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HOW CAN PLASMA P-TAU DIAGNOSE NEURODEGENERATION AND COGNITIVE DECLINE FROM ALZHEIMER'S DISEASE ACROSS RACIAL GROUPS IN THE UNITED STATES?

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ABSTRACT Biomarkers can aid in diagnosis and have been used to predict risk of psychological decline and Alzheimer's disease. The ease and cost-effectiveness of blood collection mean that these biomarkers could be applied more broadly in population-based screening; however, it is critical first to understand which other factors could affect blood biomarker levels. The pathway to receiving a diagnosis of Alzheimer's disease (AD) can be long and complex, involving detailed medical assessments, laboratory tests, cognitive assessments, and neurological examinations. A diagnosis of AD currently relies on positron emission tomography (PET) imaging or measurement of amyloid beta (Aβ) and phosphorylated Tau (p-tau) in cerebrospinal fluid (CSF) . However, the high cost, invasiveness, and relatively low availability of these specialized tools have prevented their widespread use. Furthermore, many individuals only receive a dementia diagnosis at an advanced stage of the disease, even though deposition of amyloid plaques and neurofibrillary tangles commences years before the onset of clinical symptoms. Early detection of AD pathology would enable timely treatments, including recruitment into clinical trials, tracking progression of the disease, and even early interventions for individuals at high risk of AD before the onset of symptoms. Ultrasensitive assays have now been developed that permit Aβ and p-tau to be measured in blood. The findings from multiple studies have demonstrated the utility of these biomarkers to aid in the diagnosis of AD and to predict cognitive decline and the risk of AD. The ratio of A 42/40 appears to be a surrogate biomarker of cortical Aβ deposition, independent of clinical AD diagnosis. Plasma p-tau 181 and p-tau 217 show high concordance with levels of brain amyloid (based on PET imaging), and have excellent diagnostic performance for differentiating individuals with AD from other forms of dementia. Neurofilament light chain (NfL), a non-specific marker of neuronal injury, has been associated with the risk of AD, vascular dementia, and other types of dementia (e.g., frontotemporal lobe dementia.

KEYWORDS : Alzheimer's disease (AD), Positron emission tomography (PET) imaging, Phosphorylated Tau (p-tau), Neurofilament light chain (NfL) , AD proteins (A 42, A 40, t.Tau, and p.Tau181),

INTRODUCTION

Objective biomarkers for Alzheimer's disease (AD) can greatly enhance its early detection and treatment. Currently established biomarkers include cerebrospinal fluid (CSF) levels of core AD proteins (Aβ42, Aβ40, tβTau, and pβTau181) and substrate-specific positron emission tomography (PET) targeting amyloid and tau aggregates (1,2)

Blood-based biomarkers for AD have long been championed as accessible and convenient, but their broader adaptation in the past has been limited by suboptimal performance or reproducibility (3,4)

More recently, mass spectrometry-based approaches or highly sensitive immunoassays have improved the detection of AD-related protein levels in blood. (5,6)

The blood-based AD biomarkers have been found to strongly associate with *post mortem* AD neuropathologic changes, discriminate between tau PET profiles, yet better correlate with amyloid PET and predict subsequent cognitive decline in the asymptomatic AD stage (7,8)

At the same time, their real-world applicability has often fallen short of these promising group-level epidemiological findings, with potential confounds from renal clearance and cardiovascular co-morbidities (9,10)

Potential blood–brain barrier (BBB) disruption in the setting of non-AD neurodegeneration and progressive dementia (11)

While plasma p-Tau217 may better predict brain AD neuropathologic changes than plasma p-Tau181, the limited number of participants with CSF p-Tau217 measurements obtained using widely available assays in prior studies makes comparisons between the two phosphorylated forms of tau difficult to interpret.(12)

Blood-based biomarkers of brain amyloid burden, particularly those derived from phosphorylated Tau (p-Tau), are gaining recognition for their clinical utility and potential for use in routine assessments for Alzheimer's disease (AD) (13)

Clinically significant p-Tau species, including p-Tau181, p-Tau217, and p-Tau231, are now quantifiable via a range of assays and platforms (14)

