# Beyond Vertical: Unraveling The PSP Enigma

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***Abstract***

*Progressive Supranuclear Palsy (PSP) is an aberrant type of Parkinsonian disorder that cognates with progressive axial rigidity, vertical gaze palsy, dysarthria and dysphagia. It is supposed to affect movement, gait, balance, speech, swallowing, vision, movements, mood, behavior and cognition. PSP increases as per age and its prevalence is 7% per 1 lakh, as reported. PSP is often misdiagnosed with Parkinson's disease, however, PSP progresses more rapidly than Parkinson's. people with PSP develop unique eye movement problems with looking up and down, speech and swallowing problems are much more common and severe in PSP than PD, leaning backwards and extend their neck in PSP (axial rigidity) while in PD -bending happens in forward direction than backward. Tremors are rare for PSP but very common in PD. The three most important primary motor symptoms are: tremors, bradykinesia, and rigidity (parkinsonism). Since this disease is termed as tauopathy, 4R-tau isoforms aggregate into straight filaments and appear as a major tau doublet (tau64 & 69). The differential diagnosis is very difficult for PSP because many neurodegenerative disorders have similar symptoms and very less discrimination between PSP and other disorders. The main objective of our study is to create awareness about PSP and its overlapping symptoms with PD as well as other and other neuro-degenerative disorders. However, based upon detailed investigations about, tau and its isoforms, these clinical features may be distinguished. However, it would require abundant knowledge of the molecular functioning and structure of tau proteins.*

***Keywords:*** *tauopathy, parkinsonism, progressive axial rigidity, neuro-degenerative disorders*

## INTRODUCTION

Progressive Supranuclear Palsy, often designated as PSP is a type of aberrant type of Parkinsonian disorder which is characterized by a gradual increase in stiffness along body's central axis, impairment in vertical eye movement , and challenges with speed and swallowing. It was first outlined in the 20th century by the trio of researchers: Steele ,Richardson and Olszewski. This complex medical condition's understanding and treatment approaches continue to be influenced by their groundbreaking work. Their research has left an indelible mark in the field , offering significant insights for ongoing studies and therapeutic strategies. It is a neuro-degerative disorder that is categorized by the supranuclear gaze palsy and the extrapyramidal symptoms that encompass slow movement (bradykinesia) and abnormal muscle contractions affecting the body's central axis (axial dystonia). Getting more deeper into the clinical picture and its ways of manifesting , it includes postural instability, frequent falls, frontal-type behavioural and includes cognitive disturbances. Diagnostic problems are very much prominent in the preliminary stages due to its versatile clinical presentation and also in those cases with atypical gaze palsy and does not have or develop any severe or isolated akinetic-rigid syndrome. Out of many patients with PSP its difficult to discern them from the unrecognized Parkinson's disease, in the initial stages at least[1,2].

In the presence of various clinical presentations and manifestations of the disease, it would not be The diagnostic accuracy rate for PSP is surprisingly high overall which is 70%-75%. Roughly 15% of the occurrences have a

hierarchy of neurological disorders that includes, parkinsonism and dementia. Supranuclear ophthalmoplegia is the primary neurological abnormality crucial for diagnosing PSP.. Oculomotor and eyelid irregularities frequently manifest in individuals with PSP, highlighting notable abnormalities in these areas.[1].

**Understanding PSP**

Tau, a protein associated with microtubules, is encoded by the MAPT gene located on chromosome 17. A broad spectrum of neurodegenerative diseases is associated with abnormalities in tau metabolism. The malfunction of the tau protein has been confirmed to have a significant impact on frontotemporal dementia(FTD) and a variety of other tauopathies , such as corticobasal degeneration (CBD) and progressive supranuclear palsy(PSP). PSP is also considered a 4R-taupathy which is principally characterized by subcortical pathology affecting neurons and oligodendroglia across a variety of clinical phenotypic presentations. It belongs to the class of disorders involving degeneration of the frontal and temporal lobes [2].

The neuropathy of the diagnosis of PSP relies on the detection of neurofibrillary tangles and threads within subcortical nuclei, coupled with the identification of tufted astrocytes[2].

