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The role of neuroinflammation in the pathophysiology of Alzheimer’s disease

El rol de la neuroinflamación en la fisiopatología de la enfermedad de Alzheimer

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Editorial

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In 1906, Alois Alzheimer described Alzheimer's disease (1). He reported the clinical presentation of this patient, Augusta Deter, and explored the neuropathology after her death. Alzheimer described extracellular senile (amyloid) plaques and intracellular neurofibrillary tangles. These two alterations remain the disease’s characteristic neuropathological hallmarks of this day (1,2). The subsequent “amyloid cascade” hypothesis described the molecular mechanism by which amyloid plaques form through the pathological cleavage of a transmembrane protein called the amyloid precursor protein (APP) (3). This leads to the aggregation of β-amyloid and the formation of oligomers and fibrils, which finally result in amyloid plaques. Neurofibrillary tangles were found to be caused by the intracellular hyperphosphorylation of the tau protein (3). This leads to microtubule destabilization, resulting in neurofibrillary degeneration and neuronal death (3).

Alzheimer's disease biomarkers enable the identification of neuropathological alterations of the disease, allowing a biological diagnosis to be made during the patient's lifetime. Previously, diagnosis was based solely on neuropathology (4). However, with the development of Alzheimer's disease biomarkers, it has become possible to establish a more accurate chronology of the disease’s progression. Consequently, amyloid (A), tau (T), and neurodegeneration biomarkers were identified **(see Table 1)**.

Table 1. Biomarkers of Alzheimer’s disease.

	Neuroimaging	**CSF**	**Blood**
Amyloid Aβ proteinopathy **(A)**	Brain PET scan with amyloid marker (PiB, Florbetaben)	Aβ42, Aβ42/Aβ40	Aβ42/Aβ40
Tau **(T)**	Brain PET scan with tau marker	p-tau 181 p-tau 217 p-tau-234	p-tau 181 p-tau 217 p-tau-234
Neuro-degeneration **(N)**	Brain MRI (atrophy) Brain PET scan with metabolic marker (FDG)	Total tau NfL	Total tau NfL
Inflammation **(I)**	Brain PET scan with inflammation marker (TSPO)	sTREM2, YKL40	GFAP

Aβ: Amyloid Beta; CSF: Cerebrospinal Fluid; FDG: Fluorodeoxyglucose; GFAP: Glial Fibrillary Acidic Protein; MRI: Magnetic Resonance Imaging; NfL: Neurofilament Light; PET: Positron Emission Tomography; sTREM2: Soluble Triggering Receptor Expressed on Myeloid Cells 2; TSPO: Translocator Protein. Modified de Simrén J, et al. Adv Clin Chem 2023;112:2492–281.

The link between neuroinflammation and Alzheimer's disease was first established in 1985, when Edith and Patrick McGeer identified activated microglia in the vicinity of amyloid plaques in patients with Alzheimer's disease (1,2). They also noted that patients with rheumatoid arthritis who were treated with anti-inflammatory drugs had a lower incidence of the disease. The use of non-steroidal anti-inflammatory drugs for prevention or treatment was attempted for several years, but the results were not significant (3,5).

However, in recent years, the number of studies on inflammation and Alzheimer's disease has grown significantly, increasing from one publication in 1985 to over 1,840 in 2024, according to PubMed (1). Inflammation is present throughout the course of the disease, as demonstrated by the activation of microglia and astrocytes, the release of cytokines and chemokines, and the activation of the complement system (5) **(see Figure 1)**.

However, the inflammatory process does not behave in the same way throughout the disease. As can be seen with microglia and astrocytes, it evolves in two-phases (3,5).

Microglia originate from the mesoderm and migrate to the central nervous system (CNS) during development (3,5). They account for 10 to 15% of all brain cells. Their main functions in the CNS include maintaining homeostasis, phagocytosis, surveillance, communication, and synaptic selection. Microglia cells have three phenotypes: M0 which is neutral or resting, and two active ones, M1 proinflammatory and M2 which is anti-inflammatory (2,3) **(see Figure 2)**. Their morphology is branched when at resting phase and amoeboid when activated. The M2 phenotype is characterized by the presence of anti-inflammatory cytokines including TGF-B (transforming growth factor B), IL-4, IL-10, and IL-12, and enhances phagocytosis (4,6). In contrast the M1 phenotype promotes inflammation and increases the concentrations of pro-inflammatory cytokines, including TNF alpha, IL-4, IL-6, IL-12, and IL-18, whilst impairing phagocytosis. In AD, neuroinflammation increases with disease progression (5,6).

