

Article

# Alzheimer disease categorization and fundamental anatomy

Mariam Hussian Hameed <sup>1</sup>, 

<sup>1</sup> Cosmetic and Laser Department, Collage of Health and Medical Technology, Imam Ja'afar Al-Sadiq University, Baghdad, Iraq; mariam\_hussian@ijsu.edu.iq

**Abstract:** The pathological features of Alzheimer's disease include protein buildup, neuronal and synaptic loss, and changes associated with reactive processes. Extracellular antibody buildup manifests in the parenchyma as diffuse, localized, or stellate deposits. It may pertain to the vascular walls of arteries, veins, and capillaries. Instances where the capillary vessel walls are compromised show an elevated likelihood of possessing one or two apoe 4 alleles. Parenchymal and vascular antibody deposition occurs in a sequential manner. Tau accumulation, likely the most significant histological correlate of clinical symptoms, manifests in three forms: inside the neuronal cell body as neurofibrillary tangles, in the dendrites as neuropil threads, and in the axons as the neuritic corona of senile plaques. Tau disease advances in a sequential and predictable manner from the entorhinal cortex, via the hippocampus, to the isocortex. The neuronal loss is variable and particular to certain areas. The mechanism remains a subject of discussion. The timing of synapse loss, likely associated with the Ab peptide, maybe in the form of oligomers, remains contentious. Multiple clinico-pathological variants of Alzheimer disease have been characterized based on lesion type (plaque-only and tangle-predominant), onset type (focal onset), etiology (genetic or spontaneous), and accompanying lesions (Lewy bodies).

**Keywords:** basic pathology; Alzheimer disease; Classification

**MSC:**

**Citation:** To be added by editorial staff during production.

Academic Editor: Firstname Last-name

Received: 10/5/2025

Revised: 27/5/2025

Accepted: 15/7/2025

Published: 20/7/2025



**Copyright:** © 2025 by the authors. Submitted for possible open access publication under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

## 1. Introduction

The pathogenesis of Alzheimer's disease (AD) has been extensively researched during the last two decades. Animal models have yielded significant insights into the pathogenetic pathways. Reviewing this extensive material in a single piece has proven unfeasible. This is why we will not systematically evaluate the animal models; the reader is directed to another review by the same authors.

The lesions associated with accumulation mostly consist of extracellular deposition of Ab peptide and intracellular aggregation of tau protein. Both Ab peptides and tau protein are normal biological components that, in Alzheimer's disease, adopt an aberrant fibrillary form characterized by low solubility in aqueous solutions. Nonetheless, the correlation between the two lesion types remains ambiguous [1].

The deposition of Ab pertains to a discrepancy between its synthesis and elimination. The Ab peptide is derived from its precursor, the amyloid precursor protein (APP), a transmembrane protein, through two successive enzymatic processes: b-secretase cleaves APP in its extracellular domain, resulting in a fragment known as C99, which is subsequently cleaved by the transmembrane gamma-secretase complex that comprises presenilin. The subcellular compartmentalization of these sequential cleavages is still under discussion. It is now widely acknowledged that the last stages occur inside the endosomal-lysosomal pathway. The deposits include a combination of different Ab isoforms,

with some starting at amino acid (AA) 11 (referred to as "N-truncated" isoforms) or concluding at AA 39 to 42. A prevalent variant starts at position 3, with the first glutamine residue having undergone cyclization into pyroglutamate [2]. The isoform terminating at AA 42 has two more amino acids at the C-terminus of the peptide, resulting in an extended section integrated inside the cell membrane; it exhibits increased hydrophobicity and a tendency to precipitate in aqueous solution. Mutations in APP, presenilin 1, and presenilin 2 are linked to an elevation in Ab production and an increased ratio of Ab42 to Ab40.

The Ab peptide has an inherent propensity to oligomerize; oligomers, often referred to as ADLL (Ab-derived diffusible ligands), may represent the hazardous entities. Oligomers likely develop intracellularly [3].

## 2. Materials and Methods

The Ab peptide is often undetectable by immunohistochemistry in the brains of healthy young people. Ab deposition occurs in some elderly individuals deemed cognitively normal (pathological aging), in patients with moderate cognitive impairment (MCI), in those with advanced sporadic or familial Alzheimer's disease (AD), and in individuals with trisomy 21. The terminology about Ab peptide deposition is perplexing. The word "senile plaque" has been used in several contexts, rendering it imprecise. We consciously sought to restrict its use to the so-called mature neuritic plaque, particularly when discussing the lesion without specifying the method employed for its revelation. In different contexts and for clarity, all forms of extracellular accumulation are referred to as deposits, followed by a qualifying phrase that characterizes their mode of revelation, e.g. Antibody deposits are identified by anti-antibody antibodies, whereas amyloid deposits are detected using Congo red or thioflavin S staining (Figure 1). A further qualifying phrase may indicate their morphology: diffuse, localized, or stellate Ab deposits [4]. The neuritic element of the plaque forms its corona (Figure 1).

