4th International Alzheimer's Disease Conference

مؤتمر ألزهايمر الدولي الرابع ٢٠٢٠

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2-4 Jumada II 1441 / 27-29 January 2020
Conference Hall – KACST HQ
Riyadh, Saudi Arabia

Organized by

الجمعية السعودية الخيرية لمرض الزهايمر
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The Challenges of Diagnosis in Alzheimer's Disease

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Outline

- Introduction
- Terminologies & Definition
- Historical background
- Progress in Alzheimer's disease definition
- The different presentations of Alzheimer's disease
- The effect of comorbid pathology
- Summary

Objectives

- Appreciate the historical background of Alzheimer’s disease definition
- Recognize the current progress of Alzheimer's disease definition
- Determine the early signs and atypical phenotypes of Alzheimer's disease
- Recognize the effect of co-morbid pathology on the Alzheimer's disease presentation and progression
- Associate the value of early diagnosis of Alzheimer's disease to your current model of practice

Alzheimer’s Disease, Syndrome or both

- What is the difference between Dementia and Alzheimer’s?
- Dementia is a syndrome where a substantial progressive cognitive impairment that affects **several domains** and/or neurobehavioral symptoms. May be reported by the individual or by an observer (e.g., study partner) or observed by change on longitudinal cognitive testing.
- Cognitive impairment and/or neurobehavioral symptoms result in clearly evident functional impact on daily life. No longer fully independent/ requires assistance with daily life activities.
- A syndrome is not an **etiology** but rather a clinical consequence of one or more diseases.

Historical background of Alzheimer disease

- Alzheimer’s disease is named after Dr. Alois Alzheimer.
- In 1906 he described the pathological change of a middle age female who passed away from late onset mental illness.
- Her symptoms included memory loss, language problems, and unpredictable behavior.
- He autopsied her brain and found many abnormal clumps (now called amyloid plaques) and tangled bundles of fibers (now called neurofibrillary, or tau, tangles).
- Alzheimer’s disease: (AD) since then has been defined as a clinical-pathologic entity, which was diagnosed definitely at autopsy and in life as possible or probable AD.

The progress in Alzheimer's disease definition

- The concept of the chronic organic brain syndrome codified in the DSM in 1952.
- The DSM-II in 1968 evolved to current criteria for dementia and Alzheimer’s disease in the third and subsequent editions
- NINCDS-ADRDA Work Group in 1984 put forward the clinical criteria for diagnosing AD
- Alzheimer’s disease = Dementia
- Alzheimer disease was a diagnosis of exclusion

I. The criteria for the clinical diagnosis of PROBABLE Alzheimer's disease include:

dementia established by clinical examination and documented by the Mini-Mental Test,' Blessed Dementia Scale,' or some similar examination, and confirmed by neuropsychological tests;

deficits in two or more areas of cognition;

progressive worsening of memory and other cognitive functions;

no disturbance of consciousness;

onset between ages 40 and 90, most often after age 65; and

absence of systemic disorders or other brain diseases that in and of themselves could account for the progressive deficits in memory and cognition.

II. The diagnosis of PROBABLE Alzheimer's disease is supported by:

progressive deterioration of specific cognitive functions such as language (aphasia), motor skills (apraxia), and perception (agnosia);

impaired activities of daily living and altered patterns of behavior;

family history of similar disorders, particularly if confirmed neuropathologically; and

laboratory results of:

normal lumbar puncture as evaluated by standard techniques,

normal pattern or nonspecific changes in EEG, such as increased slow-wave activity, and

evidence of cerebral atrophy on CT with progression documented by serial observation.

III. Other clinical features consistent with the diagnosis of PROBABLE Alzheimer's disease, after exclusion of causes of dementia other than Alzheimer's disease, include:

plateaus in the course of progression of the illness;

associated symptoms of depression, insomnia, incontinence, delusions, illusions, hallucinations, catastrophic verbal, emotional, or physical outbursts, sexual disorders, and weight loss;

other neurologic abnormalities in some patients, especially with more advanced disease and including motor signs such as increased muscle tone, myoclonus, or gait disorder;

seizures in advanced disease; and

CT normal for age.

IV. Features that make the diagnosis of PROBABLE Alzheimer's disease uncertain or unlikely include:

sudden, apoplectic onset;

focal neurologic findings such as hemiparesis, sensory loss, visual field deficits, and incoordination early in the course of the illness; and

seizures or gait disturbances at the onset or very early in the course of the illness.

V. Clinical diagnosis of POSSIBLE Alzheimer's disease:

may be made on the basis of the dementia syndrome, in the absence of other neurologic, psychiatric, or systemic disorders sufficient to cause dementia, and in the presence of variations in the onset, in the presentation, or in the clinical course;

may be made in the presence of a second systemic or brain disorder sufficient to produce dementia, which is not considered to be the cause of the dementia; and

should be used in research studies when a single, gradually progressive severe cognitive deficit is identified in the absence of other identifiable cause.

VI. Criteria for diagnosis of DEFINITE Alzheimer's disease are:

the clinical criteria for probable Alzheimer's disease and

histopathologic evidence obtained from a biopsy or autopsy.

VII. Classification of Alzheimer's disease for research purposes should specify features that may differentiate subtypes of the disorder, such as:

familial occurrence;

onset before age of 65;

presence of trisomy-21; and

coexistence of other relevant conditions such as Parkinson's disease.

NEUROLOGY 34 July 1984

The 1984 NINCDS-ADRDA clinical criteria for diagnosing AD

Criteria for dementia syndrome. Dementia is the decline of memory and other cognitive functions in comparison with the patient's previous level of function as determined by a history of decline in performance and by abnormalities noted from clinical examination and neuropsychological tests. A diagnosis of dementia cannot be made when consciousness is impaired by delirium, drowsiness, stupor, or coma or when other clinical abnormalities prevent adequate evaluation of mental status. Dementia is a diagnosis based on behavior and cannot be determined by computerized tomography, electroencephalography, or other laboratory instru-

Criteria for Alzheimer's disease. Alzheimer's disease is a progressive, dementing disorder, usually of middle or late life. The clinical criteria for the diagnosis of PROBABLE, POSSIBLE, and DEFINITE Alzheimer's disease are outlined in table 1. A clinical diagnosis of probable Alzheimer's disease can be made with confidence if there is a typical insidious onset of dementia with progression and if there are no other systemic or brain diseases that could account for the progressive memory and other cognitive deficits. Among the disorders that must be excluded are manic-depressive disorder, Parkinson's

