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Research Article

Clinical Impact of the Use of Biomarkers in the Diagnosis of Alzheimer's Dementia

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Abstracts

Alzheimer's disease (AD) is the most common type of dementia, a condition caused by neuronal death or dysfunction. AD has an extensive preclinical stage, that initiates 15 to 20 years prior to the emergence of clinical signs that are characterized by the gradual inability to remember new information. As the disease progresses, higher cognitive functions are impaired.

In 2011, the National Institute on Aging and Alzheimer's Association (NIA-A) created separate sets of diagnostic guidelines for the symptomatic or "clinical" stages of AD and the preclinical AD. The recommendations for preclinical AD were not designed for routine clinical care but rather to provide researchers a common language to identify and stage research participants who were not cognitively impaired but had abnormal AD biomarkers. A biomarker is objectively measured and evolved as an indicator of a normal biological process, pathogenic process or pharmacological response to a therapeutic intervention. The charge to the 2018 NIA-AA work group was to unify and update the 2011 recommendations.

This study tries to fulfill all the knowledge around the AD and bring some clarity and perspectives about the role of the biomarkers in AD diagnosis by doing a descriptive review of the most relevant recent studies published in scientific articles. So it will be used the database of scientific websites as the International Literature in Health Science (Medline), Scientific Electronic Library (Scielo), National Library of Medicine-NIH (PUBMED) that includes researches from the period of 2010 to 2022.

Keywords: Alzheimer; Biomarkers; Diagnosis; Neuroimaging; CSF

Introduction

Alzheimer's disease (AD) is the most common type of dementia, a condition caused by neuronal death or dysfunction [1]. AD is characterized by the gradual inability to remember new information. As the disease progresses, higher cognitive functions, such as problem solving and task completion, are impaired [2].

The Alzheimer's Association 2017 Alzheimer's Disease Facts and Figures reports the prevalence and incidence of Alzheimer's in the U.S. Among individuals age 65 and older, the prevalence in 2017 is estimated to be 5.3 million (one in 10 people age 65 and older or 10 percent have Alzheimer's dementia), and 480,000 people age 65 or older will develop Alzheimer's dementia in the U.S. in 2017 [3].

By the time that AD is clinically diagnosed, neuronal loss and neuropathologic lesions occur in many brain regions [4]. This Happens because Alzheimer's disease (AD) has an extensive preclinical stage, which is initiated 15 to 20 years prior to the emergence of clinical signs [5]. Crucial role for the suspension of

the potential damages is the timely drug delivery of neuroprotective medications before AD turns into mildly symptomatic[4]. To approach this goal, our capability to identify individuals with very mild symptoms prior to dementia needs to be improved [4].

That´s to say. the gap between the pathological processes and the cognitive symptoms has proven itself quite large, and the risk of generating hypotheses that were not based on the pathophysiological changes of AD was a reality, the NIA-AA proposed a new framework for the use of biomarkers in observational and interventional research [5]. Since the publication of the 2011 guidelines, data have continued to accumulate indicating that the cognitive decline in AD occurs continuously over a long period, and that progression of biomarker measures is also a continuous process that begins before symptoms [6].

The last advance in this field was the new research framework defined by the NIA-AA in 2018. Although not indicated for use in clinical settings, this framework unifies all the biomarkers and their use and identifies them as the most important diagnostic factors. This vision ultimately changes the idea of AD as a clinical disease into a biological disease that, in reality, begins decades before any symptom start. This creates many new future possibilities, not only in the search for a more accurate and early diagnosis, but also in the search for more specific and efficient treatments [5].

Objective

Alzheimer's disease (AD) was initially defined as a clinical-pathologic entity, which was diagnosed at autopsy and in life as possible or probable AD. However studies shown that Alzheimer's disease has an extensive preclinical stage, which is initiated 15 to 20 years prior to the emergence of clinical signs [5]. Diagnosing AD has been an absolute challenge since it was described by Alzheimer at the beginning of the 20th century [5]. In 2011, the National Institute on Aging and Alzheimer's Association (NIA-AA) created separate sets of diagnostic guidelines for the symptomatic or "clinical" stages of AD, that is, MCI and dementia [6]. The charge to the 2018 NIA-AA work group was to unify and update the 2011 recommendations in a manner that is consistent with current understanding of the AD continuum [6]. That´s to say this study tries to embrace all the knowledge around the AD and bring so clarity and perspectives about the role of the biomarkers in AD diagnosis.