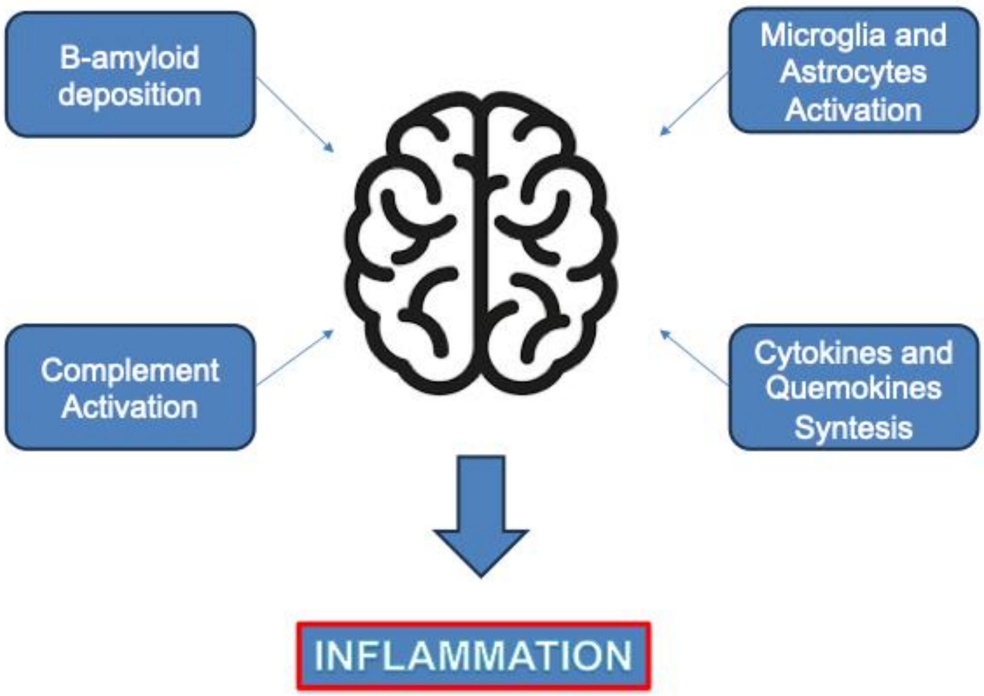

Figure 1. Inflammatory process in Alzheimer's disease. Source: authors.

Astrocytes, which develop from neural stem cells, are the most abundant glial cells in the CNS. Their primary functions include maintaining homeostasis, supporting the blood-brain barrier, and providing synaptic support. There are two types of astrocytes: neurotoxic A1 and neuroprotective A2. When activated, they become thinner and have a larger cytoplasmic body (6).

Activation of the classical complement cascade also leads to greater neuroinflammation. There are two pathways: one classical and one alternative. The presence of β-amyloid deposits activates the classical complement pathway (3,4,6).

The presence of small amyloid B oligomers activates microglia and astrocytes, which are neurotoxic. This activates M2 microglia, which have an anti-inflammatory effect (releasing IL-10, TGF-β; and IGF1) and promote the clearance of β amyloid by phagocytosis (3). However, when inflammation becomes chronic, the microglia transform into M1 (releasing TNF- α; IL-1 β, and ROS/NRS) while the astrocytes transform into A1 (6). This generates a pro-inflammatory effect, attenuates phagocytosis, and significantly increases inflammation and tau hyperphosphorylation (5). The result is synaptic dysfunction, neuronal injury, neurodegeneration, and neuronal death. Subsequently, tau aggregates are released into the extracellular space, also activating glia and increasing neuroinflammation (5,6).

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All of this led to a modification of the classic **Figure 3** of the chronopathology of Alzheimer's disease being modified to include neuroinflammation and its biphasic component, initially anti-inflammatory, then pro-inflammatory (5).

