최초 증례 보고에서 NINCDS-ADRDA 진단 기준까지

2011년도 한국노년신경정신약물학회 추계 학술대회

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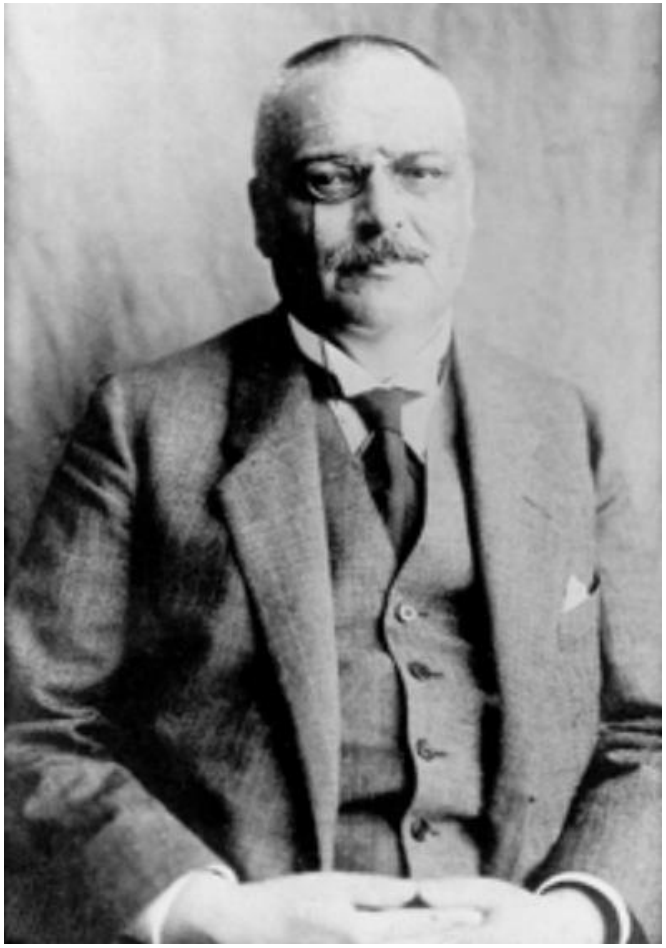
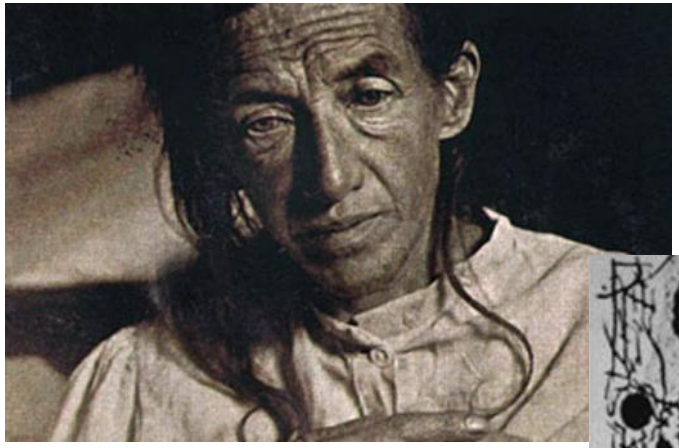
History of Alzheimer's Disease (AD)

- Plaques found and related to the pathology of senile dementia
  - 1892, Blocq and Marinesco; 1898, Redlich
- 1907, Alzheimer
  - NF changes described and related to the pathology of presenile dementia
  - Kraepelin names illness "Alzheimer's disease"
  - Alzheimer believes plaques and NF tangles don't occur after age 65 and senile dementia is caused by atherosclerosis

Alois Alzheimer and Auguste D.