Localized deposits Alongside diffuse deposits, immunohistochemistry reveals dense, spherical accumulations of Ab peptide, referred to as focal deposits. The focused deposits are visible on slides stained with hematein and eosin (Figure 2), but the diffuse deposits remain unstained. Focal deposits may be amyloid or non-amyloid, with or without an accompanying neuritic corona.

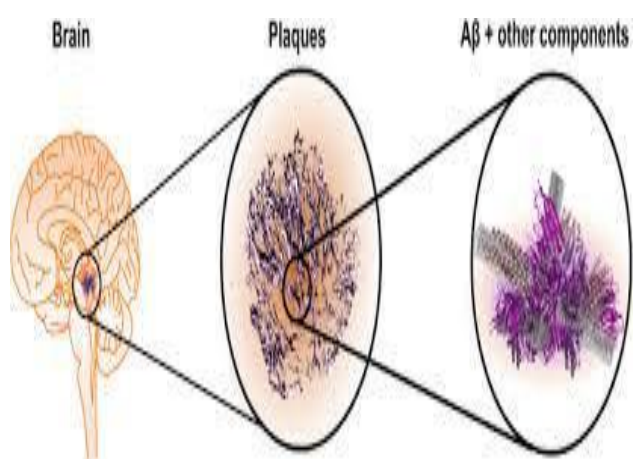


Figure 1. Terms used to describe Ab deposits and senile plaques.  
Various aspects of Ab deposition, as seen with Ab and tau immunohistochemistry

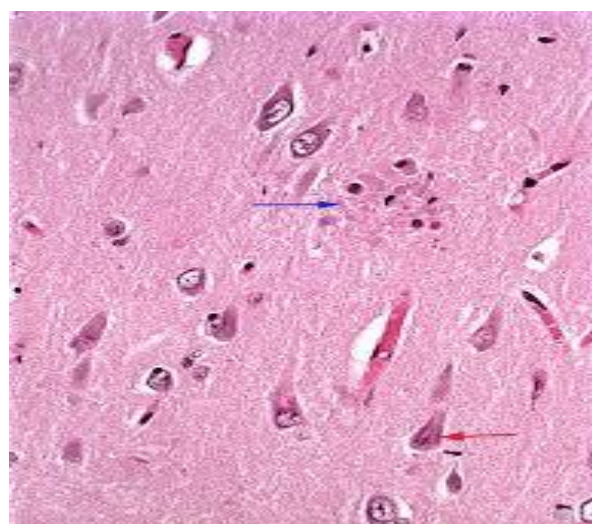


Figure 2. Aspects of the senile plaque, the senile plaque as seen after hematein-eosin stain.

Amyloid or otherwise Certain localized deposits lack amyloid tinctorial properties yet may be readily identified using antibody immunohistochemistry. It is reported that they mostly comprise the Ab-40 peptide. Additional focal deposits consist of amyloid, identifiable by Congo red or thioflavin S staining. CD-68 positive, active microglia are almost always associated with the amyloid focal deposits [5]. This discovery may be elucidated by two distinct scenarios: either the microglial cell is essential for the conversion of diffuse amyloid deposits into amyloid, or it is the structure of amyloid that triggers microglial activation. A multitude of microglial receptors, outside the purview of this study, have been shown to participate in this response. Microglial cells release cytokines that initiate and maintain persistent non-immune inflammation.

The astrocytic element Neuritic plaques are encircled by astrocytic processes; in contrast to microglial cells that interact with the amyloid core, the fibrous astrocytes are situated in the plaque's perimeter. Evidence suggests that the astrocytic component emerges later in the development of the senile plaque; the prevalence of astrocytic processes infiltrating the plaque's core may be associated with a regressive phase of the lesion [6].