A wide array of research has emphasized the distinct biochemical markers of tau pathology in Progressive Supranuclear Palsy with Parkinsonism (PSP-P) compared to its typical form, Richardson Syndrome (PSP-R). In addition, various clinical diagnostic criteria have been formally established to identify different PSP variants. These include PSP associated with corticobasal syndrome (PSP-CBS), PSP characterized by progressive gait freezing (PSP-PGF), PSP with prominent ocular motor dysfunction (PSP-OM), PSP with primary postural instability (PSP-PI), PSP with a frontal presentation as the primary feature (PSP-F), and PSP with significant speech and language disorders (PSP-SL)[5].

Tauopathies are a collection of all the degenerative neurological conditions that involves the deposition of abnormal tau protein. This buildup happens in the brain. These tauopathies unveil a vast extent of phenotypic incarnation that includes congnitive and behavioral disarray , movement clutters , language disorders and well as non-specific amnestic symptoms in the old age. Tauopathies are grouped based on predominant isoforms of tau that are situated within the inclusion bodies. These are basically 3R,4R,or equal 3R:4R ratio. The tau based biomarkers are dormant to be used in the diagnostic strategies and the assessment of patients with different tauopathies. Since , the tauopathies are intrinsically linked with irregularities in the tau protein associated both at the neuropathological and genetic levels, there is a mushrooming interest in the tailing of the tau-based therapeutics for these diorders. The tauopathies are unredeemable and many initiatives have been undertaken to illustrate the concept of these clinical and pathological characteristics to identify the biomarkers and to aim at achieving budding diagnosis and in developing disease rectification therapies[4,5].

People with PSP commonly develop specific difficulties in moving their eyes upwards and downwards, while speech and swallowing issues are notably more frequent and pronounced in PSP as compared to Parkinson's disease, leaning backwards and extend their neck in PSP (axial rigidity) while in PD -bending happens in forward direction than backward. Tremors are rare for PSP but very common in PD. The three most important primary motor symptoms are: tremors, bradykinesia and rigidity (parkinsonism). The diversity among tau-related disorders undermines the effectiveness of tau as a biomarker for distinguishing them biologically. [1,6].

**TAU PATHOLOGY AND PATTERNS OF TAU ISOFORMS IN PROGRESSIVE SUPRANUCLEAR PALSY**

This impairment of the tau protein has been established as a significant factor in frontotemporal dementia (FTD) and several other tau-related disorders, such as PSP and CBD.

Tau proteins that are encoded by the MAPT gene that play a critical role in preserving neuronal structure and the function. These proteins are essential for the intracellular transport and maintaining the neuronal shape. Although the various neurodegenerative diseases such as Alzheimer’s disease , progressive supranuclear palsy (PSP) , corticobasal degeneration (CBD) , pick’s disease, and the argyrophilic grain disease , the tau proteins undergo abnormal

modification. These alterations lead to the accumulation of tau aggregates in specific regions of the brain that contribute to neuronal dysfunction and cell death. The process of alternative splicing in the MAPT gene in the adult brain of a human results in the six distinct isoforms of the tau protein. These isoforms differ based on the presence and absence of the specific exons. Researchers continue to explore these intricate mechanisms to develop targeted therapies and diagnostic markers for these complex disorders[5,8].

***Table 1**: Main clinical features and less frequent features in PSP[2]*

| A | Main Clinical Features | B | Uncommon or Less Frequent Features |
|---|---|---|---|
| Supranuclear gaze palsy | | Pyramidal tract signs | |
| Axial dystonia | | Focal dystonia | |
| Bradykinesia | | Segmental dystonia | |
| Pseudobulbar palsy | | Abnormal sleep patterns | |
| Postural instability | | Seizures | |
| Falls | | Major depression | |
| Behavioural disturbances | | Autonomic dysfunction | |
| Cognitive disturbances | | Muscle atrophy and weakness | |

Progressive Supranuclear Palsy , also established as Steele-Richardson-Olszewski syndrome , is a scarce neurological condition that has an impact not only on the aspects of movements but also the coordination. Clinical presentations such as slow movements, muscle stiffness , eye movement problems, tendency to fall backwards , speech and swallowing problems and cognitive dysfunction. PSP progresses faster and results in more severe muscle rigidity and disability in comparison to Parkinson's disease. The hallmark of this anomaly is the buildup of the microtubule protein tau within neurons and glial cells. These tau proteins play an important role in the assembly and stabilization of microtubules. The alternative splicing of tau gene manuscripts results in six different isoforms of neuron-specific tau proteins, which differ based on the amino terminal inserts and the carboxyl terminal repeat sequences. Tauopathies refer to a group of disorders where the microtubule-associated protein tau that aggregates abnormally in the neuronal and glial cells. These abnormal condition is marked by the emergence of the filamentous phosphorylated tau protein deposits. Taupopathies exhibit various clinical manifestations that exhibit distinct neuropathological patterns[8,11].