History of Alzheimer's Disease (AD)

Senile plaques, neurofibrillary tangles, and granulovacuolar degeneration demonstrated in normal aging and senile dementia.	1927 1933	Grunthal[16] Gellerstedt[17]
Neurofibrillary change related to pathology of senile dementia.	1959 1962	Margolis[18] Hirano and Zimmerman[19]
Cerebral arteriosclerosis differentiated from senile dementia.	1965	Corsellis and Evans[20]
Correlation between senile plaques and senile dementia established.	1962 1966 1968	Corsellis[21] Roth et al[9] Blessed et al[10]
Senile dementia and presenile dementia demonstrated to be similar or identical entities.	1968 1970	Tomlinson et al[11] Tomlinson et al[12]
Alzheimer's disease proclaimed a major illness.	1974	Hachinski et al[8]

Follow-up of the First AD Case

Neurogenetics (1998) 1:223–228

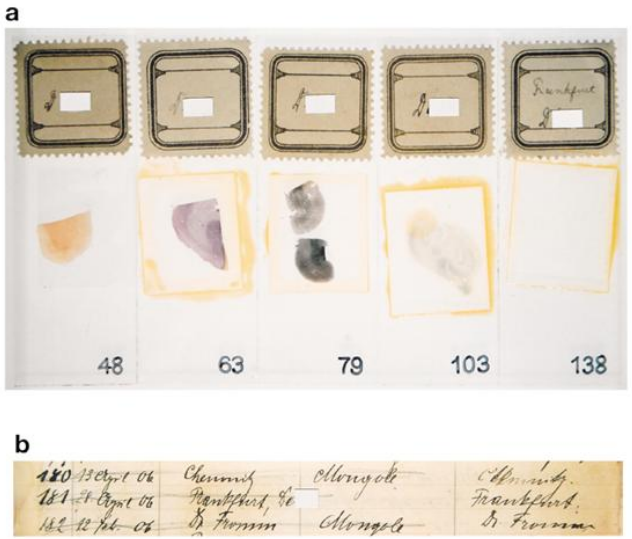
© Springer-Verlag 1998

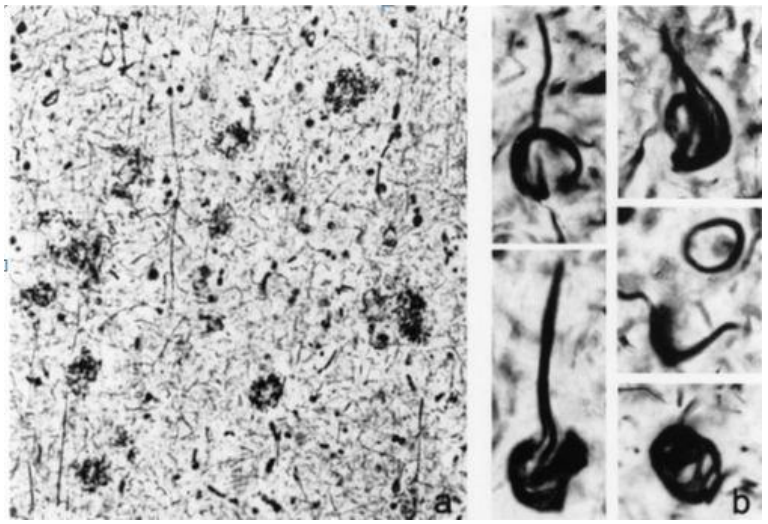
Original article

Histopathology and *APOE* genotype of the first Alzheimer disease patient, Auguste D.

M.B. Graeber · S. Kösel · E. Grasbon-Frodl · H.J. Möller · P. Mehraein

Fig. 1a Tissue sections from Auguste D.'s brain stained according to Herxheimer (*48*), Mallory? (*63*), Bielschowsky (*79*), Nissl (*103*) and Nissl (faded)? (*138*). The slide on the very right also shows "Frankfurt" on its label. All sections are marked "D...". **b** Entry no. 181 in the autopsy book of Kraepelin's clinic shows a date, "28 April 06", "Frankfurt" followed by the last name "D...", and the source of the tissue, i.e., "Frankfurt". "D..." is the last name of Auguste D., who died in Frankfurt on 8 April 1906

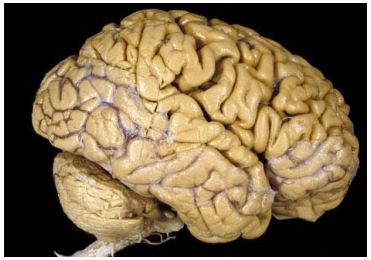




치매란?

