daily living function, emotion, and behavior. Another goal is to synthesize them to determine the severity of dementia. Additionally, such evaluation aims to objectively and quantitatively track spectral changes related to research topics.

Cognitive function assessment

Cognitive function evaluation is conducted objectively to evaluate participants' cognitive functions. Through comparison with norms, the normality of cognitive function was confirmed and used for diagnosing patients with cognitive complains. Because the degree

Table 3. Diagnosis of Alzheimer's disease in a clinical setting suggested by the International Working Group, 2021[3]

Amyloid	Tau	Possibility of Alzheimer's disease as a primary diagnosis	Further investigation
Common Alzheimer's disease phenotypes (amnestic variant, logopenic variant of primary progressive aphasia, and posterior cortical atrophy)			
+	+	Highly probable–established	None required
+	Unknown	probable	Consider a tau measure (PET, CSF)
+	–	Probable	Consider an additional tau measure (PET, CSF)
Unknown	+	Possible	Consider an amyloid measure (PET, CSF)
–	+	Possible	Consider an additional amyloid measure (PET, CSF)
–	Unknown	Unlikely	Full investigation of cause and consider a tau measure (PET, CSF)*
Unknown	–	Unlikely	Full investigation of cause and consider an amyloid measure (PET, CSF)*
–	–	Highly unlikely–excluded	Full investigation of cause*†
Unknown	Unknown	Non-assessable	Consider tau and amyloid measures (PET, CSF)
Uncommon Alzheimer's disease phenotypes (behavioural or dysexecutive variant, corticobasal syndrome, non-fluent variant of primary progressive aphasia, and semantic variant of primary progressive aphasia)			
+	+	Probable	None required; careful follow-up needed: an incongruent clinical phenotype and neurodegeneration pattern should trigger a new investigation*
+	Unknown	Possible	Consider a tau measure (PET, CSF)
+	–	Possible	Consider an additional tau measure (PET, CSF)
Unknown	+	Unlikely	Full investigation of cause and consider an amyloid measure (PET, CSF)
–	+	Unlikely	Full investigation of cause*
–	Unknown	Highly unlikely–excluded	Full investigation of cause*†
Unknown	–	Highly unlikely–excluded	Full investigation of cause*†
–	–	Highly unlikely–excluded	Full investigation of cause*†
Unknown	Unknown	Non-assessable	Full investigation of cause and consider tau and amyloid measures (PET, CSF)*
Other phenotypes (e.g., dementia with Lewy bodies, Richardson syndrome, Huntington's disease, and amyotrophic lateral sclerosis)			
Amyloid positive, or tau positive, or both		Unlikely	Full investigation of cause
–	Unknown	Highly unlikely–excluded	Full investigation of cause
Unknown	–	Highly unlikely–excluded	Full investigation of cause
–	–	Highly unlikely–excluded	Full investigation of cause
Unknown	Unknown	Highly unlikely–excluded	Full investigation of cause

PET: positron emission tomography, CSF: cerebrospinal fluid.
*Full investigation of the cause depends on the specific clinical phenotype and can imply, for example, 18F-fluorodeoxyglucose PET, dopamine imaging, progranulin serum dosage, genetic analysis, oculomotor recordings, or electromyoneurography.
†Consider a new Alzheimer's disease biomarker investigation only if there is reasonable doubt regarding the validity of the biomarker results.

of performance is scored, it can be used for effect verification such as for before and after the comparison. Brief evaluation can be used as a marker for dementia screening, target selection, and overall popularity. The Korean Mini-Mental Status Examination-2 (K-MMSE- 2), the Korean Montreal Cognitive Assessment (K-MoCA), and the Montreal Cognitive Assessment-Korea (MoCA-K) are used. A comprehensive evaluation examines various cognitive domains in detail. The Seoul Neuropsychological Battery-II (SNSB-II), the Seoul Neuropsychological Battery-Core (SNSB-C), the Consortium to Establish a Registry for Alzheimer's Disease-Korea (CERAD-K), the Literacy Independent Cognitive Assessment (LICA), short form of the Literacy Independent Cognitive Assessment (LICA-S), the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), and Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog) are used as comprehensive evaluation tools.