Brain imaging outcomes for patients with Parkinson's disease typically appear normal, yet these results are instrumental in distinguishing other conditions that are frequently misidentified as Parkinson's disease[4].

Brain MR images are a distinctive characteristic of Progressive Supranuclear Palsy (PSP), marked by atrophy in the midbrain and the superior cerebellar peduncle. This midbrain atrphy results in a unique 'hummingbird sign' in the dorsal midbrain and a 'morning glory sign' with a concave lateral margin in the midbrain tegmentum, both of which are key radiological signs of PSP. However, the subjective assessment of MR scans lack objectivity and only has a sensitivity of about 50-60 % for diagnosing PSP, with many patients who do not exhibit these symptoms at the beginning of the illness. [14].

The gene responsible for encoding the tau protein is MAPT, and it is situated on the 17th chromosome, specifically in the q21 region. An adult human brain expresses both 3R and 4R tau in approximately 1:1 ratio. The alternative splicing generates six different isoforms with different N-terminal inserts and the repeat region consists of either three or four repetitive sequences. (3R or 4R)[11].

These tau aggregates were classified into two main classifications established through electrophoretic examination patterns:-

The standard PSP-tau showcases a band pattern with two upper bands, which are likely to signify the abnormal phosphorylation of four-repeat tau isoforms. On the other hand, the non-standard PSP-tau consists of bands in the range of six to eight that mimic the soluble form of tau which is found in the brain[8].

In the experiment that employed western blot and probed samples with the use of a polyclonal antibody against tau (TP70), there were noticeable disparities in the insoluble tau species across various PSP cases. The insoluble tau was plentiful in cortisol tissue from Alzheimer's brains, but it was virtually non-existent in normal brains (cortisol brain). The PSP-tau doublet was evident in the study assessed 60% of the PSP brain specimens included in the investigation.. The research suggested that around 40% of all PSP brains might not exhibit the prototypical tau doublet, which is typically associated predominantly with 4R tau isoforms[6,8,9].

Many studies highlighted the existence of many different clinical and neuropathological variations within the PSP patient population . the research also highlighted the significant heterogenetity in the insoluble tau samples that were obtained from the PSP brains. Despite the presence of heterogeneity there were no different tau patterns that were observed in the different tau haplotypes in PSP.

For understanding the different reasons for this biochemical variation , many different proficient methodologies which included dephosphorylation of both soluble and insoluble tau fractions post-dephosphorylation enabled a finer assessment of the distinct tau isoforms appearing on western blots. This technique was augmented by employing antibodies specific to tau isoforms for probing PSP brain extracts.Tau isoform ratios were observed and the data suggested that 4R/3R ratio could possibly increase in specific proportion of PSP cases in comparison to the soluble tau from the control brain specimen and aggregated PHF-tau in the alzheimer's disease[9].

*TABLE 2. MAPT mutations in different tauopathies[9]*

| **Clinical Syndrome** | **Key Features** |
|---|---|
| Frontotemporal Lobar Degeneration (FTLD) | - Cognitive decline<br>- Parkinsonism-like symptoms<br>- Behavioral changes |
| Behavioral Variant of Frontotemporal Dementia (bvFTD) | - Behavioral alterations<br>- Personality changes<br>- Impulsivity |
| Pick Disease | - Specific type of frontotemporal dementia<br>-Tau pathology in brain |
| Progressive Supranuclear Palsy-like (PSP-like) | - Resembles PSP in motor symptoms<br>- Gaze abnormalities |
| Corticobasal Degeneration-like (CBD-like) | - Features similar to corticobasal degeneration<br>- Motor and cognitive impairments |
| Neurodegeneration with Overlapping Features | - Complex presentation with mixed symptoms<br>- Overlapping features from different syndromes |

*TABLE 3. the 4R/3R ratio[9]*

| **PSP Type** | **Mean 4R/3R Ratio** |
|---|---|
| Type 1 | 3.5 |
| Type 2 | 1.2 |
| Type 3 | 1.4 |

These ratios provide with a perception into the tau isoform composition within the different PSP cases. This helps in the differential diagnosis that could possibly help in distinguishing PSP from other neurodegenerative disorders[11].