The predominant quantity of Ab deposits is situated in the gray matter; however, streaks of diffuse deposits may be seen in the white matter. Neuritic plaques are mostly located in layers II and III. The areal architecture of Ab deposition is contingent upon the illness stage and is not arbitrary. Two methods for staging this process have been documented. In the Braak system, just the cerebral cortex is considered. In stage A, amyloid deposits are located in the basal sections of the cortex; in stage B, the whole isocortex is affected, except the primary cortices, with moderate involvement of the hippocampus; in stage C, deposits are present across all regions of the isocortex, including sensory and motor core fields.

The microscopic alterations discussed in the previous paragraphs explain the macroscopic observations. The atrophy typical of Alzheimer's disease encompasses regions where tau pathology is predominant, with neuronal loss, including in the entorhinal cortex, hippocampus, and amygdala. The inferior temporal and superior and middle frontal gyri are significantly impacted, although the inferior frontal and orbitofrontal gyri remain unaffected. The causative relationship between synaptic loss or process loss and atrophy, independent of neuronal loss, remains uncertain; nonetheless, a robust association has been shown between neuronal loss and atrophy in Alzheimer's disease [7]. Atrophy is not associated with the amyloid load.

The oldest-old population has a weaker clinico-pathological connection. Three subgroups were created within the 317-case population by Haroutunian et al.: young-old, middle-old, and oldest-old. The oldest-old category did not show any relationships with NFT and neuritic plaque density, which rose more than tenfold with disease severity, mostly due to the reduced lesion density at that age.

identified neurofibrillary tangle density in the medial temporal lobe as the most effective indicator for differentiating between normal and MCI (amnestic type) individuals. This region includes the entorhinal cortex, subiculum, CA1, and amygdala. According to neuropathologists, "from a neuropathologic perspective, it appears that amnestic MCI is, in reality, early Alzheimer disease" since the density of neurofibrillary tangles and neuritic plaques was often greater in early AD cases compared to MCI patients. Similarly, Bennett et al. discovered AD cases in their "normal" population that met the criteria for the disease. However, after conducting more thorough tests, they came to the conclusion that AD lesions (in the intermediate or high probability range of the NIA Reagan criteria, see later) were linked to subtle changes in memory even in the so-called pre-symptomatic phase [8]. Notably, the diffuse deposits (sometimes called "diffuse plaques") do not serve as a discriminative variable in either the Knopman et al. or Markesbery et al. trials. As we will show in the next section, the accompanying changes, particularly those involving the blood vessels, and in the oldest of the lesions reduce the threshold at which symptoms begin to manifest [9].

### 3. Results

Those published under the name of Khachaturian were the first formal neuropathological criteria that were accepted globally. The researchers leaned heavily toward the idea that senile plaques, not neurofibrillary tangles, were the hallmark lesions of Alzheimer's disease. Neurofibrillary tangles were originally considered to be nonspecific since they were seen in a wide variety of diseases. This led to the development of this idea. The Khachaturian criteria outlined a method for sampling and recommended quantitative cutoff values for the density of senile plaques; these values would be affected by the patient's age and would lead to a "black and white" diagnosis of Alzheimer's disease. Looking back, it's possible that these criteria weren't stringent enough. For example, the senile plaque number threshold wasn't grounded in theory or epidemiological evidence; it was determined conventionally. In addition, the "threshold" method required a level of measurement accuracy that was not feasible back then.

The relationship between clinically determined dementia and the density of amyloid and tau pathology was formalized by the NIA Reagan criteria [349], which were based on the findings that tau pathology was the best predictor of dementia and that plaque counts could be high in subjects with minimal cognitive impairment. Lesions having a "high," "intermediate," or "low likelihood" were associated with dementia. Additional research has to be conducted to determine if lesions may have been detected even when no clinical symptoms were present. Because Alzheimer's disease lesions do not always affect adjacent areas, seemingly healthy nerve tissue borders regions with significant damage; this has led some to question if the emphasis on diagnosis was deceptive for a number of reasons.

Therefore, a scientist may sometimes get a "normal" or at least a "minimal" sample from a brain that is supposedly affected by AD. However, lesions-free entorhinal cortex or hippocampi in elderly individuals is very unusual, suggesting that Alzheimer's disease pathology is much more common than previously believed. At long last

One characteristic in the established course of AD is the presence of amyloid deposits in the neocortex and neurofibrillary tangles restricted to the hippocampus (Braak III-IV; Thal phase 1), as previously discussed. When there is no accompanying disease, these instances often progress to later stages. Poor prognosis of even these early lesions when accompanied with Lewy pathology is connected to the plaque-only phenotype, according to this theory.