Recently, in addition to these single neuropsychological tests, a composite score has been developed and used by combining each sub-cognitive test.[4] The development of a composite score for evaluating preclinical patients with AD based on clinical test results is currently in progress. Furthermore, composite scores with various configurations and purposes have been developed and used thus far. While this cognitive composite score has the advantage of being able to sensitively detect early cognitive function deterioration such as preclinical AD and prodromal AD (meaning that patients do not have cognitive decline assessed by

neuropsychological test, although they are positive for biomarkers), it might be insufficient to reflect the overall cognitive function spectrum of AD. In addition, score changes in one cognitive function domain (mainly memory) have the disadvantage of canceling out all small changes in other domains. Therefore, a cautious approach is needed for use and interpretation.

Assessment of dementia severity

Dementia severity assessment refers to the process of rating a patient dementia-related severity from normal to severe. The clinical dementia rating (CDR) scale is the most widely used scale with 6 areas individually evaluated and combined. Together with the global CDR score, CDR-sum of boxes (CDR-SB) score is actively used as a representative score for tracking overall state change and severity. The global deterioration scale (GDS) is used for a relatively simple evaluation of a patient's overall condition. Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC) is used when the change in a patient's state is reflected in the score.

Activities of daily living assessment

Dementia is defined as a condition in which life functioning difficulties are caused by cognitive decline. Therefore, daily living assessment is an essential part of dementia evaluation. The Korea Instrumental Activities of Daily Living Scale (K-IADL) is the most actively used scale in clinical trials in Korea. Additionally, Alzheimer Disease Cooperative Study ADL (ADCS-ADL) scale can be used to identify specific activities of daily living in detail for clinical research. It is highly useful. Therefore, it is important to secure guardians who can report with a high reliability.

Neurobehavioral symptom assessment

Neurobehavioral symptom assessment is important for improving the quality of life of patients and guardians. It is a major topic of research. Neurobehavioral symptoms have various categories, such as psychotic symptoms (e.g., delusions and hallucinations), abnormal behaviors (e.g., disinhibition or repetitive behaviors), emotional labilities, personality changes, insomnia, and dietary changes. The Behavioral Pathology in Alzheimer's Disease (BEHAVE-AD) rating scale, Neuropsychiatric Inventory (NPI), and Neuropsychiatric Inventory-Questionnaire (NPI-Q) are mainly used to quantify neurobehavioral symptoms of dementia patients. The Mild Behavioral Impairment Checklist (MBI-C) developed to identify minor abnormal behaviors that might appear in the pre-stage of dementia is frequently used. Since most cases depend on guardian reports, the presence of guardians who can reliably report differences between pre-morbidities is important. For some symptoms, patient interviews need to be combined.

NEUROIMAGING TEST: MAGNETIC RESONANCE IMAGING (MRI)

Primary role of MRI for AD is to evaluate AD-related brain atrophy and underlying small vessel disease (SVD). Researchers can also assess blood-brain barrier (BBB) integrity using dynamic contrast enhancement (DCE) and iron accumulation with quantitative susceptibility mapping (QSM).

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Cortical atrophy

The Global Cortical Atrophy (GCA) scale was first developed to measure cortical atrophy in stroke patients with or without dementia. The GCA is a visual scale that assesses atrophy in 13 different brain regions and assigns a sub-score (0 to 3) for each of brain regions (frontal, parieto-occipital, and temporal sulcal dilation, and dilatation of the ventricles).[5]

A typical finding of cortical atrophy in AD is medial temporal atrophy (MTA). The Scheltens scale is mostly used to identify this atrophy (**Supplementary Fig. 1**).[6] However, entorhinal cortex atrophy, which has been demonstrated to occur early in the development of AD, is not captured by the MTA score, despite its frequent use. To distinguish between individuals with AD and healthy controls, another scoring system named entorhinal cortical atrophy has been established.[7]