1909-1950	1950-1980	1980-현재
65세 미만: AD(Presenile D) 65세 이상: Senile D Multi-infarct D	65세 미만: early onset AD 65세 이상: late onset AD	AD, VD, FTD, DLB, etc…

Brain damage



Cognition

ADL

Definition of Alzheimer's Disease

- ICD-10
  - "Dementia in Alzheimer's disease"
  - "Alzheimer's disease is a primary degenerative cerebral disease of unknown etiology with characteristic neuropathological and neurochemical features. The disorder is usually insidious in onset and develops slowly but steadily over a period of several years."
- Lacks descriptions on clinical features and course of the disease

Definition of Alzheimer's Disease

- DSM-IV-TR
  - "Dementia of Alzheimer's Type" (DAT)
  - "The diagnosis can be made only when other etiologies for the dementia have been ruled out.
  - "Early deficits in recent memory, followed by the development of aphasia, apraxia and agnosia after several years."
- Diagnosis by "Exclusion?"
- Historical Background: '60s, '70s, '80s

Consensus Conference

- IPA, ADI, EFNS, WHO, WPA: Reisberg, 1997
  - "The diagnosis of AD should no longer be considered one of exclusion. Rather, the diagnostic process is one of recognition of the characteristic features of AD."
- AAGP, AA, AGS: Small, 1997
  - "Although the diagnosis of AD is often missed or delayed, it is primarily one of inclusion, not exclusion, and usually can be made using standardized clinical criteria."

