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P-tau217 in Early Disease Detection: True Biomarker Value or Diagnostic Mirage?

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ABSTRACT

Introduction: Phosphorylated tau (p-tau217) at the threonine 217 site is considered to be one of the most sensitive and specific biomarkers of early Alzheimer's disease (AD). But it is facing new evidence showing that p-tau217 is present in unexpectedly high levels in the brains of neonatal brains, which is problematic with regard to its diagnostic specificity in different age groups.

Methods: The analysis of the literature through a narrative was performed in PubMed/MEDLINE, Scopus, and Web of Science (2020-2025).

Results: The results suggest that in the neonatal brains the levels of p-tau 217 are equal or higher than in the AD brains without amyloid- 217 deposition, neurofibrillary tangles or neurodegeneration. During early stages, non-aggregative, transient, and reversible, p-tau217 is required to facilitate critical processes including axonal development, synaptogenesis, synaptic pruning and neural plasticity.

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Discussion: These findings underline that p-tau217 is a developmental and disease-related form of tau. Use of fixed diagnostic thresholds without age contextualization can produce a greater risk of false-positive interpretation especially among pediatric or asymptomatic groups.

Conclusion: p-tau217 is not a purely pathological biomarker to consider. It is important to have age-adjusted reference ranges, multimodal diagnostic frameworks, and clinical correlation in order to interpret them accurately. The identification of the physiological role of p-tau217 in developing the human brain will be more diagnostic and less misclassified in biomarker-based neurology.

Keywords: p-tau217, Alzheimer's disease, neonatal brain, biomarkers, tau pathology, synaptogenesis, neurodevelopment, diagnostics

1. INTRODUCTION

Among the different phosphorylated tau isoforms studied, the phosphorylated tau at threonine 217 (p-tau217) has shown the best specificity and sensitivity as a fluid biomarker of early Alzheimer's disease (AD) (1). The close association between PET tau imaging of tau disease and cognitive decline and increased levels of p-tau217 in plasma and cerebrospinal fluid (CSF) may be expressed years before a person experiences clinical symptoms (2). One of the many proposed frameworks to support early detection and disease staging, which includes p-tau217, is the NIA-AA AT(N) system, in which p-tau217 is now at the front of the parade of Alzheimer's biomarkers (3). The growing use of p-tau217 tests in clinical and scientific practice has had its calling card as a substantial resonance in increasing the accuracy of diagnosis and shaping treatment strategies (4).

The recent research, however, has led to a shocking paradox: babies do not exhibit any symptoms of cognitive decline or neurodegeneration but express even more abundance of p-tau217 than even diagnosed Alzheimer patients (5). This observation puts into question the physiological significance of elevated p-tau217 in early neurodevelopment and discredits the historical

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interpretation of this marker as a specific pathogenic process (5). Considering that the processes occur during infancy and are mostly silenced in adulthood, the occurrence of p-tau217 in the neonatal brain could support a role as an agent in pruning, plasticity, or cytoskeletal remodelling in brain development (6). When confirmed, this p-tau217 developmental expression would suggest a working, non-pathological, rather than a neurodegenerative status. Questions are also asked about the specificity of p-tau217 in various age groups in the context of diagnosis. Without some form of age-specific framework, early diagnostic screening for neurodegenerative illnesses is at risk of misdiagnosis (7). Thus, one should reconsider the usefulness of p-tau217 as an independent biomarker, especially in the asymptomatic or pediatric population.