Although severe astrogliosis and neuronal loss in the CA1 sector and subiculum may be seen in elderly people on their own, they can also be seen in AD, the most frequent disease involving sclerosis of the hippocampus, and other forms of the disease. Among 650 instances of Alzheimer's disease confirmed by autopsy, 3.1% had hippocampal sclerosis, according to a Viennese study. Cases with hippocampus sclerosis were older on average and more likely to have coronary heart disease, which raises the possibility that hypoxic-ischemic events were a contributing cause. Pathology involving TDP-43 may potentially increase the likelihood of developing hippocampal sclerosis.

In severe instances of Alzheimer's disease (AD), the argyrophilic grain disease (AGD) lesions could be hard to tell apart. To differentiate between neurofibrillary lesions (4R and 3R tau positive) and grains (only 4R tau positive), Fujino et al. used a particular 4 repeats (4R) tau antibody. There was a 26% prevalence of AGD in AD. AGD was associated with a somewhat older age group, an overrepresentation of the H1 tau haplotype, and a lack of the Apoe4 allele in AD patients. Given the prevalence of both conditions, it is unclear from the available research if AGD is indeed more common in the AD population or whether the correlation between the two is coincidental.

Dentate gyrus localization of TDP-43, a phosphorylated, ubiquitinated protein that abnormally accumulates in the cytoplasm of neurons in some forms of frontotemporal dementia, has been seen in up to 34% of AD patients. Compared to patients devoid of TDP-43 inclusions, they were in a more advanced clinical stage. Both hippocampus sclerosis and medial temporal atrophy were more common. In several amyotrophic lateral

sclerosis (AD) lesions, including tangles, reactive astrocytes, and neuritic plaques, caspase-cleaved TDP-43 was found. While tau buildup is not associated with TDP-43, a-synuclein pathology is in instances of AD and Lewy body disease.

## 5. Conclusions

Important strides in our knowledge of AD pathology have been achieved in the past 20 years, including the identification of lesion components, the description of pathology progression, and the clinical correlates of changes in patient or community cohorts. The progression and underlying causes of the lesions may now be better understood thanks to cutting-edge imaging methods and robust animal models. But there are still some fundamental mysteries: how sporadic AD occurs is still up for discussion, and how Ab buildup relates to tau pathology is still poorly known. We need fresh postmortem and in vivo neuropathological evidence to confirm the following theories: an increase in Ab peptide synthesis, a failure in its clearance, or an initial disruption of tau metabolism.

## References

1. Akiyama, H., et al., *Occurrence of the diffuse amyloid  $\beta$  -protein ( $A\beta$ ) deposits with numerous  $A\beta$  -containing glial cells in the cerebral cortex of patients with Alzheimer's disease.* *Glia*, 1999. **25**(4): p. 324-331.
2. Abraham, C.R., D.J. Selkoe, and H. Potter, *Immunochemical identification of the serine protease inhibitor  $\alpha$ 1-antichymotrypsin in the brain amyloid deposits of Alzheimer's disease.* *Cell*, 1988. **52**(4): p. 487-501.
3. Adalbert, R., et al., *Severely dystrophic axons at amyloid plaques remain continuous and connected to viable cell bodies.* *Brain*, 2009. **132**(2): p. 402-416.
4. Alafuzoff, I., et al., *Staging of neurofibrillary pathology in Alzheimer's disease: a study of the BrainNet Europe Consortium.* *Brain pathology*, 2008. **18**(4): p. 484-496.
5. Alafuzoff, I., et al., *Inter-laboratory comparison of neuropathological assessments of  $\beta$ -amyloid protein: a study of the BrainNet Europe consortium.* *Acta neuropathologica*, 2008. **115**(5): p. 533-546.
6. Aletrino, M., et al., *Cell loss in the nucleus raphe dorsalis in Alzheimer's disease.* *Neurobiology of aging*, 1992. **13**(4): p. 461-468.
7. Amador - Ortiz, C. and D.W. Dickson, *Neuropathology of hippocampal sclerosis.* *Handbook of clinical neurology*, 2008. **89**: p. 569-572.
8. Amador - Ortiz, C., et al., *TDP - 43 immunoreactivity in hippocampal sclerosis and Alzheimer's disease.* *Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society*, 2007. **61**(5): p. 435-445.
9. Anderson, A.J., et al., *Morphological and biochemical assessment of DNA damage and apoptosis in Down syndrome and Alzheimer disease, and effect of postmortem tissue archival on TUNEL.* *Neurobiology of aging*, 2000. **21**(4): p. 511-524.