The MTA scale should be rated on coronal T1-weighted images (T1WIs) of a slice through the corpus of the hippocampus (at the anterior pons level). The scale is based on a visual score of the width of the choroid fissure, width of the temporal horn, and height of the hippocampal formation. Inter-examiner agreement is higher in the coronal plane perpendicular to the anterior commissure-posterior commissure line than in the coronal plane parallel to the brain stem axis.[8,9]

Originally, a score of ≥2 for those aged <75 years and a score of ≥3 for those aged ≥75 years were interpreted as abnormal. However, recently, decade-specific MTA cut-off scores for clinical use have been proposed and used. However, in patients aged >85 years old, the practical usefulness of the MTA cutoff is limited (**Table 4**).[10]

White matter hyperintensity (WMH)

Imaging findings of microvascular pathology, also known as a SVD in AD, include lacunes, WMH, cerebral microbleed, and enlarged perivascular spaces (ePVSs).[11] Among them, WMH is the most widely investigated and validated for SVD marker until now. WMH is also an imaging factor that is correlated with cognitive aging and AD.[12] Although the severity of WMH can be measured statistically or semi-quantitatively, currently no gold standard exists. In 1987, Fazekas et al.[13] first described WMH as a periventricular halo, punctate, or early confluent hyperintensity observed in AD. This Fazekas scale is the most commonly used. It can distinguish periventricular versus deep WMH and score them according to a 4-point scale (0–3).

The modified rating scale of WMH proposed by the Clinical Research for Dementia of South Korea (CREDOS) study was used to evaluate the severity of WMH. The WMH scale was classified as minimal, moderate, or severe according to periventricular and deep WMH ratings. T1-weighted axial, T2-weighted axial, and fluid attenuated inversion recovery (FLAIR) images were used for assessment. Rating mechanisms for periventricular and deep WMH ratings are described in **Table 5**.[14]

Table 4. Optimal medial temporal atrophy cut-off values according to age[10]

Age (yr)	Abnormal value	Sensitivity (%)	Specificity (%)	AUC
<65	≥1	83.3	86.4	84.8
65–74	≥1.5	73.7	84.6	79.1
75–84	≥2	73.7	76.2	75.0
>85	≥2	84.0	62.5	73.3

Sensitivity and specificity values and (computed with receiver operator characteristic curves) for medial temporal atrophy visual rating scale (Scheltens) on computed tomography as markers for patients with Alzheimer's disease compared to patients with subjective cognitive impairment.
AUC: area under the curve.

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Table 5. Modified rating scale of white matter hyperintensity according to Clinical Research for Dementia of South Korea[14]

Variable	D1 (<10 mm)	D2 (10–24 mm)	D3 (>25 mm)
P1 (capping/banding, both <5 mm)	Minimal	Minimal	Moderate
P2 (in between)	Minimal	Moderate	Moderate
P3 (capping/banding, either ≥10 mm)	Minimal	Moderate	Severe

The longest length of the perpendicular or radial deep white matter was selected to measure D. To measure P, we selected the longest capping or banding length of the periventricular white matter.
D: deep white matter changes, P: periventricular white matter changes.

Quantification of barrier leakage

In 1991, Toft first proposed a mathematical model for BBB permeability calculations using a DCE technique. In the case of a gadolinium contrast agent, the molecular weight is as low as 550 Da, Thus, a relatively fine degree of transmittance can be measured.

The basic principle of DCE imaging is to measure temporal changes in tissue T1 by administering a gadolinium contrast agent and repeatedly acquiring T1WIs for at least several minutes. At this time, the contrast agent concentration can be estimated from T1 signal change. After obtaining the contrast agent-time curve, the degree of distribution of the contrast agent in the tissue can be determined through pharmacokinetic analysis. This distribution is determined based on several physiological indicators, such as arterial input function, which is one of the least affected indicators by imaging conditions or imaging techniques.[11]