Methods

Descriptive researches are the ones that has as objective discover the frequency that some phenomenon occurs and its features, causes, interplays, and connections with another phenomenon [7].

This project has the initiative of realizing a descriptive review by gathering the most relevant and recent studies published that present the relevance of biomarkers in the Diagnosis of AD to promote a better analysis of the current scenario around the disease. For this research, was done a literary review using scientific articles already published, from 2009 to November of 2022. As a database, scientific research sites such as International Literature in Health Sciences (Medline), Scientific Electronic Library Online (SciELO) and PUBMED were used.

The selections criteria were article in Portuguese and English with text in full during the established time and indexed with the followed terms of the Health Sciences Descriptors (DeCS): "Alzheimer", "Biomarkers", "Diagnosis", "Neuroimaging", "CSF". The search included different combinations of the previously described words, but all the described terms will be analyzed by a initial search with the combined aspects Alzheimer + Biomarkers + 01 final term between the ones previously cited. It was considered observational studies descriptive or analytic that approach an analysis about Biomarkers in the Alzheimer diagnosis and were excluded any case report or studies that does not approach the proposed theme.

Preclinical Stages of AD

Preclinical AD is as a long continuum where AD neuropathological abnormalities begin to accumulate but cognitive ability is normal. The recommendations for preclinical AD were not designed for routine clinical care but rather to provide researchers a common language to identify and stage research participants who were not cognitively impaired but had abnormal AD biomarkers

The NIA-AA criteria for preclinical AD are conceptualized as having 3 stages (Figure 1, Table 1).

Table 1: The brain pathology and biomarkers of preclinical AD divided into 03 stages

	Stage 1	Stage 2	Stage 3
Pathology	Aβ; Plaques; Synaptic deficits	Aβ; Plaques; Synaptic deficits; P-TAU	Aβ; Plaques; Synaptic deficits; P-TAU; Neuron Loss; NFT´s
Biomarkers	CSF Aβ +++	CSF Aβ ++	CSF Aβ ++
	PET Aβ +	PET Aβ ++	PET Aβ ++
		FDG PET+	FDG PET++
		CSF tau +	CSF tau ++
		MRI +	MRI ++