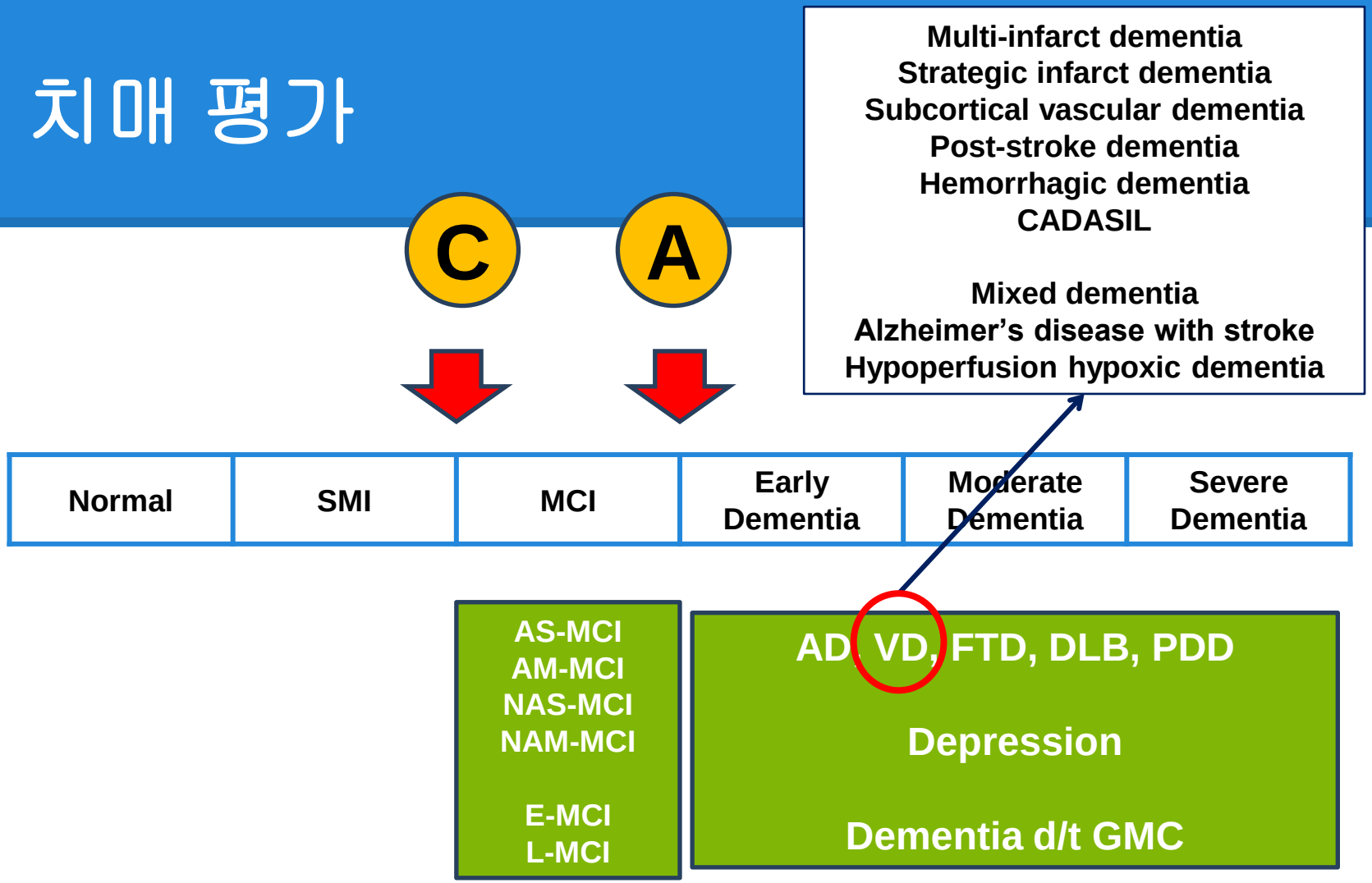
NINCDS-ADRDA Criteria for AD 1

- Definite Alzheimer's disease
  - Probable AD with histopathologic evidence of AD
- Probable Alzheimer's disease
  - Dementia established by clinical and neuropsychological examination and
    - (a) progressive deficits in two or more areas of cognition, including memory,
    - (b) onset between the ages of 40 and 90 years, and
    - (c) absence of systemic or other brain diseases capable of producing a dementia syndrome, including delirium

NINCDS-ADRDA Criteria for AD 2

- Possible Alzheimer's disease
  - With an atypical onset, presentation, or progression
- Unlikely Alzheimer's disease
  - With any of the following: sudden onset, focal neurologic signs, or seizures or gait disturbance early in the course of the illness