2. UNDERSTANDING TAU PATHOLOGY

2.1 Tau Isoforms and Phosphorylation

The MAPT gene produces tau, which is a microtubule-associated protein, and is especially produced in neurons to help provide stability to the microtubules of the axons. In the adult human brain, six different tau isoforms, with up to two N-terminal inserts and three (3R) or four (4R) microtubule-binding domains, are created by alternative mRNA splicing. Developmental regulation (8, 9). On the one hand, when tau is produced in the adult brain, both 3R and 4R forms are found; but in fetal brains, there exists predominantly 3R tau. Phosphorylation is the most important post-translational modification of tau (10). The phosphorylation of Tau physiologically controls its ability to bind microtubules and influences neuronal growth, plasticity, and signal transduction. However, upon being hyperphosphorylated, particularly at key sites, such as p-tau217, it detaches itself, reorganizes its structure, and aggregates to form dangerous oligomers and paired helical filaments, eventually leading to the formation of neurofibrillary tangles (11, 12). Tau phosphorylation is balanced with phosphatases (such as PP2A) and the kinases (such as GSK3beta and CDK5). Disruption of these balances leads to the promotion of tauopathy and neuronal dysfunction that, in turn, can be induced by oxidative stress, inflammation, or amyloid-B pathology (13).

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2.2 Role of p-tau217 in Neurodegeneration

In the case of AD, the p-tau217 has proved to be a very successful marker. As a result of multiple recent studies, the presence of tau PET imaging and amyloid-beta PET positivity is strongly intertwined with the increase of p-tau217 in CSF and plasma years before clinical symptoms (14, 15). Despite its tendency to give imprecise results when distinguishing AD and non-AD tauopathies, including progressive supranuclear palsy and frontotemporal dementia, p-tau181, compared to total tau, is more precise (16). Its diagnostic sensitivity is shown by increasing use of p-tau217 in clinical testing and diagnosis schemes. It is nowadays a fundamental component of biomarker-grounded systems, such as the AT(N) classification (17). However, the brains of babies express more p-tau 217 than those of older individuals with AD, as determined in a recent paradigm-altering study. Despite this increase, the neonatal brains do not display any neurotoxic symptoms, which suggests that p-tau217 has a non-pathological role during the early neurodevelopment (18, 19). This finding calls into question the notion that p-tau217 is simply toxic and increases the possibility that it performs a physiological developmental role, such as in the building of synapses, neuronal migration, or organizing the cytoskeleton (20). These disclosures make it quite important to consider tau measures on an age-based scale. In the absence of any concomitant structural and functional changes, high p-tau217 levels may not represent illness. To ensure that biomarkers become valid tools, instead of misleading alarms, throughout a lifetime, this complexity will need to guide researchers and clinical practice (21).

3. P-TAU217 IN NEONATAL VS. ALZHEIMER'S BRAIN

3.1 Recent Findings in Neonatal Brain Studies

The recent advances in postmortem brain tissue analyses and proteomic profiling have allowed a startling new biological discovery: in the newborn brain, p-tau217 is at significantly higher levels even in the absence of neurodegenerative symptoms. With the application of high-resolution mass spectrometry and phospho-specific antibodies (22), carried out a pioneering study that has

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demonstrated that full-term infants display a 2-3-fold increase of p-tau217 expression in the cortex and hippocampus compared to elderly individuals affected by AD (23). In newborns, importantly, there is no commensurate rise in pathological markers such as gliosis, amyloid-beta accumulation, or neurofibrillary tangles. Instead, it is observed in a period of intense synaptogenesis, pruning of the neural network, and neuroplasticity. The researchers say that phosphorylation of tau at threonine 217 could be a physiological, developmentally related phenomenon and linked to any temporary instability of the microtubules necessary for the rapid structural rearrangement of the neonatal brain (24). Conversely, p-tau217 is an important biomarker of disease-related pathological misfolding and aggregation of tau protein as well as synaptic dysfunction in AD. The difference highlights the importance of biological context when explaining biomarker data (25).

3.2 Comparative Analysis of p-tau217 Levels

A comparative overview of p-tau 217 values is drawn from the existing studies to put the paradox in perspective. Despite being associated with, little is known about progressive p-tau217 developments in infants, though there is a basal expression in neonates (Table 1) (26).