The 1st International Working Group 2007 IWG-1 revised NINCDS-ADRDA criteria

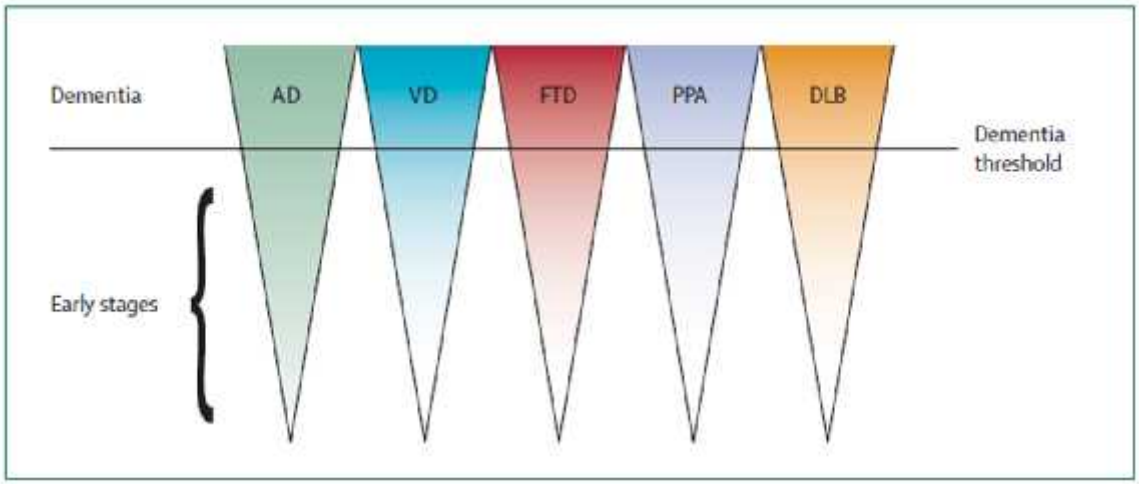
Mild cognitive impairment
Variably defined but includes subjective memory or cognitive symptoms or both, objective memory or cognitive impairment or both, and generally unaffected activities of daily living; affected people do not meet currently accepted dementia or AD diagnostic criteria

Amnestic mild cognitive impairment
A more specified term describing a subtype of mild cognitive impairment, in which there are subjective memory symptoms and objective memory impairment; other cognitive domains and activities of daily living are generally unaffected; affected people do not meet currently accepted dementia or AD diagnostic criteria

Preclinical AD
The long asymptomatic period between the first brain lesions and the first appearance of symptoms and which concerns normal individuals that later fulfil AD diagnostic criteria

Prodromal AD
The symptomatic predementia phase of AD, generally included in the mild cognitive impairment category; this phase is characterised by symptoms not severe enough to meet currently accepted diagnostic criteria for AD

AD dementia
The phase of AD where symptoms are sufficiently severe to meet currently accepted dementia and AD diagnostic criteria



Lancet Neurol 2007; 6: 734–46

National Institute on Aging-Alzheimer's NIA-AA 2011 guidelines

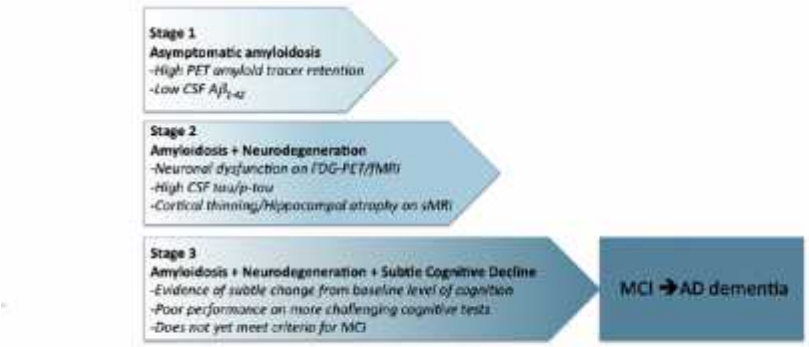


Fig. 5. Graphic representation of the proposed staging framework for preclinical AD. Note that some individuals will not progress beyond Stage 1 or Stage 2. Individuals in Stage 3 are postulated to be more likely to progress to MCI and AD dementia. Abbreviations: AD, Alzheimer's disease; Ab, amyloid beta; PET, position emission tomography; CSF, cerebrospinal fluid; FDG, fluorodeoxyglucose, fMRI, functional magnetic resonance imaging, sMRI, structural magnetic resonance imaging.

R.A. Sperling et al. Alzheimer's & Dementia- (2011) 1–13

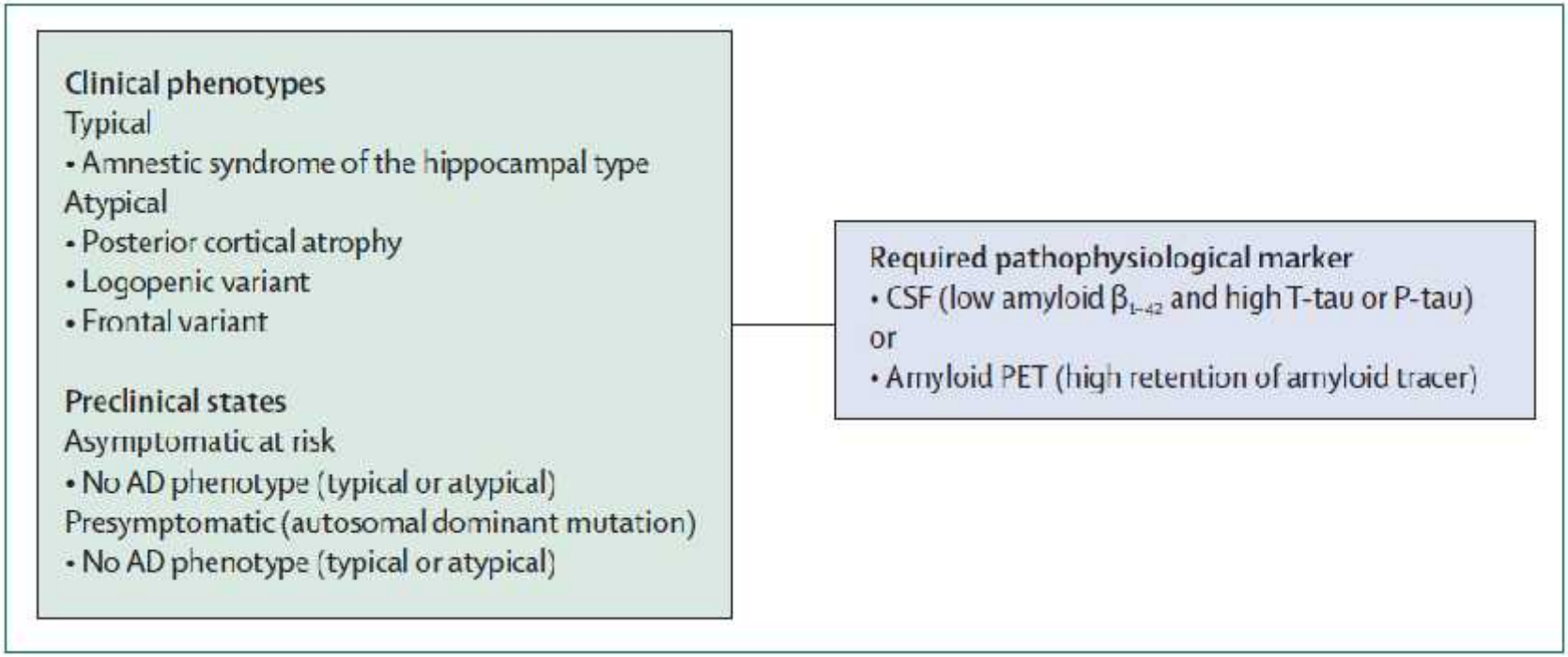
AD dementia criteria incorporating biomarkers