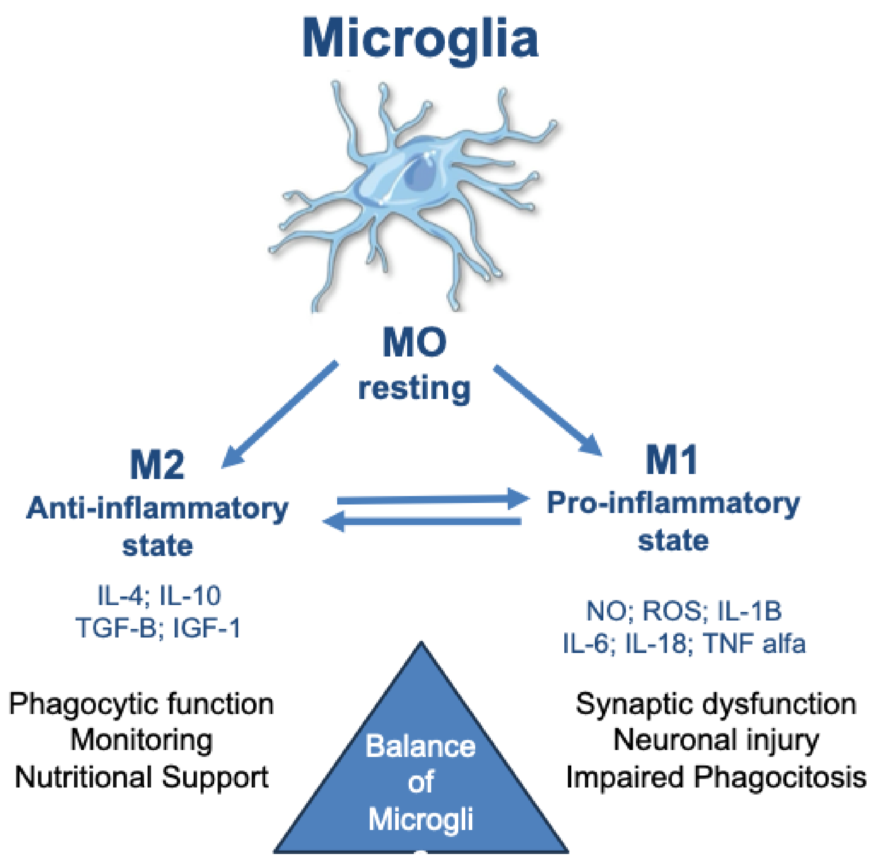

Figure 2. Microglia in Alzheimer's Disease.

The inflammatory component also features in the new diagnostic criteria for Alzheimer's disease by Jack et al. (2), from the Alzheimer's Association. These authors categorize Alzheimer's disease biomarkers as follows 1) core biomarkers; 2) non-specific biomarkers that are part of the pathophysiology; and 3) biomarkers of non-Alzheimer's co-pathologies **(see Table 2)**.

Finally, given that anti-inflammatory treatments for Alzheimer's disease are being researched, we wonder how much importance is being given to neuroinflammation. Cummings et al. (1) review of drugs in development reports, two phase 3 clinical trials, 19 phase 2 trials, and four phase 3 trials. The two phase 3 trials are: 1) Semaglutide (a GLP-1 agonist with insulin-sensitive and anti-inflammatory effects produced by Novonordisk pharmaceutical industry) and Masitinib (a small-molecule tyrosine kinase inhibitor with neuroprotective properties via the inhibition of mast cell and microglia activity produced by AB Science laboratory) (1). However, neuroinflammation is given greater importance in phase 2, where compounds that act on neuroinflammation account for 23% of the total, compared to 12% for anti-amyloid antibodies and 7% for anti-tau antibodies (1).

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Among Alzheimer's researchers, there has long been a distinction between “amyloidists” and “tauoists”, depending on whether they consider amyloid pathology or tau pathology to be central to the disease’s pathophysiology (1). Recently, a third group has emerged, the “inflammatoists”, who believe that inflammation is essential to the development of the disease (1,2).