치매 평가

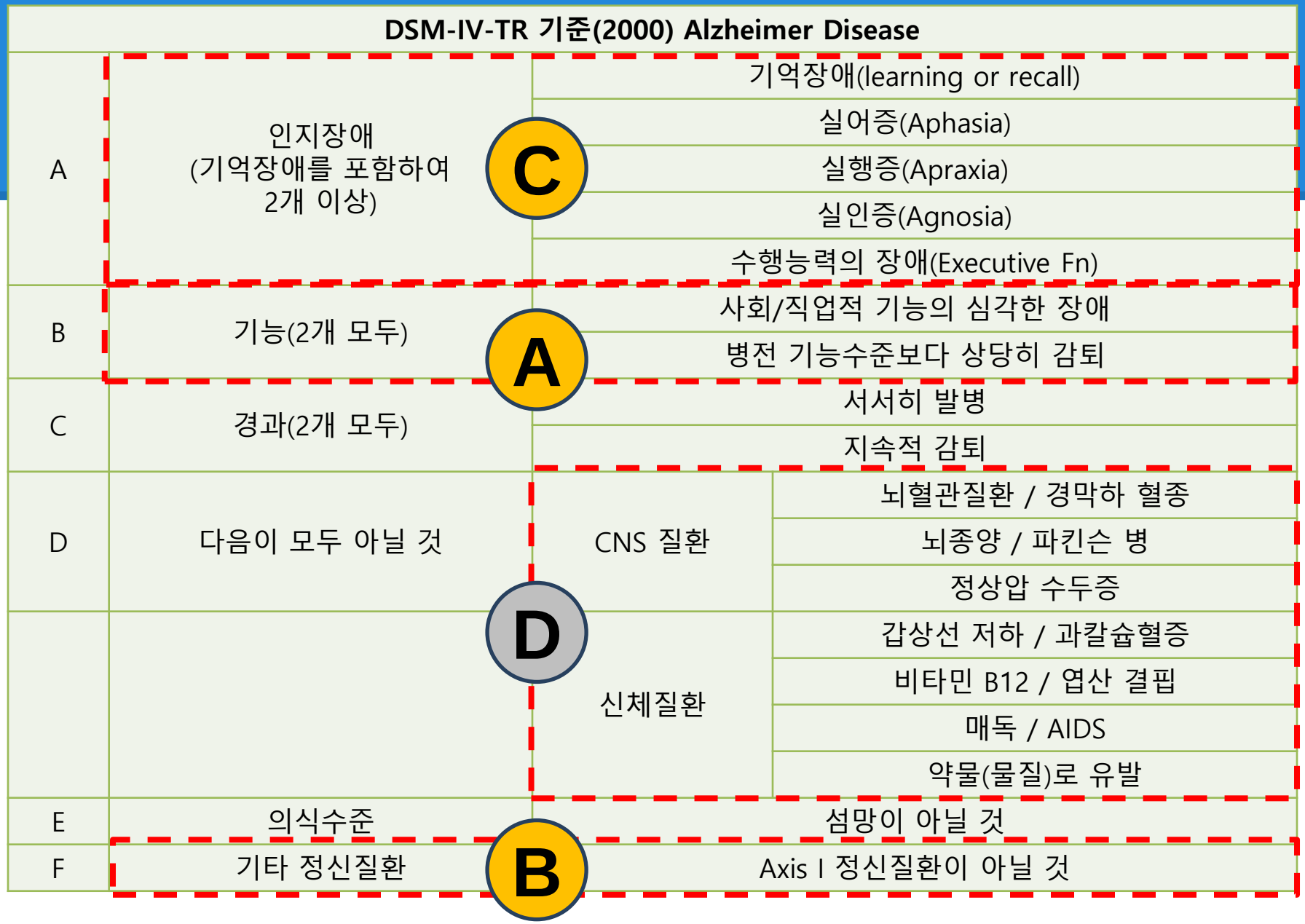


Pubmed 검색 : Alzheimer disease (n=58,953), Vascular dementia (n=8,461)

진단 기준 비교

- NINCDS ADRDA workgroup in 1984 (kappa=0.64)
  - National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association(ADRDA)
  - Sn: 49%, Sp: 100%, Ac: 66%
- DSM-III in 1980 (kappa=0.55)
  - American Psychiatric Association, Diagnostic and Statistical Manual
  - Sn: 51%, Sp: 97%, Ac: 66%

Int Psychogeriatr. 1997


DSM-IV-TR 기준(2000) Alzheimer Disease
A
인지장애
(기억장애를 포함하여
2개 이상)
C
기억장애(learning or recall)
실어증(Aphasia)
실행증(Apraxia)
실인증(Agnosia)
수행능력의 장애(Executive Fn)
B
기능(2개 모두)
A
사회/직업적 기능의 심각한 장애
병전 기능수준보다 상당히 감퇴
C
경과(2개 모두)
서서히 발병
지속적 감퇴
D
다음이 모두 아닐 것
CNS 질환
뇌혈관질환 / 경막하 혈종
뇌종양 / 파킨슨 병
정상압 수두증
D
신체질환
갑상선 저하 / 과칼슘혈증
비타민 B12 / 엽산 결핍
매독 / AIDS
약물(물질)로 유발
E
의식수준
섬망이 아닐 것
B
F
기타 정신질환
Axis I 정신질환이 아닐 것

NINCDS/ADRDA 기준(1984) Probable Alzheimer Disease			
A	인지장애 (2개 이상)	Clinical examination	
		Documented by MMSE or Blessed dementia scale	
		Confirmed by Neuropsychological test	
B	경과(2개 모두)	기억력과 다른 인지기능의 점진적 악화	
C	다음이 모두 아닐 것	CNS 질환	뇌혈관질환 / 경막하 혈종
			뇌종양 / 파킨슨 병
			정상압 수두증
		신체질환	갑상선 저하 / 과칼슘혈증
			비타민 B12 / 엽산 결핍
			매독 / AIDS
			약물(물질)로 유발
D	의식수준	섬망이 아닐 것	
E	기타 정신질환	Axis I 정신질환이 아닐 것	
F	발병나이	**40-90세**	