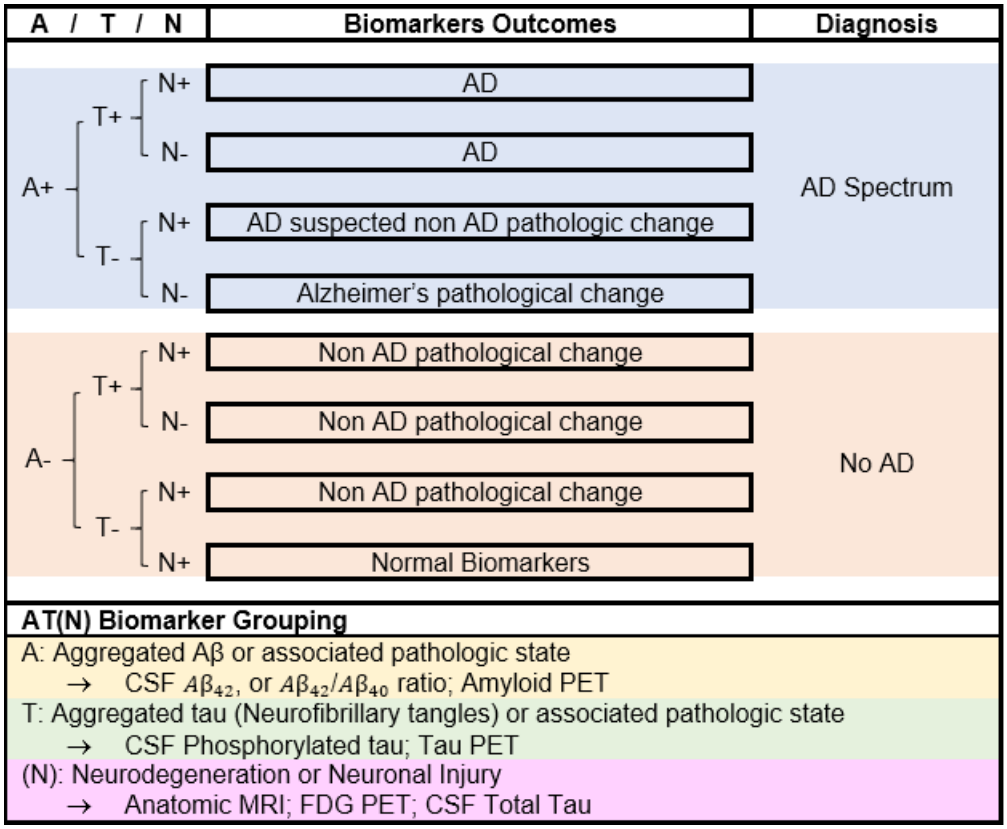

Figure 1:

Stage 1- Asymptomatic cerebral amyloidosis; Stage 2- Amyloid deposition + evidence of synaptic dysfunction and/or early neurodegeneration); Stage 03- Amyloid deposition plus evidence of neurodegeneration_

This stages represents a successive course from completely asymptomatic individuals with biomarker evidence of AD pathophysiologic changes to biomarker-positive individuals who are already demonstrating very subtle decline but not yet meeting standardized criteria for mild cognitive impairment (MCI) .

Stage 1 is where individual have a positive biomarker evidence of Aβ which can be demonstrated by positron emission tomography (PET) amyloid imaging or cerebrospinal fluid (CSF) amyloid-β (Aβ) levels, but no detectable evidence of additional brain alterations suggestive of neurodegeneration or subtle cognitive and/or behavioral symptomatology.

Stage 2 is characterized by Aβ positivity and neuronal injury markers evidenced by brain atrophy on structural MRI, hypometabolism on 18F-fluorodeoxyglucose (FDG) PET, or elevated levels of CSF tau.

Stage 3 the individuals have biomarker evidence of Aβ accumulation, Early neurodegeneration and present evidence of subtle cognitive decline [5].

The order of the NIA-AA stages promotes increasing studies to investigate the prevalence and long-term outcome of preclinical AD according to these criteria, and ultimately, aids the field in moving toward earlier intervention [8].

Although the NIA-AA criteria are based on observational data, they make specific assumptions about relationships among biomarkers and cognitive testing that have not been adequately validate [8].

Biomarcadores

A biomarker is objectively measured and evolved as an indicator of a normal biological process, pathogenic process or pharmacological response to a therapeutic intervention [1].

Biomarkers also allow researchers to monitor the effects of these treatments. The more a change in a biomarker maps onto the health of the patient, the better that biomarker is to assess whether a treatment is effective. Research on new strategies for earlier diagnosis, including ongoing efforts to identify and validate biomarkers for Alzheimer's disease, is among the most active areas in Alzheimer's Science [2].

Biomarcadores Profile

The NIA-AA proposed a new framework for the use of biomarkers in observational and interventional research.

A/T/N system was described to classify subjects according to the number of positive (Figure 2) biomarkers they presented. This system is a binary system that depends on the biomarker that is

measured. "A" refers to the value of a β-amyloid biomarker (amyloid PET or CSF Aβ42), "T" to the value of a tau biomarker (CSF pTAU, or tau PET), and "N" to biomarkers of neurodegeneration or neuronal injury (18FDG–PET, structural MRI, or CSF total-tau) [8].

If a person have an "A" biomarker positive it is classified as being in the "Alzheimer's continuum", it says that either Alzheimer's pathologic changes or AD, and those who have an positive biomarkers for both "A" and "T" categories are classified as having AD. The possible outcomes of this classification system are illustrated in Table 2 [8, 9].

Biomarker´S Grouping A/T/N Classification and Possible Outcomes

The current form of the NIA-AA research framework is designed around biomarker technology that is presently available. The AT(N) biomarker scheme is expandable to incorporate new biomarkers [8].

Biomarkers Characteristics

CSF

CSF biomarkers measures the concentration of proteins in the CSF from the lumbar sac and that is a reflection of both:

1. Production (Secretion from brain cels and neuros / protein expression)
2. Protein clearance (that comes from degradation or removal) [6].

