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Review

Early Detection of Alzheimer's Disease: The Role of Plasma Glial Fibrillary Acidic Protein and Norepinephrine

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ABSTRACT

Alzheimer's disease (AD) stands as a prominent etiological factor in dementia, affecting millions of individuals worldwide. Despite being the most prevalent cause of dementia, the definitive diagnosis of AD typically occurs only after the manifestation of symptoms. This diagnostic process is subsequently associated with considerable costs and relies on tests that are often challenging to access. While clinical findings play a pivotal role in diagnosing AD, it is crucial to acknowledge that the neuropathological changes characteristic of the disease commence several decades before the onset of symptoms. Detecting these pathological alterations during the asymptomatic phase of the disease holds profound implications for patients, as it offers valuable insights into disease progression and informs treatment strategies. Early detection remains a primary obstacle in effectively managing the disease, making these biomarkers of particular interest for advancing diagnostic and therapeutic approaches. In this review, our objective is to provide a comprehensive overview of the literature about two potential biomarkers that offer promise in the early detection of AD.

Keywords: Alzheimer's disease, biomarkers, dementia, early diagnosis, GFAP, norepinephrine.

Dementia represents a clinical syndrome characterized by the progressive deterioration of multiple cognitive functions, while consciousness remains intact. This decline in cognitive abilities significantly impacts the individual's capacity to engage in routine activities. Manifestations of dementia encompass impairments in memory, behavior, motor function, and language proficiency, as well as alterations in emotional and cognitive patterns. Various neuropathological conditions can precipitate the development of dementia, including cerebrovascular incidents, neurodegenerative disorders, vascular dementia, dementia with Lewy bodies, frontotemporal dementia, mixed dementia, Parkinson's disease, syphilis, human immunodeficiency virus, and Creutzfeldt-Jakob disease. Primary dementias, which are neurological diseases primarily characterized by cognitive impairments, encompass the majority of dementia cases. Among these, Alzheimer's disease stands out as the most prevalent cause of dementia.[1]

According to the World Health Organization, the global prevalence of dementia exceeds 55 million individuals, with projections indicating a surge to 139 million by the year 2050.[2]

Notably, among individuals aged 65 and above, Alzheimer's disease (AD) emerges as the foremost etiological factor contributing to the onset of dementia.[3,4]

In AD the pathological changes resulting in progressive neuronal loss begin decades before clinical symptoms arise.[5,6]

The neuropathological hallmarks of AD include the formation of amyloid plaques resulting from the extracellular accumulation of amyloid β peptide (Aβ1-42) and neurofibrillary tangles formed by the intraneuronal accumulation of phosphorylated Tau protein (p-Tau).[4]

Although the Aβ and tau neuropathology can be observed approximately 15-20 years prior to symptom onset through positron emission

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tomography and cerebrospinal fluid analysis, these diagnostic procedures are characterized by their expense, time-consuming nature, invasiveness, and limited accessibility to clinicians. Consequently, they are not routinely employed in standard clinical practice.[4,7] Presently, AD lacks a definitive cure, with available treatments primarily focused on symptom management, aiming to mitigate disease progression or alleviate associated symptoms. Notably, once the symptomatic phase has been initiated, there exists no efficacious intervention to halt the disease's progressive trajectory. Consequently, considerable scientific endeavors have been directed toward advancing early detection, treatment, and preventive initiatives.[5,7]

Therefore, the existence of cheap and easily obtained, less invasive highly sensitive plasma biomarkers can be crucially important in early detection of possible AD progression in the future, and essential in monitoring these cases in preventive and therapeutic processes.[5,8] In this article, we conduct a review of studies demonstrating the predictive capacity of glial fibrillary acidic protein (GFAP) and norepinephrine (NE) in identifying AD even several decades prior to symptom onset.

ASSOCIATION BETWEEN ALZHEIMER'S DISEASE AND GFAP

Astrocytes, constituting 20–40% of total brain cells, are the most prevalent cell type in the human central nervous system (CNS). They are an integral part of the blood-brain barrier, they play a pivotal role in synaptic function and contribute to the maintenance of axonal metabolism by regulating ion balance.[9]

These cells possess a distinctive cytoskeleton comprised of glial filaments, with GFAP serving as the primary structural protein.[10] Beyond its structural role, GFAP also exerts significant influence over neuronal physiology.