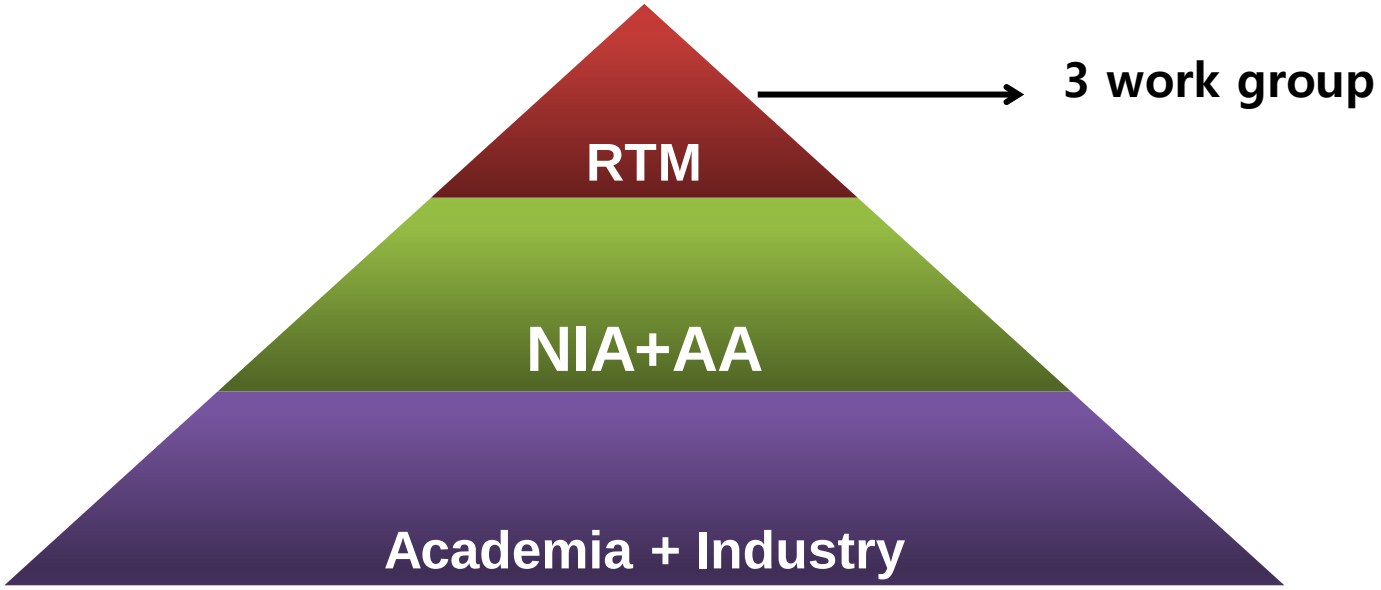
G	Supported by	**ADL의 장애** FHx, EEG, CT, MRI, CSF

새로운 AD 진단기준 제안 (ICAD 2010)