Table 1: Comparative p-tau217 levels in newborns and Alzheimer's Patients (17, 18, 27)

Parameter	Newborn Brain	Alzheimer's Disease Brain
p-tau217 Expression (Relative Fold)	2–3× higher than AD patients	Lower compared to neonates
Tissue Localization	Cortical neurons, hippocampus	Cortical neurons, hippocampus
Amyloid-β Co-expression	Absent	Present in plaques
Neurofibrillary Tangles	Absent	Prominent

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Associated Neurodegeneration	None observed	Significant cortical and hippocampal loss
Functional Role (Proposed)	Neurodevelopment, plasticity	Pathological aggregation
Diagnostic Interpretation Risk	Potential false positive if misapplied	Confirmatory of AD pathology

4. PHYSIOLOGICAL FUNCTIONS OF P-TAU217 IN EARLY BRAIN DEVELOPMENT

4.1 Developmental Neurobiology Insights

There is an incredible expansion and reorganization of the human brain between the gestation stage and early infancy. Such processes as neurogenesis, synaptogenesis, axonal outgrowth and dendritic outgrowth, and programmed cell death (apoptosis) occur quickly and are coordinated. These processes rely upon microtubule dynamics, and tau proteins, particularly in the phosphorylated form, are vital to modulating microtubule assembly and disassembly. Recent proteomic studies in neonates have demonstrated that tau is overwhelmingly expressed in the developing brain as a transiently hyperphosphorylated one, including at threonine 217. Rather than being pathogenic, this phosphorylation state appears to cause microtubule flexibility needed during rapid modifications of structure during early development (28, 29).

Evidence supporting the postulate that phosphorylated tau influences the migration of the neurons, their polarity, as well as their circuit wiring, which allows the brain to refine its structure in critical periods, is found in the fetal animal and human models. More importantly, these processes decline with brain maturation and stabilization, which explains the decline in developmental tau phosphorylation with advancing age (30).

4.2 Role in Synaptogenesis, Pruning, or Plasticity

p-tau217 may serve a beneficial and developmentally essential role in early brain maturation by contributing to key

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neurobiological processes such as synaptogenesis, pruning, and plasticity (31). During synaptogenesis, tau phosphorylation modulates microtubule dynamics to support dendritic spine formation, vesicular trafficking, and the delivery of synaptic proteins. In neuronal pruning, transient p-tau217 expression may facilitate the removal of superfluous or misconnected synapses through activity-dependent cytoskeletal reorganization and axonal retraction (32). Additionally, in the highly plastic neonatal brain, phosphorylated tau supports long-term potentiation (LTP) and other forms of learning-related remodeling by enabling localized microtubule flexibility, a function that hypophosphorylated tau does not perform. Unlike in AD, this developmental phosphorylation does not lead to tau aggregation or toxicity; it is reversible, regulated, and biologically appropriate. These insights challenge the assumption that elevated p-tau217 is inherently pathological, suggesting instead that its abundance in infants could reflect a healthy, active process of brain construction rather than early signs of neurodegeneration (33, 34).

4.3 Hypothetical Role of p-tau217 in Neonatal Brain Maturation

As demonstrated in Figure 1, the alleged role of p-tau217 in the maturation of the neonatal brain can be understood based on three distinct developmental stages. During Stage 1-Axonal Growth, Tau protein is greatly expressed and also phosphorylated at threonine 217, which promotes microtubule instability (35). It is this temporary instability that provides the initial structural wiring of the brain, necessary for the elongation, directed growth of the axons. With the entry into Stage 2, Synapse production and Plasticity, p-tau217 enables the cytoskeletal rearrangement necessary to manufacture the dendritic spines, vesicular transport, and delivery of synaptic proteins the processes vital to the forward movement of synaptogenesis and the early stages of brain network formation (36). In the final stage, Stage 3-Pruning and Circuit Refinement, p-tau217 transiently enables selective synapse removal, or pruning, of unnecessary or orphaned synapses, The schematic also separates the conditions of pathological aggregation, where a red cross has been used to mark its absence in the neonatal brain versus physiological p-tau217, where it is marked in green to show its role in the non-pathogenic existence during early life. The relevance of

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interpreting the data of tau in age-specific and biological processes is further emphasized by this number, which highlights the fact that p-tau217 participates in this process as a developmental heterosticator instead of a biomarker of the disease (17, 18).