However, one important caveat with currently available, widely used p-Tau assays is that most of them utilize detection antibodies that recognize an epitope common to both brain-derived (BD), low-molecular-weight (LMW) Tau, as well as high-molecular-weight (HMW) Tau produced by the peripheral nervous system (PNS) and other organs, in effect measuring "total-Tau (15)

Blood p-Tau biomarkers correlate well with positron emission tomography (PET) measures of brain amyloid or AD cerebrospinal fluid biomarkers (16)

From a comprehensive systematic review evaluating the diagnostic performance of plasma p-Tau biomarkers and associated assays, as well as a recent study comparing 33 different plasma p-Tau assays,plasma p-Tau217 has emerged as the best-performing biomarker for identifying AD pathology, showing the highest areas under the receiver-operating characteristic curve (AUC) and the largest fold changes compared with other p-Tau species, with broadly similar performance across different p-Tau217 assays (17)

Notably, with the growing availability of commercial plasma p-Tau217 assays, a slew of recent studies have demonstrated the diagnostic utility of this biomarker for detecting abnormal brain amyloid burden in both Western and Asian populations, supporting its accessibility and generalizability across different populations.(18)

Briefly, HMW Tau (110 kDa) contains additional exons, including the 250-amino-acid exon 4a.In contrast, all six LMW isoforms (37 kDa to 46 kDa) in the brain exclude exon 4a (19)

As an illustration of the potential significance of distinguishing BD from peripheral Tau isoforms, recent studies measuring total p-Tau have reported elevated blood p-Tau217 and p-Tau181 levels in patients with amyotrophic lateral sclerosis (ALS). Assessment of p-Tau immunoreactivities in muscle biopsies suggested that the increased p-Tau may reflect changes in atrophic muscle fibers in ALS, and was independent of AD pathology in the brain (20).

Alzheimer disease (AD)

Alzheimer's disease is a progressive brain disorder that slowly destroys memory, thinking, and the ability to carry out simple tasks.

It is the most common cause of dementia, accounting for 60% to 80% of all cases.

Key Symptoms

- **Memory loss:** Forgetting recent conversations, names, or important dates.
- **Cognitive decline:** Trouble with planning, solving problems, or handling money.
- **Disorientation:** Getting lost in familiar places or losing track of time.
- **Behavioral changes:** Sudden mood swings, increased anxiety, or confusion.
- Causes and Brain Changes
- **Amyloid plaques:** Clumps of a protein called beta-amyloid that build up between nerve cells.
- **Tau tangles:** Twisted fibers of another protein called tau that build up inside brain cells.
- **Cell death:** These clumps and tangles block communication between neurons, causing them to die and the brain to shrink over time

It is the most prevalent type of dementia, accounting for at least two-thirds of cases in individuals aged 65 and older. AD is a neurodegenerative condition with insidious onset and progressive impairment of behavioral and cognitive functions. These functions include memory, comprehension, language, attention, reasoning, and judgment. While AD does not directly cause death, it substantially raises vulnerability to other complications, which can eventually lead to a person's death.

According to Centers for Disease Control and Prevention (CD C) data, AD is ranked as the seventh leading cause of death in the United States in 2022, while COVID-19 ranked fourth. Before the COVID-19 pandemic, AD was the sixth leading cause of death following stroke (21)

AD typically manifests after age 65, referred to as late-onset AD (LOAD). However, early-onset AD (EOAD), occurring before 65, is less common and seen in about 5% of AD patients. EOAD often exhibits atypical symptoms, and its diagnosis is usually delayed, leading to a more aggressive disease course (22)

Significant progress has been made in developing biomar-kers for specific and early diagnosis of AD over the past decade. These biomarkers include neuroimaging markers obtained through amyloid and tau PET scans, cerebrospinal fluid (CSF), and plasma markers, such as amyloid, tau, and phospho-tau levels (23)

There is no cure for AD, although there are treatments available that may alleviate and manage some of its symptoms. In recent years, there have been significant advancements in the development of medications that aim to moderate the progression of the disease, particularly with the discovery of new disease biomarkers (24)