The Harmonizing Brain Imaging Methods for Vascular Contributions to Neurodegeneration (www.harness-neuroimaging.org) Initiative launched in 2016 announced consensus recommendations for the implementation and future development of BBB leakage imaging in 2019.[15] These recommendations include adequate acquisition time, use of pre-injection T1 map, appropriate pharmacokinetic model (typically Patlak model), use of vascular input function in a large venous sinus, and use of Ktrans reported as “leakage rate” of the gadolinium contrast agent.[14]

QSM

QSM is an actual quantification map for local susceptibility based on multi-dynamic multi-echo 3-dimensional (3D) Gradient echo images. QSM can be used to evaluate iron accumulation that is potentially associated with neurodegenerative disease.[12]

MRI protocol details for image analysis

Table 6 shows a comprehensive MRI protocol that can be used to evaluate patients with dementia. Depending on the purpose of the research, researchers can further tailor the MRI protocol. In terms of FLAIR, researchers can choose either 3D or 2D depending on the purpose and the feasibility. 2D T2WI can be omitted if the examination time is very limited and differentiating ePVS and lacunes is not the major concern of the research. In fact, ePVSs can be best visualized and evaluated with T2W.[12]

Image analysis software

Recently, various brain volume quantitative analysis software for the brain have been introduced. Expert opinions and recommendations for clinical application of brain volume analysis software using brain MRI have also been introduced.[16] Clinical quantitative analysis software can obtain results within 5 to 6 minutes on a 1.5T or higher MRI machine based on 3D T1WIs. Thus, it can be used relatively easily in many medical institutions.[16,17] Since 2017, several quantitative analysis and classification clinical software using artificial intelligence

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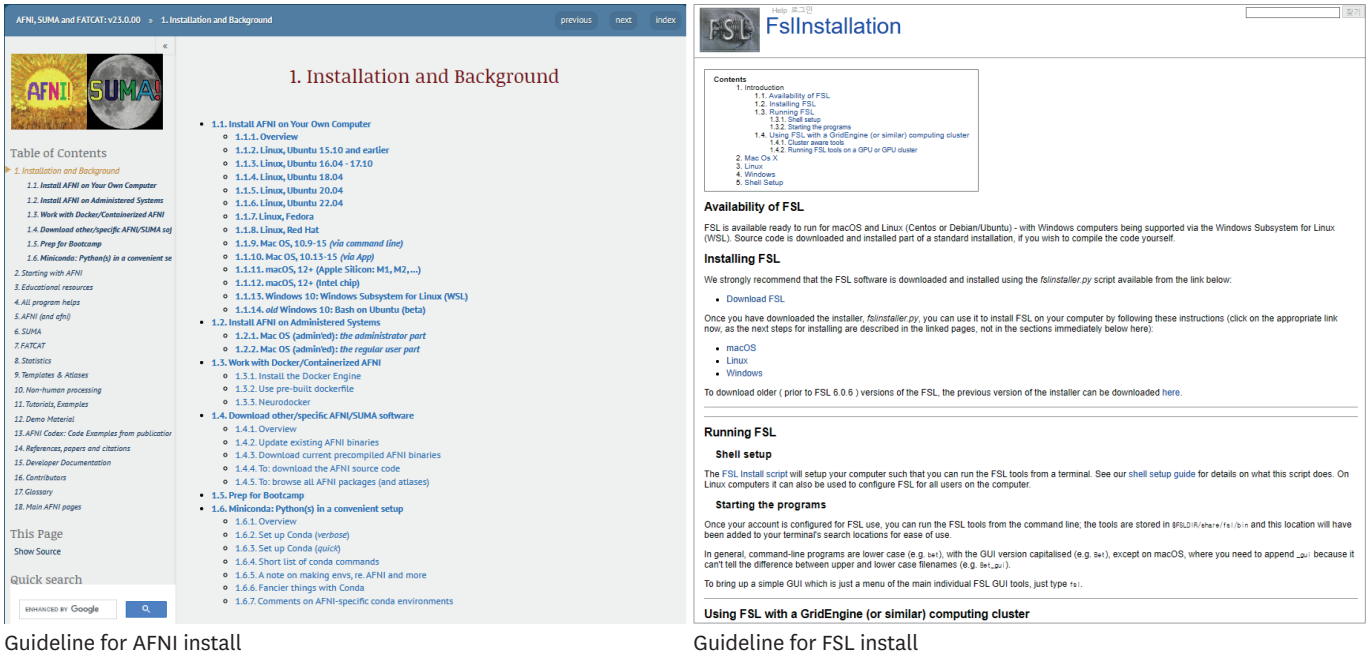
Table 6. Magnetic resonance protocol details