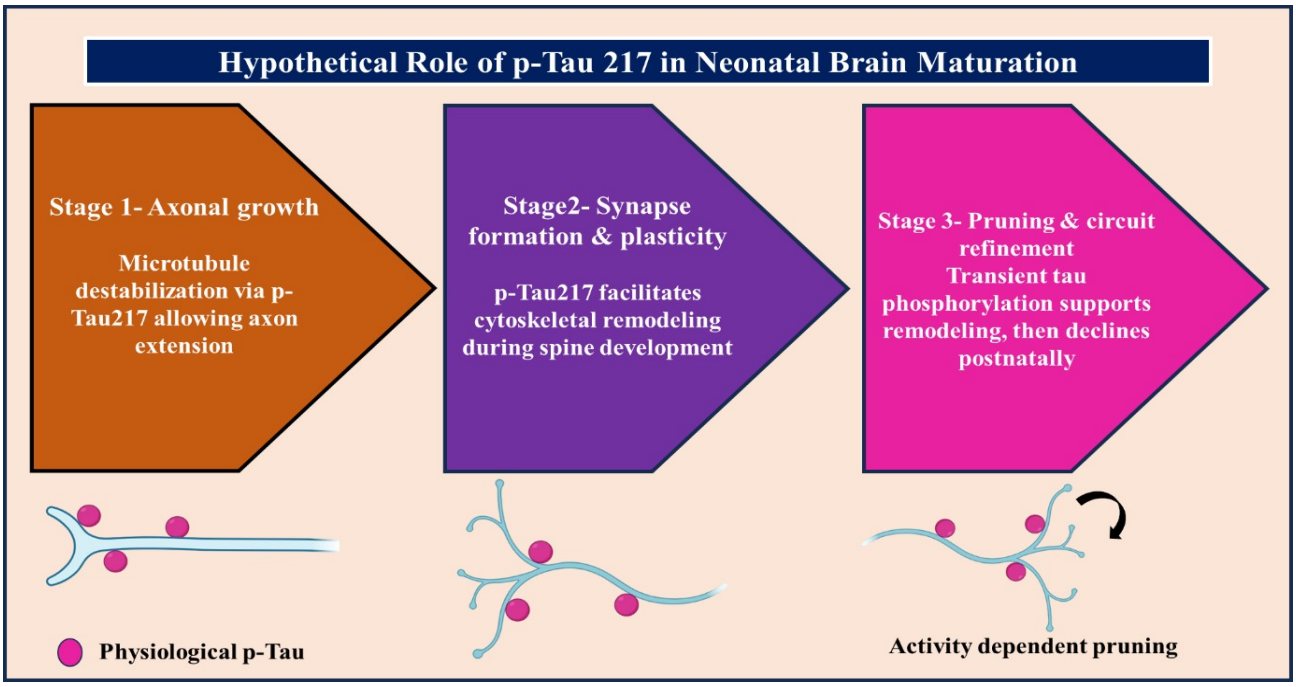

Figure 1. Hypothetical Role of p-tau217 in Neonatal Brain Maturation

Illustration of p-tau217's physiological functions during axonal growth, synapse formation, and pruning, without pathological aggregation.

5. CLINICAL IMPLICATIONS AND DIAGNOSTIC PITFALLS

5.1 Rethinking Tau as a Sole Diagnostic Marker

The discovery of p-tau217 as a highly specific biomarker of AD turned the method of early detection completely. Yet recent results of more p-tau217 in newborn children without neurodegeneration raise the question of its utility as a diagnostic tool in isolation. Although p-tau217 is highly associated with tau PET signal and amyloid pathology in older age, its

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physiological presence during early life paves the idea that tau phosphorylation (in combination with tau phosphorylation at other sites) is not necessarily pathologic (17, 37).