$A\beta_{42}$ and $A\beta_{42}/A\beta_{40}$ ratio

Amyloid precursor protein (APP) is a protein responsible of the production of amyloid β peptides by b-secretase-mediated and g-secretase-mediated cleavages [10]. When a imprecise cleavage of γ -secretase at C-terminus of Aβ occurs, two major Aβ isoforms are created: $A\beta_{42}$ (42 residues long) and $A\beta_{40}$ (40 residues long). In $A\beta_{42}$ two additional C-terminal residues can be found and this is the only difference between $A\beta_{42}$ and $A\beta_{40}$.

The concentration of $A\beta_{40}$ in CSF has been found to be several-fold more when compared to $A\beta_{42}$. $A\beta_{42}$ is the major component of amyloid plaques in AD brains and $A\beta_{40}$ is detected only in a subset of plaques. Whit these findings, important conclusions can be done: $A\beta_{42}$ deposition precedes $A\beta_{40}$ deposition and the initial $A\beta_{42}$ aggregation does not involve $A\beta_{40}$.

Nowadays, the interplay between $A\beta_{42}$ and $A\beta_{40}$ is recognized as a critical role in AD [11]. The amyloid hypothesis says that Aβ monomer is not toxic but its aggregation, especially oligomers, cause toxic effects as oxidative stress, membrane permeability, change of cell skeleton, activation of apoptosis pathways in neural cells and memory retention impairment. Aβ fibrils showed much lower toxicity when compared with Aβ oligomer [12].

T-tau and P-TAU

Tau protein is a microtubule-associated protein mainly expressed in neurons that participates of neuronal cytoskeleton stabilization [13]. Tau is a highly abundant axonal protein that can be found in the neuronal cytoplasm with an estimated average concentration of 2 μM. The amount and phosphorylation of CSF Tau correlate with AD disease state and amyloid load in AD patients and are, therefore, used as biomarkers for disease staging and for the tracking of AD therapy efficacy in clinical trials. The main sites phosphorylated in CSF Tau and characteristic for AD are T181 (the most examined epitope as a CSF biomarker for AD) and T217 in the PRD [8, 14].

CSF levels of T-tau and P-tau are tightly correlated within cohorts of AD patients and control, however both biomarkers have a divergent behavior in other diseases.

T-tau appears marked temporary increased and P-TAU does not suffer changes in traumatic brain injury and stroke and that correlates with the severity of neuronal damage. In Creutzfeldt-Jakob disease - disorder characterized by very rapid neurodegeneration but not PHF tau accumulation - a very marked increase in CSF T-tau can be found (10 to 20 times more than in AD), whereas P-TAU shows none or minor change. AD is the only disorder that consistently shows an increase in CSF P-tau [15] whereas this biomarker is normal in other neurodegenerative disorders. The level of CSF P-TAU also does correlate with severity of PHF tau accumulation after death [16].

Taken together, these data indicate that CSF T-tau reflects the intensity of neuronal damage at a specific point [17] whereas elevated CSF P-TAU reflects an abnormal pathologic state associated with PHF tau formation [8].

Neuroimaging

Imaging represents the magnitude of the neuropathologic load or damage that was accumulated over time providing an important pathologic staging information [8].

MRI Anatomic

MR images can provide excellent anatomical detail and provide a strong grey/white matter contrast. Processes believed to be pathological in nature are often described in terms of anatomical location, cortical thickness, volumetry, and morphological characteristics [18].

Coronal T1-weighted, three dimensional, high resolution images are often used in cross-sectional and longitudinal studies to measure the hippocampal volume and to assess changes in hippocampal volume over time in AD [19].

Although dramatic neuronal loss is not observed in preclinical AD or MCI, several studies have shown mild hippocampal atrophy during these stages. Hippocampal atrophy has been linked to cognitive impairment suggestive of AD [18].

Functional

Functional MRI techniques are based on blood-oxygenation-level-dependent (BOLD) contrast which is associated with neural activity at the population level. Resting-state functional magnetic resonance imaging (rsfMRI) studies examine the temporal correlation of the BOLD signal between the regions of interest (or functional connectivity) by analyzing task-independent spontaneous fluctuations in brain networks [18].

resting state fMRI can offer important information on the integrity of brain circuits and the degree to which their synaptic connectivity may be affected by the disease process [18].