Variable	3D MPRAGE	3D FLAIR (optional)	2D FLAIR	3D MDME	2D T2WI	3D SWI	DCE-MRI
TR (ms)	2,300	5,000	9,000	51	4,450	29	3.1
TE (ms)	2.98	393	95	8.9 (6 echoes with echo spacing=4.09)	81	20	1.04
TI (ms)	900	1,800	2,500	Bandwidth=150 kHz			
Flip angle (°)	9		150	20	150	15	10
FOV (mm)	256×256	256×256	220×220	240×240	220×220	220×220	225×240
Slice thickness (mm)	1	1	4 (1)	2	4 (1)	2	3
Matrix	256×256	512×512	320×320	416×416	384×384	512×512	180×192
Voxel size	1×1×1	0.5×0.5×1	0.69×0.69×5	0.6×0.6×2	0.6×0.6×5	0.43×0.43×2	1.25×1.25×3
NEX	1	1	1	1	2	1	
GRAPPA factor	2	2	2	2	2	2	
Other features	Sagittal	Sagittal	Axial	Axial 4 min 33 sec	Axial	Axial	60 dynamics, 10 sec temporal resolution

MPRAGE: magnetization prepared-rapid gradient echo, 3D: three-dimensional, 2D: two-dimensional, FLAIR: fluid-attenuated inversion recovery, MDME: multi-dynamic multi-echo, T2WI: T2 weighted image, SWI: susceptibility-weighted imaging, DCE: dynamic contrast enhancement, MRI: magnetic resonance imaging, TR: repetition time, TE: time to echo, TI: inversion time, FOV: field of view, NEX: number of excitations, GRAPPA: GeneRalized Autocalibrating Partial Parallel Acquisition.

have been developed in Korea. Comparison results and their potential limitations are well summarized in recently published review papers.[16,17]

For brain volume analysis with research purpose, FreeSurfer, the most commonly used research software, is currently regarded as a reference standard. However, depending on the direction of analysis, 2 other research software—Analysis of Functional NeuroImage (AFNI) or FMRIB Software Library (FSL)—can be used. FSL is an image analysis and statistical tool for structural, functional, and diffusion tensor MRI data. AFNI is suitable for analyzing multiple MR modalities. For installation of AFNI (https://afni.nimh.nih.gov/), FSL (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki), and AFNI viewer, please refer to Guidelines for Researchers in Immunomodulation-Based Precision Medicine in Alzheimer's Disease (**Fig. 1**).[18]



Guideline for AFNI install (https://afni.nimh.nih.gov/pub/dist/doc/htmldoc/background_install/main_toc.html)

Guideline for FSL install (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FslInstallation)

Fig. 1. Software installation guidelines for image analysis. For brain volume analysis, FreeSurfer is currently the most widely used reference standard. However, depending on the direction of analysis, AFNI or FSL can be used following installation guidelines.
AFNI: Analysis of Functional NeuroImages, FSL: FMRIB Software Library.

CEREBROSPINAL FLUID (CSF) TEST

CSF reflects brain metabolism and pathology. It is important for initial diagnosis, treatment, and prevention strategies. In addition, CSF can be easily and safely obtained by lumbar puncture, making it important for biomarker research. Amyloid deposition, neurofibrillary tangles (NFTs), and neuronal degeneration can be used as CSF biomarkers.