In cases of brain injury such as neurodegenerative disorders, astrocytes undergo a "molecular, morphological, and functional reaction" known as astrogliosis.[10,11]

It has been indicated that astrogliosis, characterized by an increase in GFAP levels, acts as a marker of astroglia activation.[11] Several studies have demonstrated that astrogliosis is an early characteristic in the pathological progression and is a hallmark of AD. Increasing evidence suggests heightened astrocyte reactivity in AD, resulting in cytoskeletal breakdown. This phenomenon leads to the elevation of GFAP levels in blood samples.[9]

Consequently, GFAP is recognized as an important plasma biomarker signaling the onset of the disease before symptoms emerge in AD.[12]

Traub et al.[12] assert GFAP as an "emerging biomarker of cognitive decline in disorders of primary neurodegeneration such as Alzheimer's disease". Their study identifies GFAP as a promising candidate for a serum marker associated with predicting cognitive decline.

According to a review of blood-based biomarkers on Alzheimer's disease[3], GFAP demonstrated a significant association with clinical AD, even preceding diagnosis by 9-17 years. Among all biomarkers that were assessed, GFAP showed the highest accuracy in predicting AD diagnosis. Elevated levels of GFAP in blood have also shown a strong predictive ability to determine AD/dementia and cognitive decline.

Another study revealed alterations in hippocampal volume and cortical thickness associated with these biomarkers.[13]

Oeckle et al.[14] investigated sampled from 610 individuals. They reported in their study that GFAP levels were higher in individuals with AD compared to the control group. Furthermore, they found they measured the GFAP levels of patients taken during periods when individuals were without cognitive impairment. The study showed that the initial GFAP levels of individuals who later developed dementia were higher than those in individuals who did not develop dementia. The study reported a diagnostic accuracy of GFAP in AD of 98% sensitivity and 60% specificity.

Stocker et al.[15] reported in their longitudinal study, encompassing a 17-year follow-up of individuals initially devoid of cognitive impairment, that subjects exhibiting elevated baseline levels of GFAP displayed a notably increased likelihood of developing AD compared to their counterparts without subsequent AD manifestation. Their findings underscore the significance of GFAP as a pivotal predictive screening-diagnostic biomarker, offering early detection of AD progression nearly a quarter-century prior to clinical onset. Notably, higher levels of GFAP were found to correlate with an augmented risk of clinical AD incidence.

In relevant review publications, GFAP has been identified as a potential biomarker indicating brain injury and was found to be elevated in early-onset

AD. It also has been correlated with functional and cognitive impairment. Consequently, plasma GFAP levels have been suggested as a predictive indicator of dementia development when showing a correlation with cognitive dysfunction.[9]

Cicognola et. al.[5] demonstrated that plasma GFAP levels were elevated in AD and other neurodegenerative diseases compared to healthy controls. It has been suggested that GFAP was a relatively strong indicator of AD pathology and could accurately predict the future development of AD dementia.

In a study by Verberk et al.[16], encompassing a cohort of 300 subjects followed over a span of 15 years, it was observed that 27 out of 300 patients (9%) developed AD dementia during the follow-up period. The researchers found that individuals with elevated baseline levels of GFAP exhibited a significantly heightened risk of AD development. They further reported that the presence of heightened GFAP levels among individuals with initially normal cognitive function served as a predictive indicator for subsequent AD onset later in life. Moreover, the study concluded that elevated GFAP levels may serve as potentially valuable tools for identifying individuals at high risk of AD.

It has been shown that higher blood concentrations of GFAP are linked to accelerated cognitive decline, increased dementia occurrence, and a higher probability of transitioning to symptomatic cognitive impairment, particularly in the presence of amyloid pathology.[10]

Shir et al.[17] have defined GFAP as a specific marker for AD and reported a correlation between plasma GFAP levels and dementia.

It was reported that individuals with mild cognitive impairment and high GFAP levels had a high rate of developing AD. Furthermore, elevated GFAP levels of individuals with normal cognitive function were associated with "steeper rates of cognitive decline."[8]

A study concluded that elevated plasma GFAP may serve as an early blood-based biomarker to identify high-risk individuals for developing AD, prior to manifestation of clinical symptoms. It has been suggested that this biomarker could assist with reducing screening costs, and facilitate prevention programs and clinical intervention trials.[7]

ASSOCIATION BETWEEN ALZHEIMER'S DISEASE AND NOREPINEPHRINE

Norepinephrine is a neurotransmitter that acts in synapses to regulate neuronal and non-neuronal cells. Its functions encompass vital roles in the swift modulation of cortical circuits, cellular energy metabolism, neuroplasticity, and inflammatory processes.[18] The locus coeruleus (LC), situated within the lateral floor of the fourth ventricle and upper dorsolateral pons, serves as the principal and exclusive site for NE synthesis.[19]