Diagnostic category	Biomarker probability of AD etiology	Aβ (PET or CSF)	Neuronal injury (CSF tau, FDG-PET, structural MRI)
Probable AD dementia			
Based on clinical criteria	Uninformative	Unavailable, conflicting, or indeterminate	Unavailable, conflicting, or indeterminate
With three levels of evidence of AD pathophysiological process	Intermediate	Unavailable or indeterminate	Positive
	Intermediate	Positive	Unavailable or indeterminate
	High	Positive	Positive
Possible AD dementia (atypical clinical presentation)			
Based on clinical criteria	Uninformative	Unavailable, conflicting, or indeterminate	Unavailable, conflicting, or indeterminate
With evidence of AD pathophysiological process	High but does not rule out second etiology	Positive	Positive
Dementia-unlikely due to AD	Lowest	Negative	Negative

Abbreviations: AD, Alzheimer's disease; Aβ, amyloid-beta; PET, positron emission tomography; CSF, cerebrospinal fluid; FDG, ^{18}fluorodeoxyglucose; MRI, magnetic resonance imaging.

G.M. McKhann et al. Alzheimer's & Dementia 7 (2011) 263–269

The 2nd International Working Group IWG-2 criteria 2014



Lancet neurology **Vol 13 June 2014**

The NIA new diagnostic criteria

- The new NIA have proposed a new diagnostic criteria for Alzheimer disease:
- Alzheimer disease (AD)—refers to Ab plaques and pathologic tau deposits, defined in vivo by abnormal biomarkers of Ab and pathologic tau (both are required) NIA 2018.
- Biomarker category—biomarker profiles are grouped into three possible biomarker categories: normal AD biomarkers, A-T-(N)-

ATN grouping

AT(N) biomarker grouping
A: Aggregated Aβ or associated pathologic state
CSF $A\beta_{42}$, or $A\beta_{42}/A\beta_{40}$ ratio
Amyloid PET
T: Aggregated tau (neurofibrillary tangles) or associated pathologic state
CSF phosphorylated tau
Tau PET
(N): Neurodegeneration or neuronal injury
Anatomic MRI
FDG PET
CSF total tau

Alzheimer's & Dementia 14 (2018) 535-562

Biomarker profiles and categories

Biomarker profiles and categories

AT(N) profiles	Biomarker category	
A-T-(N)-	Normal AD biomarkers	
A+T-(N)-	Alzheimer's pathologic change	Alzheimer's continuum
A+T+(N)-	Alzheimer's disease	
A+T+(N)+	Alzheimer's disease	
A+T-(N)+	Alzheimer's and concomitant suspected non Alzheimer's pathologic change	
A-T+(N)-	Non-AD pathologic change	
A-T-(N)+	Non-AD pathologic change	
A-T+(N)+	Non-AD pathologic change	

Alzheimer's & Dementia 14 (2018) 535-562

Alzheimer's clinical syndrome

- Alzheimer's clinical syndrome—recommended terminology for clinically ascertained multi- (or single-) domain amnestic syndrome or a classic syndromal variant (i.e., what has historically been labeled "possible or probable AD").
- It applies to both mildly impaired and demented individuals.
- The term "Alzheimer's disease" is reserved for situations where neuropathologic or biomarker evidence of the disease (i.e., Ab plaques and pathologic tau deposits) is present.

The atypical forms of Alzheimer's disease

Posterior Cortical Atrophy (PCA)

- PCA is a clinico-radiologic syndrome
- PCA typically presents in the mid-50s or early 60s
- Common presentation includes unusual visuoperceptual deficits, such as diminished ability to interpret, locate, or reach for objects under visual guidance; deficits in numeracy, literacy, and praxis may also be apparent.
- Episodic memory and insight may get impaired later in the disease however, they are commonly preserved early on.
- Over 80% of patients have biological changes of Alzheimer's disease.
- Other causes include LBD, CJD (prion disease), CBD.

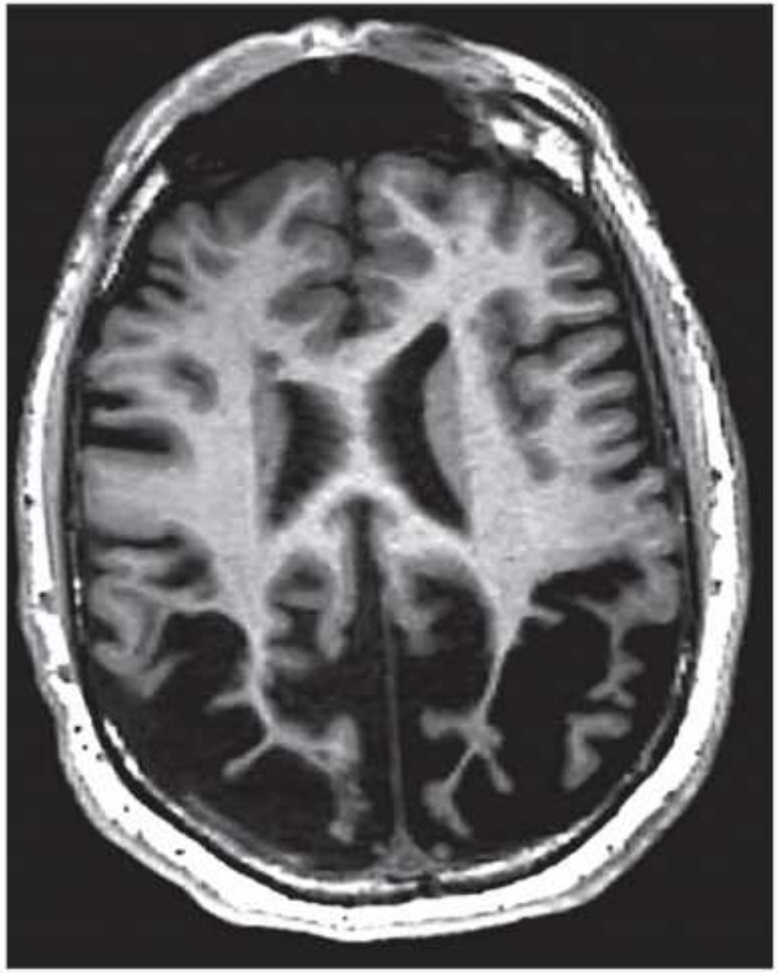
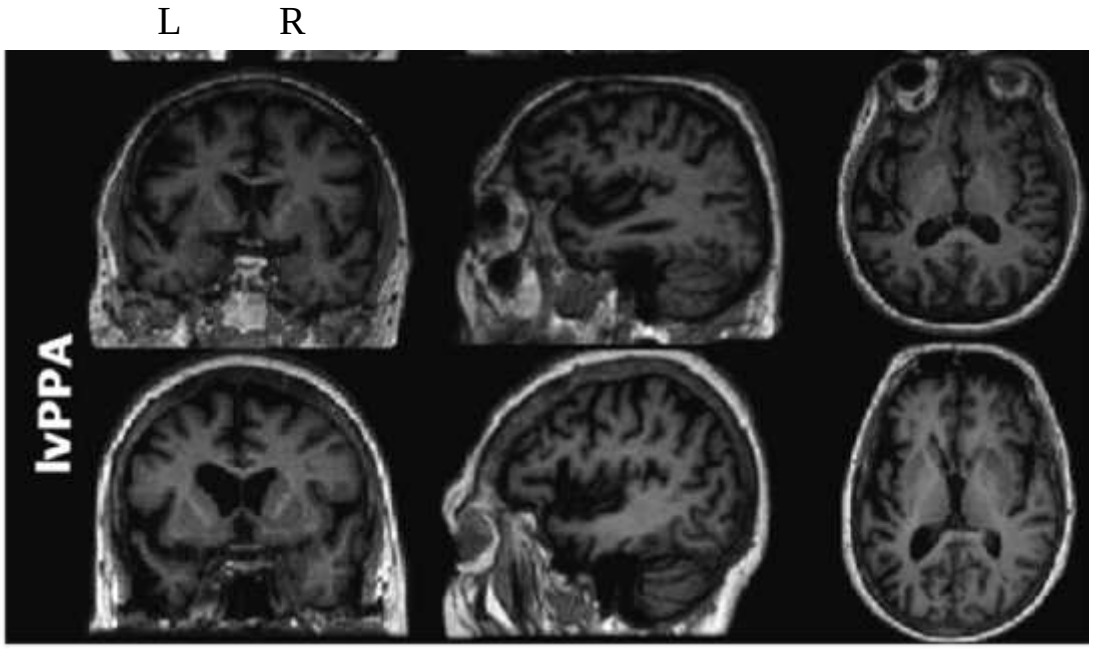