Normal	SMI	MCI	Early Dementia	Moderate Dementia	Severe Dementia

Preclinical stage of AD | MCI due to AD | AD dementia

새롭게 제안된 AD



Hypothetical Model of Dynamic Biomarkers of AD

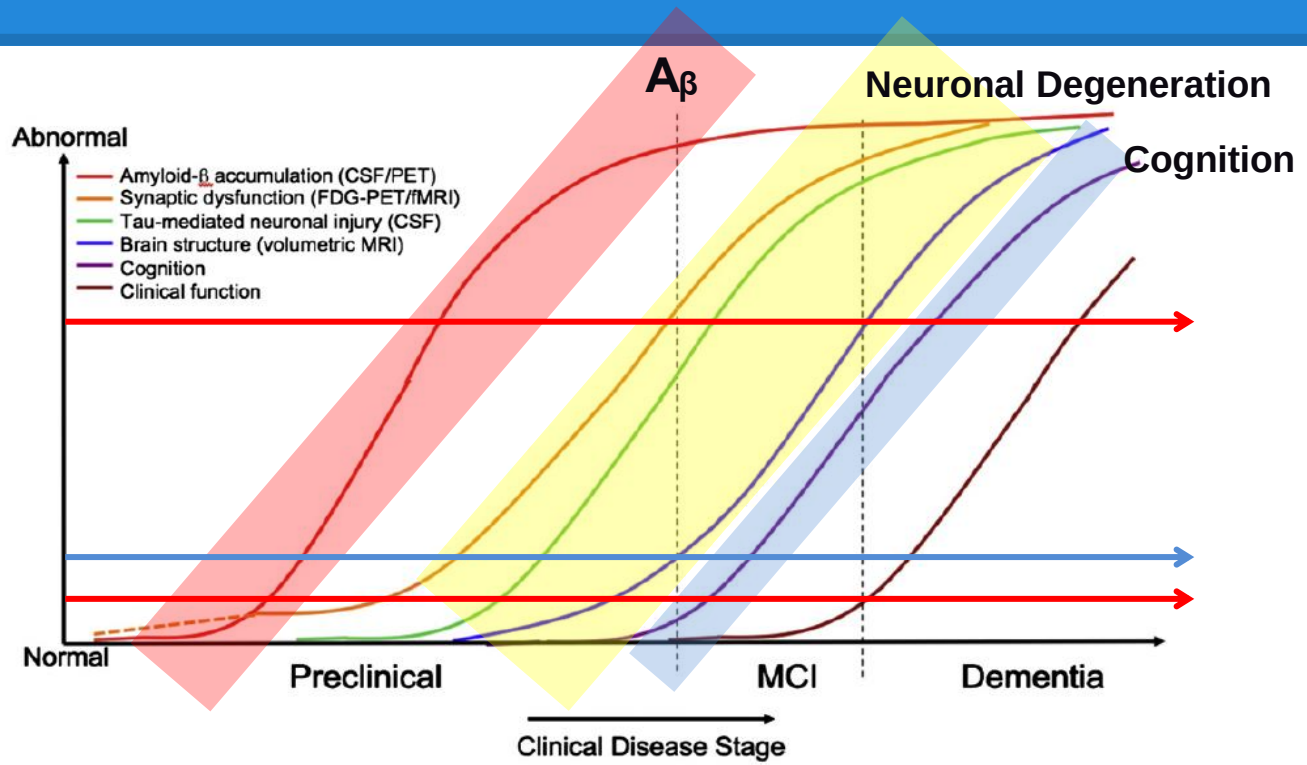


Fig. 3. Hypothetical model of dynamic biomarkers of the AD expanded to explicate the preclinical phase: Aβ as identified by cerebrospinal fluid $A\beta_{42}$ assay or PET amyloid imaging. Synaptic dysfunction evidenced by fluorodeoxyglucose (F18) positron emission tomography (FDG-PET) or functional magnetic resonance imaging (fMRI), with a dashed line to indicate that synaptic dysfunction may be detectable in carriers of the $\varepsilon 4$ allele of the apolipoprotein E gene before detectable Aβ deposition. Neuronal injury is evidenced by cerebrospinal fluid tau or phospho-tau, brain structure is evidenced by structural magnetic resonance imaging. Biomarkers change from normal to maximally abnormal (y-axis) as a function of disease stage (x-axis). The temporal trajectory of two key indicators used to stage the disease clinically, cognitive and behavioral measures, and clinical function are also illustrated. Figure adapted with permission from Jack et al [22].

Jack CR Jr,Knopman DS, JagustWJ, ShawLM, Aisen PS,WeinerMW, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Lancet Neurol 2010;9:119–28.

Dementia due to AD

ELSEVIER

Alzheimer's & Dementia ■ (2011) 1–7

The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging and the Alzheimer's Association workgroup

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Neurocognitive Disorders DSM-V 2013

S 00 - 11 Delirium

S 00 Delirium

S 01 - 10 Substanced-Induced Delirium

S 11 Alcohol Withdrawal Delirium

S 12 - 23 Mild Neurocognitive Disorder

S 12 Mild Neurocognitive Disorder

S 13 Mild Neurocognitive Disorder Associated with Alzheimer's Disease

S 14 Mild Neurocognitive Disorder Associated with Vascular Disease

S 15 Mild Neurocognitive Disorder Associated with Fronto-Temporal Lobar Degeneration