The same observation challenges the current dependence on biomarkers particularly when it involves asymptomatic individuals/or individuals of varied age. Within a biomarker-driven neurology, it raises the issue of a broader problem: a contextual definition of the molecular signature that must consider not only coinciding diseases, but age, and the neurodevelopmental stage.

5.2 Risk of False Positives in Early Diagnostics

It is possible for higher than normal levels of p-tau217 in populations of children or young adults to be diagnosed to be early stages of AD due to the results of neonatal studies, particularly in the rare cases of genetic susceptibility testing (1). Such false positives may lead to unnecessary anxiety, diagnostic cascades, or even incorrect therapeutic interventions (38). Moreover, the rigid thresholds employed in the diagnosis of AD in adult groups may not fit every group of the population, as the p-tau217 expression in the body may have various physiological roles at various points during the course of life. This underlines the importance of offering age-adjusted reference values as well as multimodal diagnostic procedures, including cognitive tools, neuroimaging, and the clinical situation (39)**.**

5.3 Diagnostic Algorithm Adjusted for Age-Based p-tau217 Variability

To eliminate these problems, a revised diagnostic algorithm, considering the age discrepancy in p-tau217, is shown in Figure 2. Having defined the groups of patients according to their age (under one year, paediatric, adult, and elderly), the flowchart enriches the information about selected patients based on their clinical symptoms, family background, and the presence of amyloid pathology. In children under the age of one year who have normal neurological abnormalities, elevated p-tau217 is taken as a probable physiological finding. On the contrary, a high p-tau217 provides a strong argument in Favor of AD diagnosis in cognitively deteriorated older adults with amyloid PET positive. To prevent misdiagnosis, an approach to biomarker

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contextualization is promoted and accentuates that the interpretation should be consistent with the neurobiological stage and clinical presentation. It also prepares the ground for future specific diagnostics where personalized systems of care and treatment will take into board biological signals, including p-tau217 (37, 40).

