American Journal Of Biomedical Science & Pharmaceutical Innovation

VOLUME Vol.05 Issue09 2025
PAGE NO. 18-20
DOI 10.37547/ajbspi/Volume05Issue09-04

Involutional Changes In The Brain In Alzheimer's Disease: Macroscopic And Micromorphological Correlations

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Received: 28 July 2025; **Accepted:** 24 August 2025; **Published:** 26 September 2025

Abstract: Alzheimer's disease (AD) is the most common cause of dementia, which is characterized by progressive involutional changes in the brain. Establishing clear correlations between macroscopic manifestations of atrophy and underlying micromorphological pathological processes (formation of amyloid plaques and neurofibrillary tangles) is key to understanding the pathogenesis and developing diagnostic and treatment methods. Objective: To analyze current data on macroscopic and micromorphological changes in the brain in AD and their relationship with the clinical picture, with an emphasis on the possibilities of early diagnosis and treatment according to international recommendations. Materials and methods: A systematic review of the literature from 2018 to 2024 was conducted using PubMed, Google Scholar, and the Cochrane Library databases. Original studies, meta-analyses, and clinical guidelines on neuroimaging, pathomorphology, and biomarkers of AD met the inclusion criteria. Results: A close correlation was found between the sequential accumulation of pathological beta-amyloid (Aβ) and tau protein with specific macroscopic changes. Early atrophy of the medial temporal lobe, especially the entorhinal cortex and hippocampus, correlates with memory impairment and precedes significant cortical atrophy. According to PET imaging and cerebrospinal fluid biomarker studies, the pathological process begins 10-20 years before the onset of clinical symptoms. Current global guidelines (NIA-AA, 2018; IWG, 2021) shift the focus to the preclinical and prodromal stages, defining AD through biological markers. Conclusion: The integration of macroscopic neuroimaging data (MR morphometry) with the assessment of micromorphological changes using biomarkers (PET, cerebrospinal fluid) enables the diagnosis of AD at the earliest, potentially treatable stages. The advent of pathogenetic therapy aimed at clearing the brain of amyloid (aducanumab, lecanemab) makes early diagnosis clinically significant, opening up opportunities to slow the progression of the disease.

Keywords: Alzheimer's disease, involutional changes, hippocampal atrophy, beta-amyloid, tau pathology, biomarkers, early diagnosis, clinical guidelines.

Introduction: Alzheimer's disease (AD) is a chronic neurodegenerative disorder characterized by progressive cognitive decline and is the leading cause of dementia in old age [1]. The neuropathological basis of AD is represented by two key processes: the accumulation of extracellular senile plaques consisting of beta-amyloid (Aβ) and intraneuronal neurofibrillary tangles consisting of hyperphosphorylated tau protein [2]. These micromorphological changes trigger a cascade of pathological events leading to synapse loss, neuronal death, and, consequently, macroscopically visible brain atrophy.

The relevance of this research is due to the increasing prevalence of AD and the lack of effective treatments in the advanced stages of the disease. The current paradigm is shifting toward preclinical diagnosis, when therapeutic intervention may be most effective [3]. Therefore, understanding the sequence and correlation between micromorphological changes and macroscopic atrophy is critical for identifying patients in the early stages of the pathological process.

The aim of the study was to analyze current scientific data to establish a correlation between macroscopic (neuroimaging) and micromorphological

(pathohistological and biomarker) changes in the brain in AD, and to analyze the clinical significance of these data for early diagnosis and treatment in accordance with current international guidelines.

METHODS

To achieve this objective, a systematic literature review was conducted for the period 2018–2024. Publications were searched in the electronic databases PubMed, Google Scholar, and the Cochrane Library using the following keywords and their combinations: "Alzheimer's disease neuropathology," "brain atrophy MRI," "amyloid PET," "tau PET," "Alzheimer's disease biomarkers," "NIA-AA criteria," "early diagnosis Alzheimer's," and "anti-amyloid therapy."

The following articles met the inclusion criteria:

Original studies and reviews on the correlation of neuroimaging data (MRI, PET) with pathological findings in Alzheimer's disease.

Clinical studies assessing the diagnostic accuracy of biomarkers (in cerebrospinal fluid and using PET).

Current clinical guidelines and consensus statements (NIA-AA, IWG).