Figure: Visual impairment in posterior cortical atrophy
Axial T1-weighted MRI scan shows marked atrophy of the occipital and parietal lobes.

The lancet.com **Vol 394 September 21, 2019**

Logopenic variant Primary Progressive Aphasia (LvPPA)

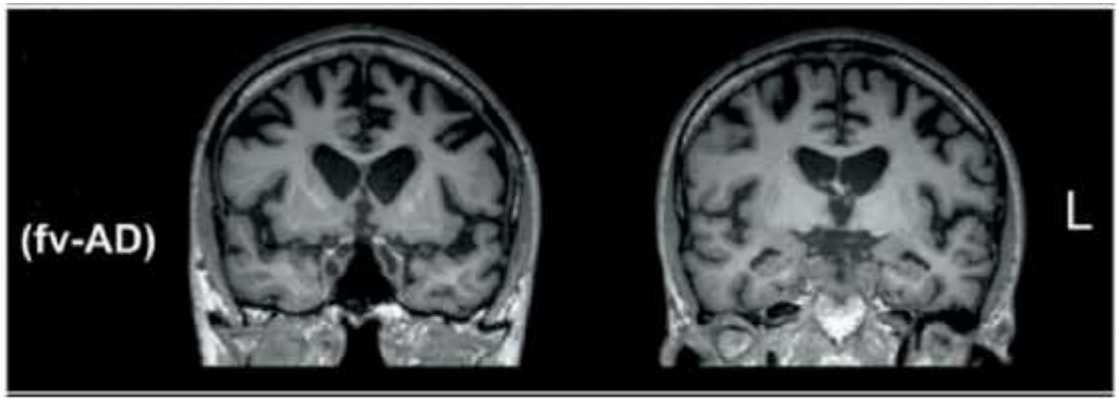
- Impaired repetition: individuals have difficulty repeating brief phrases, and have difficulty repeating a short sequence of numbers.
- Naming difficulty: Word comprehension tends to be relatively preserved, and the naming deficit in logopenic variant PPA appears to be due instead to difficulty retrieving the lexical form of the word.
- 70% of logopenic variant PPA cases are caused by Alzhemier's disease.
- The rest of cases are caused by tau related pathology.



AJNR Am J Neuroradiol 38:954–60 May 2017

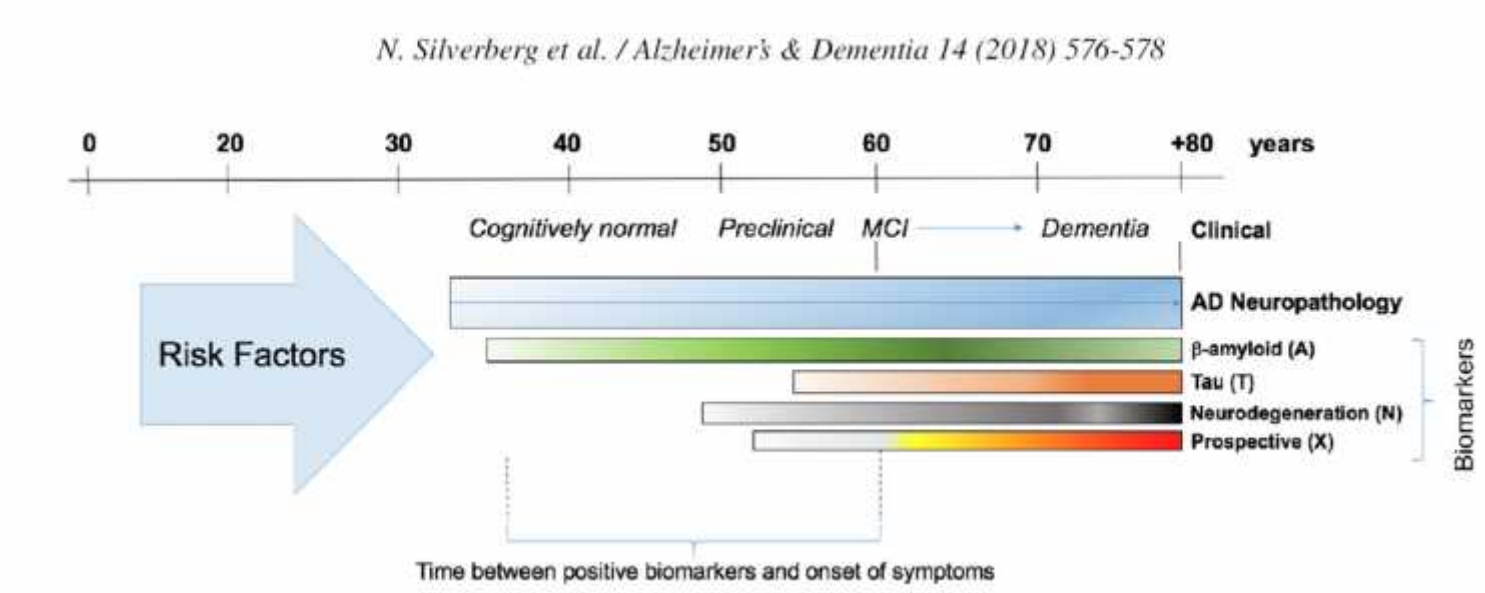
Frontal variant of AD

- First coined by JK Johnson in Arch Neurol, 56: 1233-9, 1999.
- This form is currently endorsed by the IWG-2 as a formal subtype of atypical Alzheimer disease.
- Frontal variant of AD defined by the presence of early, predominant, and progressive behavioural changes.
- Presents with primary apathy or behavioural disinhibition.
- On cognitive testing there is predominant executive dysfunction.