FDG-PET

PET methods have been used for more than three decades to analyze alterations in the glucose metabolism that happens in the brain during aging, MCI and AD. Regional cerebral metabolism can be assessed with 18F-2fluoro-2-deoxy-D-glucose (FDG) as a metabolic marker. Findings of reduced hippocampal metabolism in MCI and AD have been reported [20]. Cerebral glucose hypometabolism on FDG-PET seen to be a downstream marker related to neuronal injury and neurodegeneration. It appears reliably specially in temporal, parietal lobes but spares sensorimotor cortices, visual cortices, basal ganglia, thalamic nuclei and the cerebellum [21].

Age-related patterns of cerebral glucose metabolism differ substantially from patterns observed in AD, which has led to the utility of this technique in aiding clinical diagnosis. While classic studies (e.g. [151]) have shown that average cerebral glucose metabolism decreases with age, the regions showing the least age-related change include the medial temporal lobes, the posterior cingulate cortex and the precuneus. Those are the same regions expressing significant hypometabolism in AD. Thus, FDG-PET can be used to determine if the pattern of cerebral hypometabolism is normal or abnormal [22].

Studies have suggested that FDG-PET can be accurate at differentially diagnosing AD from other dementias and having na elevated concordance rate with clinical diagnosis.

Amyloid PET

Given the critical importance of identifying amyloid pathology in the brain as an early stage of AD progression, positron emission tomography (PET) scans with radiolabeled tracers specific to Aβ have become common place in the research setting. The pathological Aβ peptide is generated by abnormal proteolytic processing of a physiological constituent of the nerve cell membrane, the amyloid precursor protein (APP). PET scans operate based on the principle that positron-emitting radioligands accumulate in a region of interest. The positively-charged positrons encounter negatively-charged electrons, which results in annihilation of both that releases gamma photons that can be detected by scintillation detectors [23]. This method can be used to image Aβ in vivo via radiolabeled tracers, which are injected via a bolus injection, followed by a waiting period to allow for uptake by brain tissue.

Amyloid tracers were developed via the modification of the histological dye, thioflavin-T, which has a high affinity to fibrillar and cerebrovascular amyloid, is cleared rapidly from normal brain tissue, and crosses the blood-brain barrier in sufficient amounts to be imaged in vivo. The first Amyloid burden imaging was seen with a carbon-based tracer [11C] such as Pittsburgh Compound B (PiB), but the development of fluorine-based tracers [18F] has made it possible for a wider availability of these longer lasting tracers facilitating widespread use. As an example of theses tracers, we have florbetapir, florbetaben, and flutemetamol, which have an extended half-life (~110 minutes) as compared to [11C] tracers (20 minutes) there remain differences among tracers and in their sensitivity [18].

Most amyloid imaging studies point to the parietal cortices as the earliest sites of amyloid deposition [24].

A major limitation to amyloid imaging and studies of amyloid burden in general is a poorly understood relationship with cognition [18].

Tau Pet

Tau PET is a new modality so the ligands that have been evaluated to date are considered first-generation compounds. By being the first generation, these compounds suffer from limitations and the most common one is being off-target binding [25]. However, at least one first generation ligand has emerged as a reliable biomarker of 3R/4R PHF tau deposits [26]. Autoradiographic studies have shown that the most widely studied ligand, flortaucipir, does not bind to amyloid plaques, TAR DNA Binding Protein 43 (TDP43), argyrophilic grains, or a-synuclein. Flortaucipir binds weakly or not at all to sole 4R or sole 3 R tau deposits in primary tauopathies [27]. In vivo imaging to autopsy comparisons also indicates specific binding of flortaucipir to PHF tangles and correlation with the break neurofibrillary tangles stage [28]. Elevated tau PET binding in both medial temporal lobe structures and the neocortex is strongly associated with positive amyloid PET scans and with clinical impairment across the normal aging to dementia clinical spectrum [29]. New tau PET ligands are in the early stages of development and evaluation [30].

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Conflict of Interest

No Conflict of interest.

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