AIIMS Alzheimer's detection test

Alzheimer's disease was discovered by German neuroscientist Alois Alzheimer; the disease named after him has boggled the scientific community. Global life expectancy at the time of the discovery was less than 35 years. With the average lifespan increasing to more than 70 today, Alzheimer's afflicts many more times the number of people today than when it was discovered. More than 55 million people worldwide over the age of 60 today suffer cognitive impairments, and 60-70 per cent of them go on to develop the most corrosive form of dementia. Though research over the years has identified the characteristics of the disease, and in recent years, drug development has made some headway, questions remain about how best to treat Alzheimer's. In most parts of the world, including India, tests to diagnose the disease are undertaken only after the onset of symptoms. However, there is growing unanimity amongst scientists that the precursors to Alzheimer's begin to accumulate in the brain at least 10 years before the symptoms show up. That's why a blood test developed by researchers at AIIMS, Delhi, could be a significant breakthrough in Alzheimer's management.

The AIIMS researchers tested 90 people on six blood markers, the levels of which can indicate an early onset of Alzheimer's. The test can detect the biomarkers of the disease 10-15 years before it becomes full-blown. Alzheimer's develops over 15-20 years. An early diagnosis can help clinicians manage symptoms better — medicines that promise a cure for the milder form of the disease have not yet entered the treatment protocols in most parts of the world. Dementia screenings are particularly relevant for India, where cognitive impairments are often confused with "natural" signs of ageing. Though diagnostic rates are improving, the disease remains poorly understood, even amongst sections of the medical community, and many patients live with symptoms that their near ones find difficult to understand.

Alzheimer's Biomarker Discoveries

- **Blood Tests (p-tau217 and Tau):** Research highlights that measuring plasma biomarkers like p-tau217 can predict cognitive decline and dementia risks up to 25 years in advance, while general tau and amyloid markers can spot midlife risks.
- **High Accuracy Screening:** Blood assays like PrecivityAD2 demonstrate high precision (around 90%) in identifying Alzheimer's changes when mild cognitive symptoms emerge.
- **Alternative Markers:** Emerging findings suggest routine eye scans evaluating retinal blood vessel changes could act as non-invasive early indicators for neurodegenerative conditions.
- **South Asian Population Insights:** Recent genetic and biomarker analyses (such as LASI-DAD) indicate that specific rare and common gene variants impact neurodegenerative biomarker levels differently in Indian and South Asian populations.
- Blood biomarkers predict women's dementia risk 25 years before symptoms
- Blood tests that measure plasma biomarkers like p-tau217 can predict cognitive decline and dementia risks up to 25 years in advance, while general tau and amyloid markers can spot midlife risks.

Where the Research Go Next?

The science and research community has discovered lots of important information on plasma p-tau biomarkers and their associations with Alzheimer's disease symptoms, such as

associations with the formation of amyloid plaques in the brain, frontotemporal dementia, cognitive decline, and neurodegeneration. This research contributes to the existing knowledge regarding p-tau biomarkers' effects on Alzheimer's disease because it compares their effectiveness in diagnosing Alzheimer's disease across multiple races in a defined cohort. Taking into account race is important to this research, as different races can have varying risks of Alzheimer's disease due to health factors such as cardiovascular diseases like high blood pressure and diabetes being prevalent in distinct races, genetic alleles that lead to increased risk of Alzheimer's disease in certain races, varying environmental factors, and access to healthcare.

CONCLUSION

'' Tau biomarkers serve as the central focus to this research on Alzheimer's disease because they directly track the physical damage to brain cells and closely mirror a patient's cognitive decline through their abnormal hyperphosphorylation that causes toxic tangles in the brain, further leading to the death of neuronsAlzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline and memory impairment. Early diagnosis remains a critical challenge in managing the disease effectively. Biomarkers have emerged as essential tools in identifying the disease during its preclinical stages, thereby offering opportunities for early therapeutic intervention. The current landscape of AD biomarkers includes cerebrospinal fluid (CSF) markers, imaging techniques, blood-based biomarkers, and novel genetic indicators. Identification of biomarkers and proper diagnosis of AD could make its management easier. Advances in diagnostic techniques like Positron Emission Tomography (PET) imaging have greatly improved the ability to identify, detect early, monitor disease progression, and manage its therapy.

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