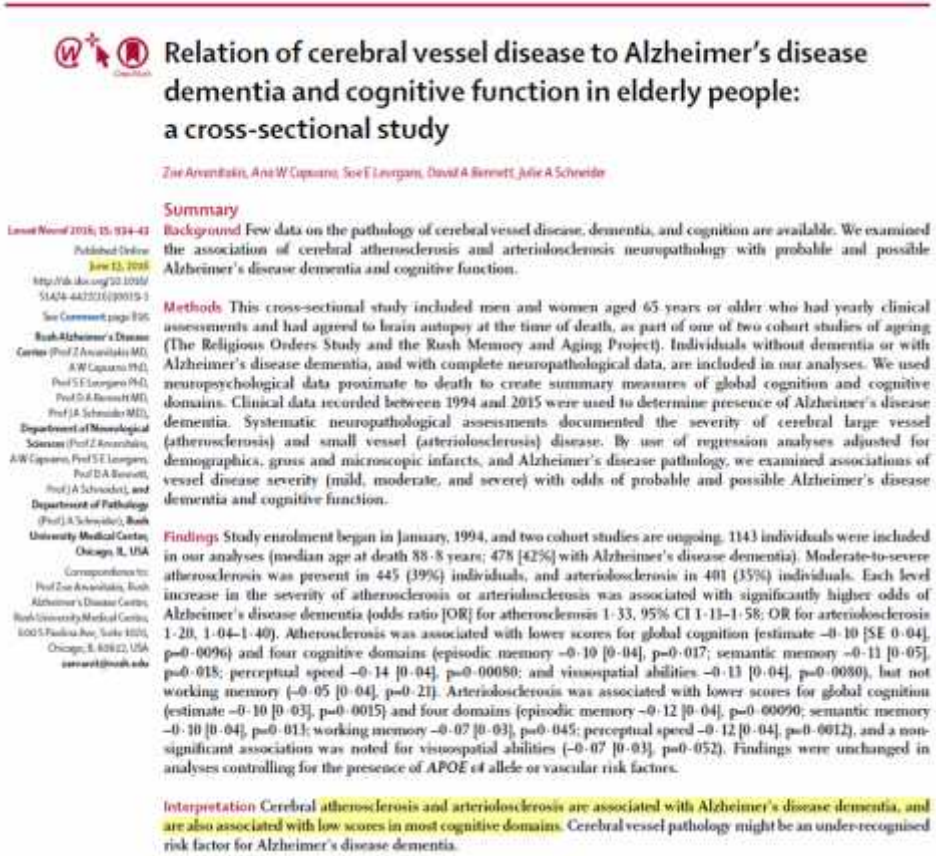
NEUROCASE 2019, VOL. 25, NOS. 1–2, 48–58

Living with Alzheimer's disease



The effect of comorbid pathology

Alzheimer's and Co-Pathologies



Relation of cerebral vessel disease to Alzheimer's disease dementia and cognitive function in elderly people: a cross-sectional study

Zoe Arvanitakis, Ana W Capuano, Sue E Leurgans, David A Bennett, Julie A Schneider

Lancet Neurol 2016; 15: 934–43
Published Online
June 13, 2016
http://dx.doi.org/10.1016/S1474-4422(16)30115-1
See Comment page 896

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Summary

Background Few data on the pathology of cerebral vessel disease, dementia, and cognition are available. We examined the association of cerebral atherosclerosis and arteriolosclerosis neuropathology with probable and possible Alzheimer's disease dementia and cognitive function.

Methods This cross-sectional study included men and women aged 65 years or older who had yearly clinical assessments and had agreed to brain autopsy at the time of death, as part of one of two cohort studies of ageing (The Religious Orders Study and the Rush Memory and Aging Project). Individuals without dementia or with Alzheimer's disease dementia, and with complete neuropathological data, are included in our analyses. We used neuropsychological data proximate to death to create summary measures of global cognition and cognitive domains. Clinical data recorded between 1994 and 2015 were used to determine presence of Alzheimer's disease dementia. Systematic neuropathological assessments documented the severity of cerebral large vessel (atherosclerosis) and small vessel (arteriolosclerosis) disease. By use of regression analyses adjusted for demographics, gross and microscopic infarcts, and Alzheimer's disease pathology, we examined associations of vessel disease severity (mild, moderate, and severe) with odds of probable and possible Alzheimer's disease dementia and cognitive function.

Findings Study enrolment began in January, 1994, and two cohort studies are ongoing. 1143 individuals were included in our analyses (median age at death 88·8 years; 478 [42%] with Alzheimer's disease dementia). Moderate-to-severe atherosclerosis was present in 445 (39%) individuals, and arteriolosclerosis in 401 (35%) individuals. Each level increase in the severity of atherosclerosis or arteriolosclerosis was associated with significantly higher odds of Alzheimer's disease dementia (odds ratio [OR] for atherosclerosis 1·33, 95% CI 1·11–1·58; OR for arteriolosclerosis 1·20, 1·04–1·40). Atherosclerosis was associated with lower scores for global cognition (estimate −0·10 [SE 0·04], p=0·0096) and four cognitive domains (episodic memory −0·10 [0·04], p=0·017; semantic memory −0·11 [0·05], p=0·018; perceptual speed −0·14 [0·04], p=0·00080; and visuospatial abilities −0·13 [0·04], p=0·0080), but not working memory (−0·05 [0·04], p=0·21). Arteriolosclerosis was associated with lower scores for global cognition (estimate −0·10 [0·03], p=0·0015) and four domains (episodic memory −0·12 [0·04], p=0·00090; semantic memory −0·10 [0·04], p=0·013; working memory −0·07 [0·03], p=0·045; perceptual speed −0·12 [0·04], p=0·0012), and a non-significant association was noted for visuospatial abilities (−0·07 [0·03], p=0·052). Findings were unchanged in analyses controlling for the presence of *APOE* ε4 allele or vascular risk factors.

Interpretation Cerebral atherosclerosis and arteriolosclerosis are associated with Alzheimer's disease dementia, and are also associated with low scores in most cognitive domains. Cerebral vessel pathology might be an under-recognised risk factor for Alzheimer's disease dementia.

Alzheimer’s and Co-pathologies

- Autopsy studies have shown coexisting AD pathology in most DLB cases.
- Up to 60% of AD cases have Lewy-type synucleinopathy (LTS) pathology.
- DLB-patients with a CSF AD profile have a more severe manifestation of the disease and a higher risk of institutionalisation and mortality.