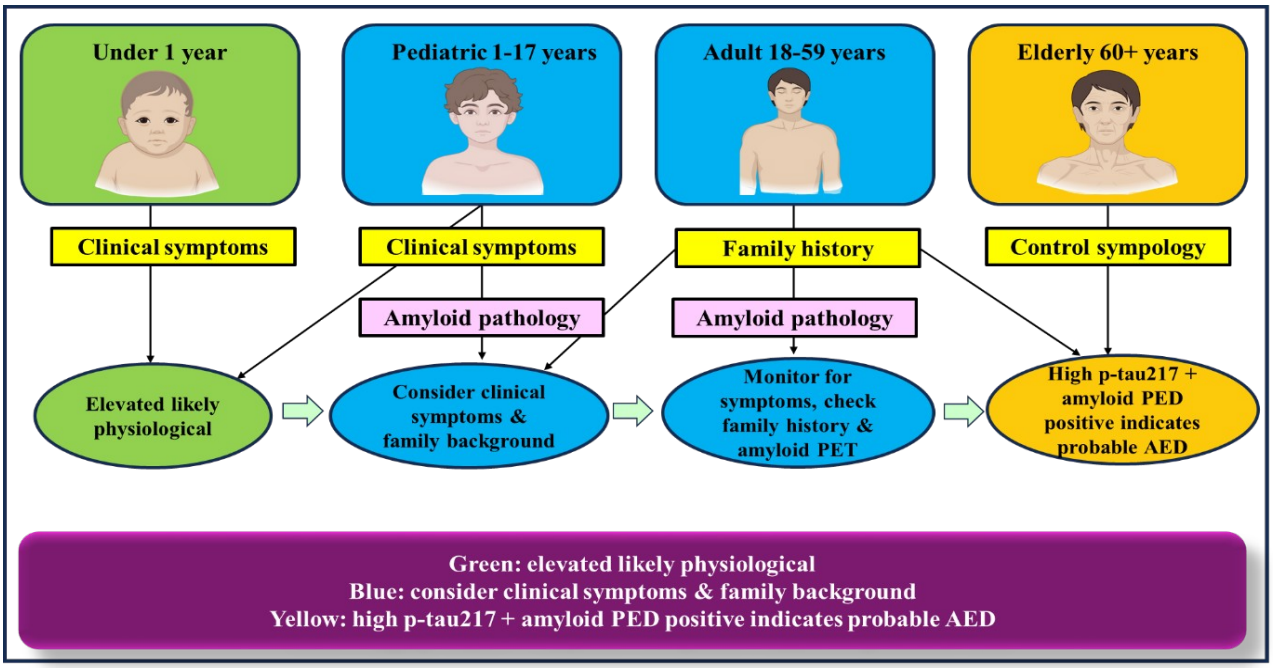

Figure 2: Age-adjusted diagnostic algorithm for interpretation of p-tau217 biomarker variability across patient populations

6. FUTURE RESEARCH DIRECTIONS

Future research should focus on longitudinal studies looking at the p-tau217 expression across childhood to adulthood to learn more about its physiological course and the possible cut-off point that can mark its pathogenic level of expression. Two potential outcomes of such studies would be to predict abnormal neurodevelopmental or neurodegenerative processes or to know whether early-life gains normalize. Moreover, there is scant information on the broader non-pathological role of tau proteins in the brain during growth, including the fact that they can take part in the polarity of the

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neurons, maintain cytoskeletal structure, and respond to metabolic stress. The acquisition of knowledge concerning these functions could lead us to a reconsideration of tau, and perhaps it is time to get over the present application of tau in the diagnosis of AD. Further research should consider the environmental, genetic, and epigenetic influences that alter tau phosphorylation status in the course of life. To avoid what we call false positives, especially when any screening is conducted in children or preclinically, precision in biomarker recommendations and age-based reference ranges is a translational priority. Clinical practice should progress toward context-sensitive diagnostics when, in addition to comorbidities and the stage of development, the cognitive profile is considered to interpret the tau levels. It is necessary to ensure that the professional associations and regulatory bodies of neurology are encouraged to update the criteria for diagnosing specific conditions so that they may consider such nuances in biomarker-based evaluations before they outweigh known biological knowledge. Techniques in precision medicine such as these will avoid wrong diagnoses and increase fast and effective action.

7. CONCLUSION

The presence of elevated p-tau217 in neonates who lack symptoms of neurodegeneration is an important paradigm shift in the understanding of the tau biomarkers during the lifespan. Even though p-tau217 has long been considered a symptom of AD, it can also be required in terms of synaptogenesis, axonal growth, and neuronal plasticity, which are not related to pathologies of brain development. It raises the question of the legitimacy of the use of p-tau217 as the sole index of the illness and underlines the importance of age-differentiated diagnostic paradigms. Without age-adjusted reference values and careful attention to clinical correlation, there is even a genuine risk of misdiagnosis, especially in younger cohorts. The work of the future should seek to understand the developmental roles of tau, establish the baseline of longitudinal markers, and enhance diagnostic algorithms that present the compromise between sensitivity and specificity. Eventually, a deeper understanding of the dual nature of tau as a pathogenic and a developmental protein would allow more accurate diagnostics, targeted novel therapies, and the reduced clinical risks of inaccurate or early biomarker observations.

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ABBREVIATIONS

AI- Artificial Intelligence

EMG- Electromyography

BMI- Brain-machine interface

p-tau217- Phosphorylated tau

CONFLICT OF INTEREST

The authors have no conflict of interest

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None

DATA AVAILABILITY

All the data presented in this manuscript are original and have not been published elsewhere.

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