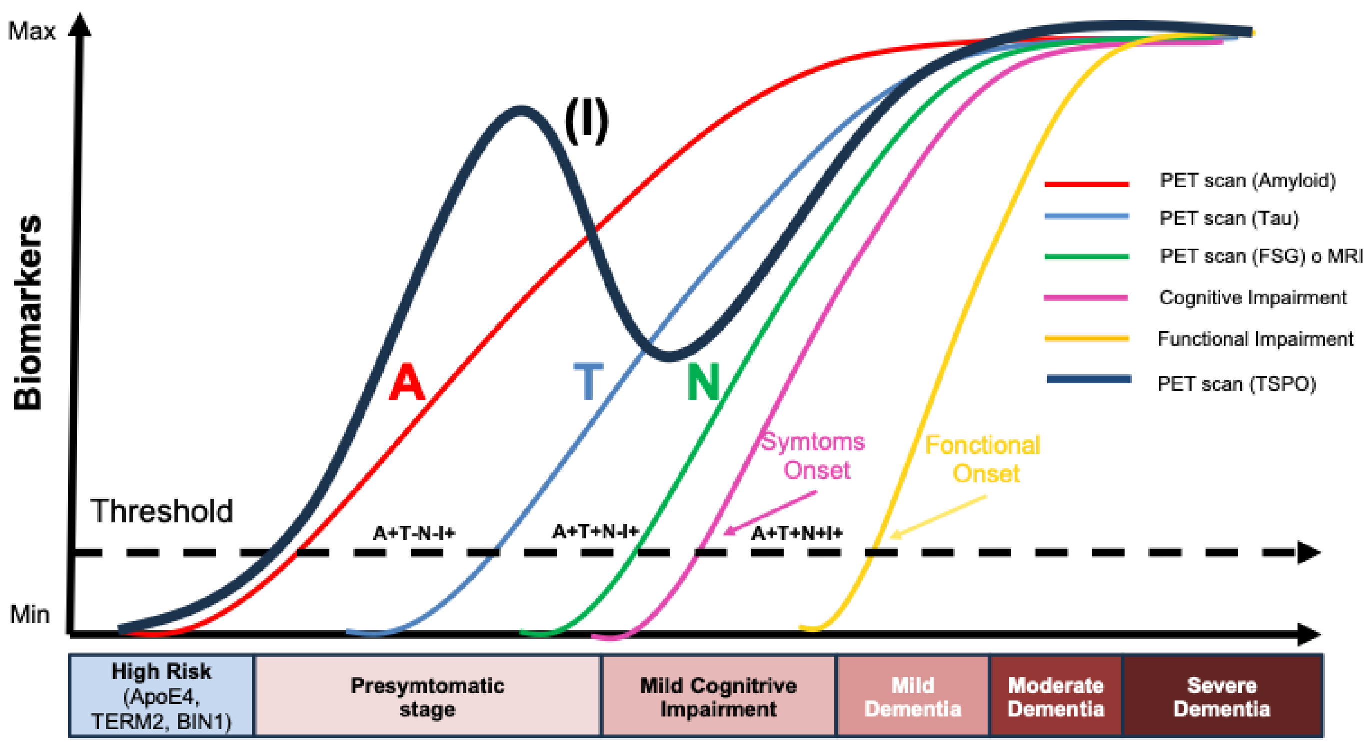

Figure 3. Chronopathology based in Alzheimer’s disease biomarkers. Modified from Budson et al, Practical Neurol, 2012.

Table 2. Categorization of biomarkers for Alzheimer’s disease.

Category of Biomarkers	CSF or Blood	Neuroimaging
Central biomarkers		
Core 1 A (Aβ proteinopathy) T1 (p-tau of Alzheimer)	Aβ-42 p-tau 188 p-tau 217 p-tau 231	Amyloid PET scan
Core 2 T2 (tau proteinopathy of AD)	MTBR-tau 243	Tau PET scan
Biomarkers non-specific but part of the process		
N (injuy, degeneration, dysfunction	NfL	MRI scan (anatomic) FDG PET scan

I (inflammation) Astrocites activation	GFAP	
Non AD biomarkers		
V (vascular)		MRI scan
S (alfa synuclein)	Alfa synuclein	

Aβ: Amyloid Beta; AD: Alzheimer's disease; CSF: Cerebrospinal Fluid; FDG: Fluorodeoxyglucose; GFAP: Glial Fibrillary Acidic Protein; MRI: Magnetic Resonance Imaging; MTBR: Microtubule-Binding Region; PET: Positron Emission Tomography.

This suggests that, in the future, treatment of the disease will depend on different pathophysiological alterations. However, it will also depend on the ideal timing of these actions for each patient (precision medicine). Exciting times lie ahead in the field of Alzheimer's disease pathophysiology and treatment.

Conflicts of interest

The authors declare no conflict of interest.

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None.

Ethics statement

Not applicable.

Data, Materials, and Code Availability

This manuscript did not conduct data analysis.

Contributor roles

Ricardo F. Allegri: Conceptualization, Investigation, Writing – original draft, Writing – review & editing. Ernesto Barceló: Conceptualization, Investigation, Writing – original draft, Writing – review & editing. Fabian Román: Conceptualization, Investigation, Writing – original draft, Writing – review & editing.

AI Usage Disclosure

This manuscript did not use artificial intelligence for information processing or writing.

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