Lemstra AW, de Beer MH, Teunissen CE, et al. J Neurol Neurosurg Psychiatry 2017;88:113– 118.

Limbic-predominant Age-related TDP-43 Encephalopathy (LATE)

- LATE-NC Neuropathological Change is present in > 20% (up to 50%) of individuals older than 80 years according to large community-based autopsy series.
- The overall public health impact of LATE is comparable to Alzheimer's disease.
- LATE is often comorbid with AD.
- LATE is associated with substantial disease-specific cognitive impairment, usually an amnestic dementia syndrome ('dementia of the Alzheimer's type').

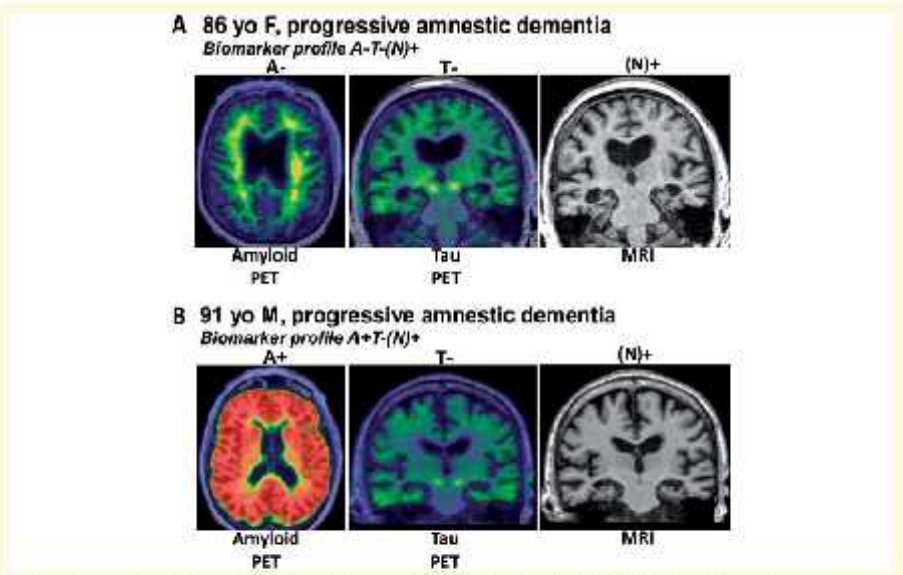


Figure 5 Biomarkers are currently not specific to LATE-NC. (A) Radiological scans from an 86-year-old female who suffered amnestic cognitive impairment compatible with 'Probable Alzheimer's disease' diagnosis. However, the amyloid-β PET scan was negative, tau PET scan was also negative, and the MRI showed appreciable atrophy of the medial temporal lobes bilaterally. This combination is considered 'A−T−N+' and was diagnosed during life as 'suspected non-Alzheimer's pathology' (SNAP). Autopsy within a year of the brain scans confirmed the presence of TDP-43 pathology and hippocampal sclerosis, which now is diagnosable as LATE-NC. (B) Another common biomarker combination, in the brain of a 91-year-old male with dementia. In this subject, the amyloid PET scan was positive, yet the tau PET scan was negative. The MRI again showed atrophy of the medial temporal lobes. The combination of pathologies—in this case presumed early ADNC and comorbid LATE-NC—is common, especially in the brains of subjects in advanced age.

BRAIN 2019: 0; 1–25

Co-morbidities with Alzheimer's disease in advanced ages

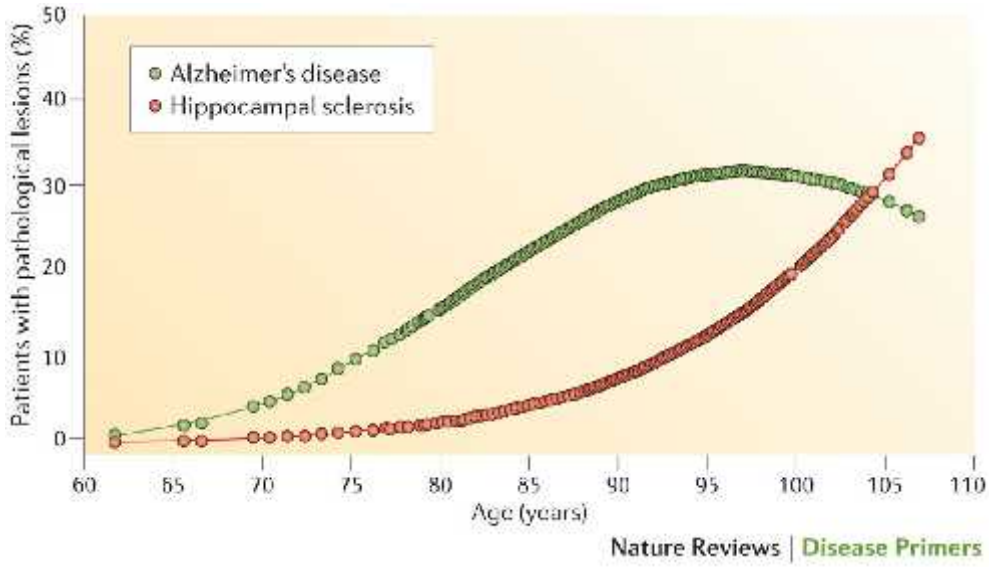


Figure adapted from Nelson, P. T. *et al.*, Hippocampal sclerosis in advanced age: clinical and pathological features, *Brain*, 2011, **134**, 1506– 1518, by permission of Oxford University Press

Masters, C. L. *et al.* (2015) Alzheimer's disease
Nat. Rev. Dis. Primers doi:10.1038/nrdp.2015.56