S 16 Mild Neurocognitive Disorder Associated with Traumatic Brain Injury

S 17 Mild Neurocognitive Disorder Associated with Lewy Body Disease

S 18 Mild Neurocognitive Disorder Associated with Parkinson's Disease

S 19 Mild Neurocognitive Disorder Associated with HIV Infection

S 20 Mild Neurocognitive Disorder Associated with Substance Use

S 21 Mild Neurocognitive Disorder Associated with Huntington's Disease

S 22 Mild Neurocognitive Disorder Associated with Prion Disease

S 23 Other Specified Mild Neurocogntive Disorder

Neurocognitive Disorders DSM-V 2013

S 24 - 35 Major Neurocognitive Disorder

S 24 Major Neurocognitive Disorder

S 25 Major Neurocognitive Disorder Associated with Alzheimer's Disease

S 26 Major Neurocognitive Disorder Associated with Vascular Disease

S 27 Major Neurocognitive Disorder Associated with Fronto-Temporal Lobar Degeneration

S 28 Major Neurocogntive Disorder Associated with Traumatic Brain Injury

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S 30 Major Neurocognitive Disorder Associated with Parkinson's Disease

S 31 Major Neurocognitive Disorder Associated with HIV Infection

S 32 Major Neurocognitive Disorder Associated with Substance Use

S 33 Major Neurocognitive Disorder Associated with Huntington's Disease

S 34 Major Neurocognitive Disorder Associated with Prion Disease

S 35 Other Specified Major Neurocogntive Disorder

Updated February 16th, 2011

Mild Neurocognitive Disorder

A. **Evidence of minor cognitive decline** from a previous level of performance in one or more of the domains outlined above based on:

1. Concerns of the **patient**, a knowledgeable **informant** or the **clinician** that there has been a mild decline in cognitive function

AND

2. Mild decline in neurocognitive performance, typically between **1 and 2 standard deviations below appropriate norms (i.e., between the 3rd and 16th percentile)** on formal testing, or equivalent clinical evaluation.

B. The cognitive deficits are insufficient to interfere with independence (i.e., **instrumental Activities of Daily Living** [more complex tasks such as paying bills or managing medications] **are preserved**), but greater effort, compensatory strategies, or accommodation may be required to maintain independence.

C. The cognitive deficits do not occur exclusively in the context of a **delirium**.

D. The cognitive deficits are not wholly or primarily attributable to another **Axis I disorder** (e.g., Major Depressive Disorder, Schizophrenia).

Major Neurocognitive Disorder

A. **Evidence of significant cognitive decline** from a previous level of performance in one or more of the domains outlined above based on:

1. Concerns of the **patient**, a knowledgeable **informant** or the **clinician** that there has been a significant decline in cognitive function

AND

2. Clear decline in neurocognitive performance, typically **2 or more standard deviations below appropriate norms (i.e., below the 3rd percentile)** on formal testing, or equivalent clinical evaluation.

B. The cognitive deficits are sufficient to interfere with independence (i.e., **requiring assistance at a minimum with instrumental Activities of Daily Living** [more complex tasks such as paying bills or managing medications]).

C. The cognitive deficits do not occur exclusively in the context of a **delirium**.

D. The cognitive deficits are not wholly or primarily attributable to another **Axis I disorder** (e.g., Major Depressive Disorder, Schizophrenia)

Alzheimer's Disease Subtype of Major and Mild Neurocognitive Disorders

A.

Major: Meets criteria for Major Neurocognitive Disorder, with **memory** being one of the impaired domains.

Mild: Meets criteria for Mild Neurocognitive Disorder with **memory** impairment **AND** there is clear supporting evidence for the Alzheimer etiology (e.g., a positive test for a known mutation in an Alzheimer's disease associated **gene**), or with evolving research, documentation based on **biomarkers or imaging.**

B.

Early and prominent impairment in the Memory domain (rarely, other domains such as visuoconstructive perceptual domain may be prominently affected, but Alzheimer's disease would not be diagnosed without clear supporting imaging, biomarker or genetic evidence).

Major: Deficits are observed in at least one other domain, often Executive Ability, and as the disease progresses, in additional domains.

Mild: Only Memory may be affected, but deficits in Executive Abilities are common.

C. The course is characterized by **gradual onset** and **continuing cognitive decline**

D. Evidence from history, examination, and investigations that deficits are not wholly or primarily attributable to other disorders. However, other such disorders may coexist.

Summary

- Historical background of AD diagnosis
- Diagnostic manual lags many years behind current scientific discoveries
  - Pathophysiological understanding of dementias
  - Biomarkers, genetic markers
  - Neuroimaging of various dementia syndromes
- Cognitive/ Biological / Functional Staging