Proposed relationships between NE and AD have been delineated by Hussain et al.[20] These relationships encompass several facets: Firstly, reductions in the volume of the LC and the presence of tyrosine hydroxylase-positive cells coincide with the aggregation of hyperphosphorylated tau proteins into neurofibrillary tangles. These tangles accumulate within the LC, resulting in neuronal degeneration and eventual cell demise. Another aspect involves the diminished levels of NE in the central nervous system, which are intricately linked to the neuroprotective and anti-inflammatory properties of NE within the CNS. Additionally, a proposed link suggests that the hippocampus experiences impaired NE transmission due to the buildup of hyperphosphorylated tau proteins and the degeneration of noradrenergic axons.

Norepinephrine is a neurotransmitter pivotal in the synaptic regulation of both neuronal and non-neuronal cells.[18] Several comprehensive reviews discuss the involvement of the LC noradrenergic system in cognitive processes, arousal, and wakefulness.[21-25]

The noradrenergic neurons originating from the LC project into diverse areas of the brain. Given this extensive innervation, they are implicated in a multitude of behavioral and physiological processes.[4,26]

The noradrenergic transmission, which has been reported to impact cognitive functions, declines with aging and in response to certain brain disorders.[26] It has been reported that noradrenergic neurons also progressively decrease starting from the prodromal stages of AD and throughout the course of disease progression.[4]

In multiple studies,[27-31] it has been stated that LC degeneration is among the earliest pathologies in AD, where LC pathology can be detected "as early as 10 years before neurocognitive signs."[18]

Alterations in NE pathways have been associated with cognitive, memory, mood dysfunctions; and resulting in neuropsychiatric symptoms. A number of studies have established a close correlation between LC cell death and the severity/ duration of dementia in AD.[32,33]

It has also been shown in many studies that LC degeneration both induces and enhances the inflammatory process that is fundamental to the pathogenesis of AD. One of the first studies on connections between LC degeneration and neuroinflammation in AD was done by Heneka et. al.[30]

There are numerous theories about how NE influences AD aggression. One hypothesis posits that the onset of AD involves heightened hyperactivation within the LC, culminating in an excessive release of noradrenaline in the cortical regions. This cascade of events is believed to contribute to the accumulation of amyloid plaques. Over time, this cycle evolves into a process that reduces NE neurons and NE secretion, exacerbating the accumulation of amyloid plaques. As a consequence, there is an initial elevation in neuronal noradrenaline secretion during the onset of AD, followed by a subsequent decline in the advanced stages of the condition.[34] However, it has been stated that this hypothesis requires further research.[4]

The first study to show the NE deregulation in AD was put forth by Adolfsson et. al.[35] in the 1970's, where postmortem brains of AD patients showed lower concentrations of NE.

A study investigating volumetric brain integrity in preclinical and prodromal Alzheimer's disease observed atrophy of the LC in individuals presenting with mild cognitive impairment and AD. Notably, a decrease in LC volume was linked to the onset of AD within a two-year period in initially asymptomatic healthy individuals.[31,36,37]

In their retrospective study, Pillet et al.[4] reported that plasma NE levels could be utilized in the early diagnosis of AD and that the level of NA, whether high or low, is a significant indicator in the staging of AD. In this study, a cohort of 71 patients presenting with initial complaints of memory impairment was examined. The study investigated the association between plasma NE levels and diagnostic criteria including Mini-Mental State Examination (MMSE) and CSF biomarkers (Aβ1–42, Tau, and p-Tau). A significant correlation was reported between NE plasma and MMSE score, suggesting a possible connection between NE plasma and cognitive decline.

In conclusion, the increase in the average human lifespan; facilitated by social, economic, and primarily medical advancements; has led to the emergence of certain chronic diseases that were previously uncommon or rare. Dementia, with Alzheimer's Disease being its most prevalent cause, is one of these conditions. Presently, the diagnosis of this disorder relies solely on the onset of symptomatic presentations, with diagnostic methodologies often entailing significant expense, invasiveness, and inadequacy in informing treatment strategies. Consequently, the imperative for research into novel, cost-effective, and readily accessible diagnostic tools, particularly targeting high-risk cohorts, assumes paramount importance. These efforts have the potential to greatly improve both preventive measures and therapeutic strategies. In this context, extant literature indicates the potential efficacy of GFAP and NE as promising predictive markers for achieving this objective.

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