Early onset Alzheimer's disease EOAD

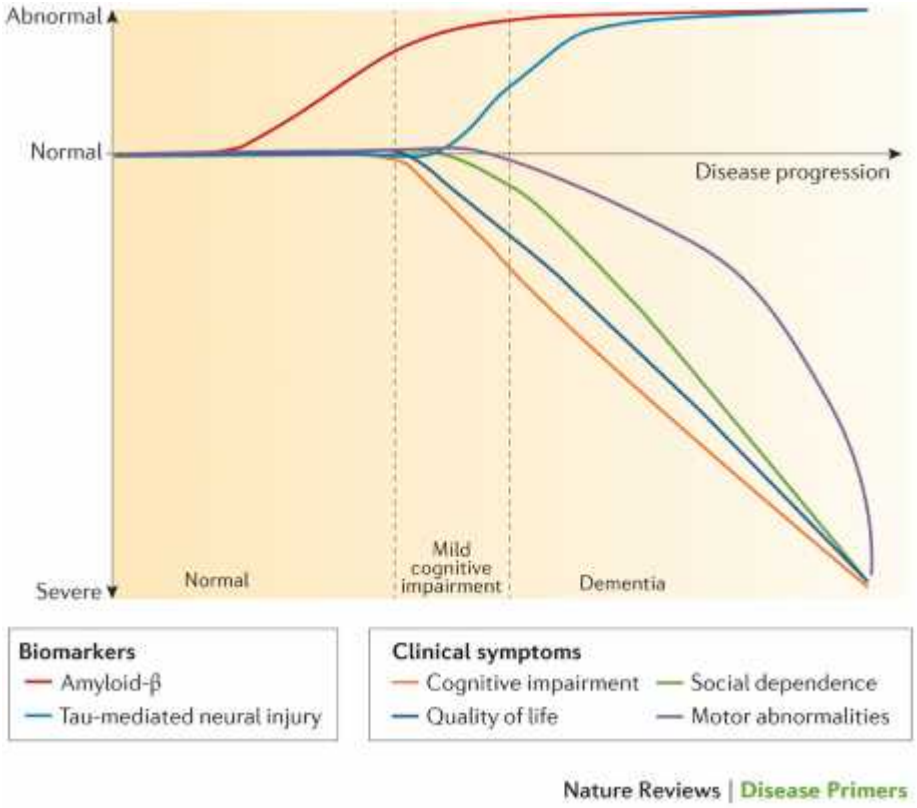
	Typical AD	Atypical AD
Presenting clinical feature	Memory	Non-memory
Disease course	Less aggressive	More aggressive
Age at onset	Mean 75 years	Mean 55 years
APOE genotype	Promoted by one or two ε4 alleles	Promoted by absence of ε4 alleles
Neuropathology	Plaques and tangles	Plaques and tangles
CSF biomarker concentrations	Decreased $A\beta_{1-42}$ and increased tau and ptau	Decreased $A\beta_{1-42}$ and increased tau and ptau
PET		
FDG	Decreased temporoparietal metabolism, especially in medial temporal lobe	Decreased temporoparietal metabolism, especially in posterior cortex
^{11}C-PiB	Increased uptake	Increased uptake
Structural MRI	Hippocampal atrophy	Temporoparietal atrophy, frontoparietal atrophy, or both

The atypical phenotype of AD seems to be promoted by a younger age at onset in the absence of the *APOE* ε4 allele. Biomarker profiles suggest that both subtypes have the same pattern of senile plaques and neurofibrillary tangles, but that hypometabolism and atrophy differ, which suggests that genetic factors, environmental factors, or both, cause vulnerability in specific and distinct regions. AD=Alzheimer's disease. $A\beta_{1-42}$=amyloid β protein 42. tau=total microtubule-associated protein tau. ptau=phosphorylated microtubule-associated protein tau. FDG=^{18}F-fluorodeoxyglucose. ^{11}C-PiB=^{11}C-Pittsburgh compound B.

Table: **Clinical and biomarker characteristics of typical and atypical AD**

The Lancet.com/neurology Vol 10 March 2011

Quality of life of patients with Alzheimer's disease



Masters, C. L. *et al.* (2015) Alzheimer's disease
Nat. Rev. Dis. Primers doi:10.1038/nrdp.2015.56

The amyloid hypothesis

An imbalance between production and clearance of Ab -42 and related Ab peptides is a very early, often initiating factor in Alzheimer's disease (AD).

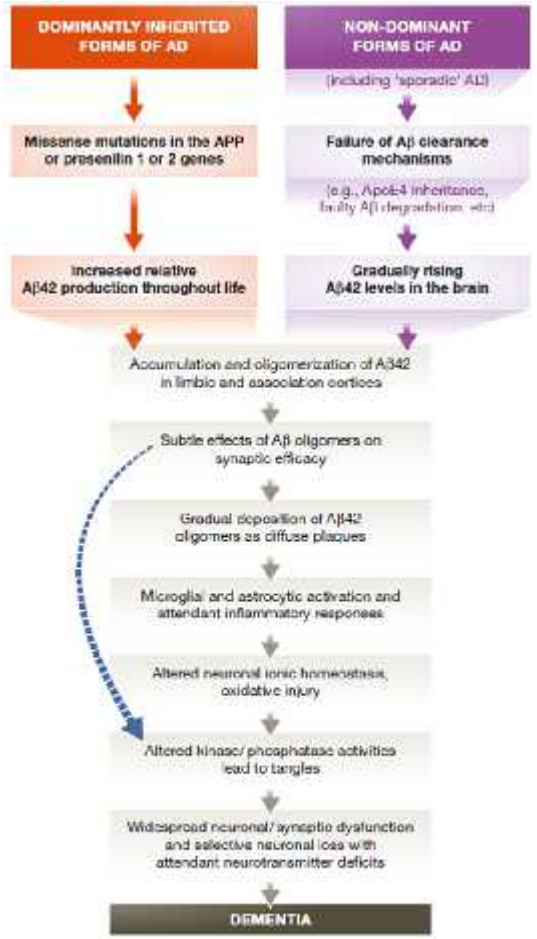
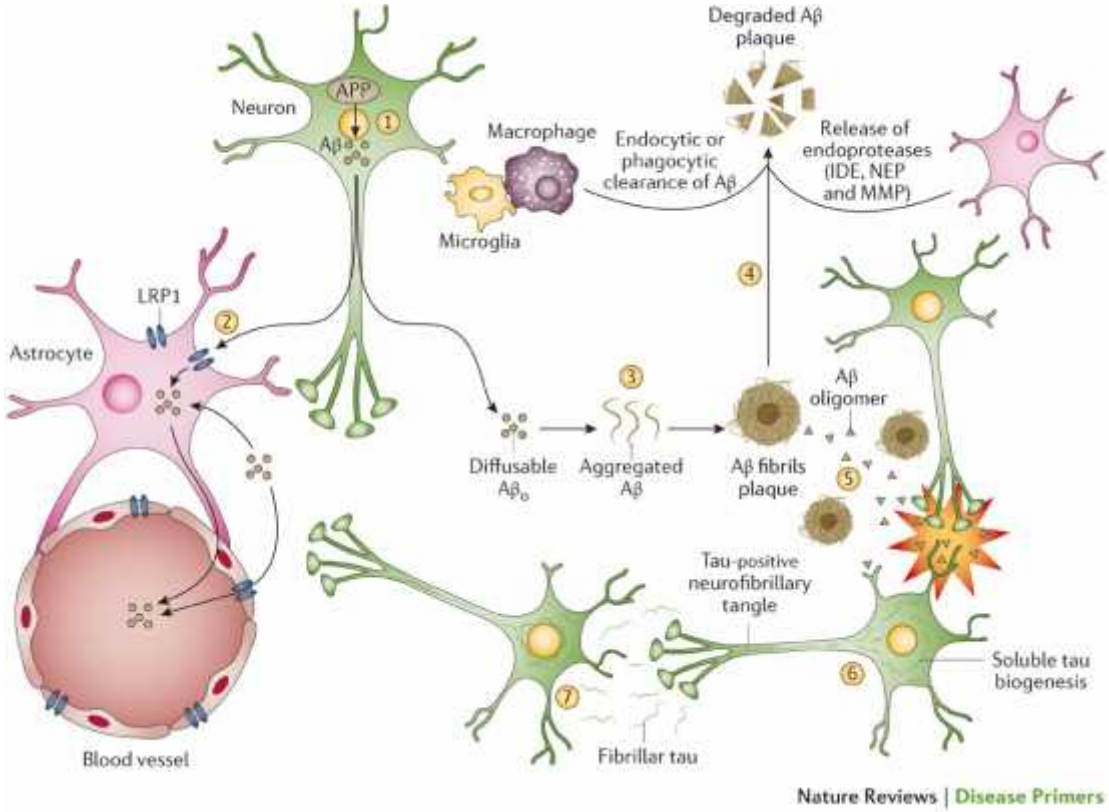


Figure 1. The sequence of major pathogenic events leading to AD proposed by the amyloid cascade hypothesis.
The curved blue arrow indicates that Aβ oligomers may directly injure the synapses and neurites of brain neurons, in addition to activating microglia and astrocytes.