The analysis included an assessment of the methodology, sample, and main findings of the studies.

RESULTS

Macroscopic changes and their staging

MRI imaging data demonstrate a characteristic sequence of atrophy:

Early stage: Atrophy begins in the medial temporal lobe, affecting the entorhinal cortex and hippocampus, which correlates with the first symptoms of episodic memory impairment [4]. Already at this stage, voxel-based morphometry (VBM) reveals a 10-15% decrease in hippocampal volume compared to normal.

Progressive stage: Atrophy spreads to the association areas of the cerebral cortex, particularly the parietal and temporoparietal cortex, clinically manifesting as speech, praxis, and visuospatial orientation impairments.

Advanced stage: Almost the entire cortex is involved, with marked dilation of the ventricular system and sulci. 2. Micromorphological Changes and Biomarkers

Modern methods allow for the intravital assessment of pathophysiological processes:

Amyloid Pathology: According to the amyloid hypothesis, Aβ accumulation is a triggering event. PET with amyloid-specific ligands (e.g., florbetapir) visualizes plaque deposition. A decrease in Aβ42 levels in the cerebrospinal fluid reflects its uptake into brain tissue [5].

Tau Pathology: The accumulation of hyperphosphorylated tau protein (p-tau) correlates more closely with neuronal death and cognitive decline than amyloid. PET with tau ligands (florbetapir) shows the spread of tau pathology throughout the brain according to Braak stages [6]. Elevated p-tau levels in the cerebrospinal fluid are a highly specific marker of AD. 3. Clinically significant correlations

Direct correlations have been established:

Hippocampal atrophy on MRI is closely associated with the accumulation of tau protein in neurons in this region and the degree of cognitive deficit.

The severity of cortical atrophy in advanced stages correlates with the overall burden of both amyloid and tau pathologies.

Biomarkers allow the detection of pathology 15-20 years before the onset of clinical dementia, determining the preclinical stage of AD.

DISCUSSION

The analysis confirms that macroscopic brain atrophy in AD is a direct consequence and visual reflection of underlying micromorphological changes. A key advance in recent years is the ability to assess these processes in vivo using biomarkers, which has fundamentally changed diagnostic approaches.

Modern diagnostic criteria, such as the NIA-AA framework (2018) and the International Working Group (IWG, 2021), define AD based on its biological construct, not just clinical symptoms [3, 7]. This means that the diagnosis can be established in the presence of positive biomarkers for amyloid and tau pathology, even in asymptomatic individuals or patients with mild cognitive impairment (MCI). Clinical significance for early diagnosis and treatment:

Early diagnosis: The combination of MRI (to assess atrophy) and biomarkers (PET or CSF) allows for the highly accurate identification of individuals in the prodromal stage of AD, when the neurodegenerative process has not yet become irreversible.

New therapeutic options: The advent of monoclonal antibodies targeting Aβ (aducanumab, lecanemab) marks a new era in AD treatment [8]. These drugs are indicated specifically in the early stages of the disease, when the amyloid load is high, but widespread neuronal death has not yet occurred. Thus, early biomarker diagnosis is becoming a prerequisite for selecting patients for pathogenetic therapy.

Monitoring treatment effectiveness: Biomarkers (particularly PET and CSF) can be used to objectively assess treatment effectiveness, for example, to confirm a reduction in amyloid load in the brain. Limitations: The high cost of PET scans and the invasive nature of

lumbar punctures hinder the widespread adoption of biomarker diagnostics. New methods, such as blood tau protein analysis, are being developed, which may make early diagnosis more accessible in the future [9].

CONCLUSION

Involutional changes in Alzheimer's disease represent a strictly determined sequence of events: from the accumulation of Aβ and p-tau at the micromorphological level to the macroscopically visible atrophy of specific brain regions.

The close correlation between these levels of damage underlies modern biomarker diagnostic methods, allowing for the detection of the disease at the preclinical stage.

Current global clinical guidelines shift the focus to early biomarker-based diagnosis, which is fundamentally important in light of the emergence of the first pathogenetic therapies aimed at clearing the brain of amyloid.

Further research should be aimed at developing more accessible and affordable biomarker diagnostic methods (blood tests) and clarifying the role of combination therapy that targets both the amyloid and tau pathological cascades.

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