β-amyloid (Aβ)

β-amyloid peptide composed of 42 amino acids (Aβ1–42) is produced by degradation of amyloid precursor protein (APP) by β- and γ-secretases. Aβ1–42 produces insoluble extracellular Aβ deposits in the AD brain Thus, Aβ1–42 is used as a marker for Aβ deposition. Additionally, CSF Aβ1–42 levels are reduced in AD. In contrast, phosphorylated tau at threonine 181 (P-tau181; marker for NFT) and total tau protein (T-tau, marker for neuronal injury) are increased in AD. Together, CSF Aβ1–42, T-tau, and P-tau181 are used for AD diagnosis.

Aβ42 is a by-product of APP degradation. It is transported from the brain interstitial fluid into the CSF and blood by the glymphatic system. In the case of AD, Aβ42 is aggregated in the brain parenchyma and eventually cleared by the CSF. To accurately diagnose Aβ pathology, the Aβ42/Aβ40 ratio is calculated. Although the ratio differs from person to person, it is consistent with amyloid positron emission tomography (PET) results.

Measurement method 1: Aβ aggregation

As aforementioned, aggregation of Aβ is a pathophysiological characteristic of diseases related to Aβ such as AD. This method measures changes in protein amount based on western blotting.

Sample preparation and sodium dodecyl sulfate-polyacrylamide gel electrophoresis gel electrophoresis protocol followed methods of Farber et al.[19] and Rosen et al.,[20] respectively.

Measurement method 2: quantification of CSF Aβ1–42 by enzyme-linked immunosorbent assay (ELISA)

Aβ1–42 of CSF is used as a marker for Aβ deposition. It is measured using a Human Aβ42 ELISA Kit (a solid-phase sandwich ELISA). Although Aβ1–42 of CSF enables highly sensitive identification of AD, it shows a low correlation with disease progression. The 1X wash buffer and sample are prepared following the information sheet of Thermo Fisher Scientific (Waltham, MA, USA) products.

P-tau

Tau is an axon protein present in the cytoplasm of neurons. It can stabilize microtubules. In AD, tau protein is hyperphosphorylated by an imbalance of kinases and phosphatases. Tau is released from microtubules. It then accumulates as NFT. The presence of tau in CSF is a pathological change that occurs later than CSF Aβ1–42. It is strongly correlated with cognitive decline. The aggregation of tau in the soma of nerve cells creates a NFT, which is one of the main pathophysiological features of AD. Tau is also aggregated in neurons or glia in patients with dementia caused by neurodegenerative disease others than AD. Tau phosphorylation and secretion are increased in neurons following Aβ exposure, which can increases tau level in the CSF. Plasma P-tau181 can be a good predictor of AD pathology as observed in the correlation between plasma P-tau181, amyloid PET, and tau PET. To detect plasma P-tau, Simoa™ Human Total Tau assay, a digital ELISA, is widely used.

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T-tau

T-tau is increased in CSFs and brains of patients with neurodegenerative diseases. Thus, T-tau can be used as a biomarker of neuronal injury with specificity for extracellular release and brain damage during nerve damage. Simoa™ Human Total Tau assay, a Digital ELISA, is widely used to measure T-tau.

Others

It has been reported that neurofilament light chain, visinin-like protein 1 (a calcium sensor protein), and growth-associated protein (GAP-43) are increased in CSFs of patients with AD.[21] ELISA can be performed to measure their levels.

CONCLUSION

The development of an effective dementia treatment agent begins with knowledge about causes of neurodegenerative diseases and disease progression mechanisms. Notwithstanding difficulties identifying pathological changes in human brains, recent advances in structural brain imaging and molecular imaging techniques have greatly contributed to the diagnosis of neurodegenerative diseases that can cause dementia. However, these tests alone have limitations in diagnosing and evaluating the progression of neurodegenerative diseases. Therefore, considering neuroanatomical tests together with clinical neurological examinations, neuropsychological tests, and CSF beta amyloid, tau, and P-tau tests is important to improve diagnosis.

This study reviewed current diagnostic tools used in patients with AD. We summarized the latest diagnostic framework, neuropsychological tests, imaging tests, and CSF tests used in current research, which could help in the diagnosis of AD.

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SUPPLEMENTARY MATERIAL

Supplementary Fig. 1

Medial temporal atrophy (Scheltens' scale).[6]

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