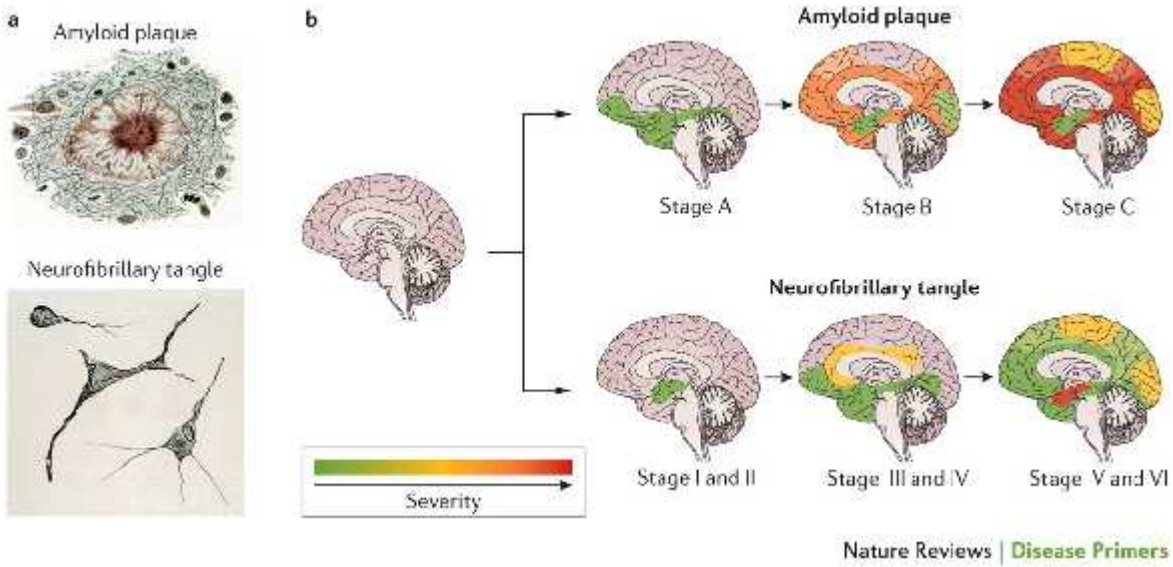
EMBO Molecular Medicine Vol 8 | No 6 | 2016

Pathways leading to plaques and tangles form the basis of the amyloid-β theory of Alzheimer's disease



Masters, C. L. *et al.* (2015) Alzheimer's disease
Nat. Rev. Dis. Primers doi:10.1038/nrdp.2015.56

The pathological evolution of Alzheimer's disease



Part **a** adapted with permission from Spielmeyer, W. *Histopathologie des Nervensystems* (Julius Springer, 1922), Julius Springer. Part **b** adapted with permission from Braak, H. & Braak, E. Frequency of stages of Alzheimer-related lesions in different age categories. *Neurobiol. Aging* **18**, 351–357 (1997), Elsevier

Masters, C. L. *et al.* (2015) Alzheimer's disease
Nat. Rev. Dis. Primers doi:10.1038/nrdp.2015.56

Potential strategies to manipulate amyloid-β in Alzheimer's disease

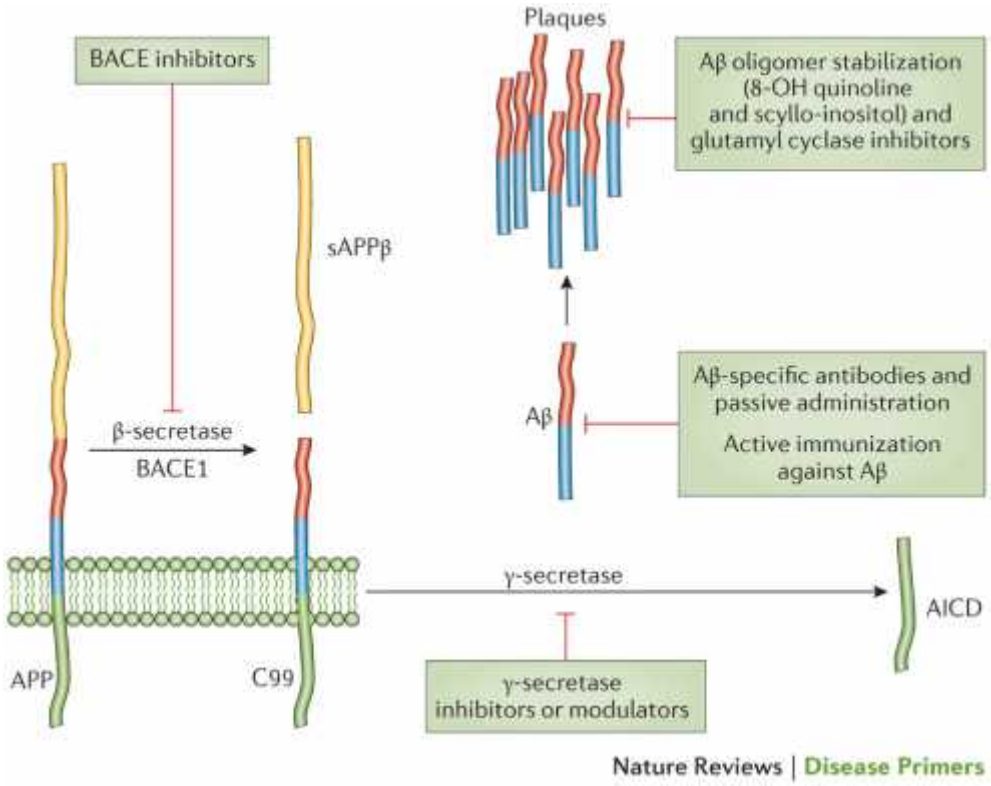


Figure from Thathiah, A. & De Strooper, B. The role of G protein-coupled receptors in the pathology of Alzheimer's disease. *Nat. Rev. Neurosci.* **12**, 73–87 (2011), Nature Publishing Group

Masters, C. L. *et al.* (2015) Alzheimer's disease
Nat. Rev. Dis. Primers doi:10.1038/nrdp.2015.56

Take home message

Alzheimer disease is a complex disease

The definition of Alzheimer disease is evolving

Alzheimer disease has many atypical forms that need to recognized for accurate diagnosis

The amyloid hypothesis is under grave scrutiny with failure of anti-amyloid therapy