**Prevalence of the disease**

This is a fatal and rare neurodegenerative movement disorder that currently does not have a disease modifying therapy . A study analyzed data from about 88 patients that were diagnosed with PSP between 2000-2018. 53% of the patients were female also the incidence rate was 1 case per 1,00,000 persons. The typical survival duration for these PSP patients was around 4.9 years and the typical duration from symptom to diagnosis is around 4.2 years. Misdiagnosis frequently encompass conditions such as Parkinson's disease, cognitive disorders, and depression. Broadly speaking , the clinical and epidemiological traits of PSP in Israel are consistent with those of PSP identified globally [11].

*TABLE 4 . Israel case study and the disease prevalence[11]*

| **Aspect** | **Findings** |
|---|---|
| **Study Period** | 2000–2018 |
| **Population** | Patients aged **≥40 years** at first diagnosis (index date) |
| **Total Patients with PSP** | **209 patients** with ≥1 diagnosis of PSP |
| **Patients Included in Study** | **88 patients** met inclusion criteria (mean age at diagnosis: 72 years, 53% female) |
| **Prevalence (2018)** | **5.3 cases per 100,000 persons** |
| **Incidence Rate (2018)** | **1 case per 100,000 persons** |
| **Middle statistic Survival Time** | **4.9 years** (95% CI 3.6–6.1) |
| **Middle statistic Time from Symptom to Diagnosis** | **4.2 years** |
| **Erroneous diagnosis** | - Parkinson's disease<br>- Cognitive disorders<br>- Depression |
| **Clinic-Epidemiological Features** | Similar to PSP worldwide |
| **Implications for DMT Trials** | Investigating PSP cohorts globally may facilitate upcoming disease-modifying therapy trials. |

In the year 2008, the estimated prevalence rates of Progressive Supranuclear Palsy (PSP) in individuals aged 40 and above were 5.3 per 100,000 members of MHS. Furthermore , the age-adjusted prevalence rates were determined to be 1.6 per 100,000 individuals. This data was calculated using the Kaplan-Meier curve that basically is a graphical

representation of the survival estimate. This curve plots the estimated survival probability and the percentage v/s the time [6,15].

**Assessing PSP: Challenges and Limitations**

The term "look-alikes" was used by Dr. Marsden that was used to describe the cases where the clinical symptoms and signs appear consistent with a particular disorder but turns out to be something different upon the investigation process. These cases challenged the initial diagnostic manifestations that were used to highlight the complexity of neurodegenerative diseases. Neurodegenerative disorders depict both convergence and divergence of the clinical features. The process of differential diagnosis aids in differentiating between hereditary neurodegenerative diseases and syndromes that exhibit similar phenotypic characteristics. This distinction is crucial for various reasons. Disorders that are hereditary and neurodegenerative in nature , and clinically resemble PSP are often referred to as PSP-look-alikes. These share characteristics such as parkinsonism which is basically the movement abnormalities and the early supranuclear gaze palsy which is difficulty in moving the eyes upward. However, their neuropathy does not align with the typical PSP[10,11,13].

There are different examples of PSP-look-alikes:-

- Frontotemporal lobar degeneration (FTLD) is a condition that arises due to the mutations in specific genes such as PGRN , C9orf72 , CHMP2B or FUS.
- Perry syndrome is a disorder that is linked with mutations occurring in the DCTN1 gene.
- Kufor-Rakeb Disease goes hand-in-hand with mutations in the ATP13A2[13].

*TABLE 5. Genetic markers associated with the disorder and the linked key findings[13]*

| **Genetic Marker** | **Associated Disorders** | **Key Findings** |
|---|---|---|
| Polymorphic marker of dinucleotide repeat within the intron of the MAPT gene | **PSP (Progressive Supranuclear Palsy)** | - Specifically associated with PSP, not other tauopathies. |
| Single nucleotide polymorphisms (SNPs) present within an expanded haplotype | **Complete linkage disequilibrium** | - H1 haplotype (belonging to the MAPT H1 clade) was significantly more prevalent in patients with Progressive Supranuclear Palsy. |
| H2 haplotype | **Exclusive to Caucasians** | - Identified as an inversion polymorphism. |
| Sub-haplotypes within H1 | **MAPT H1c** | - Overrepresented in PSP patients and PSP-parkinsonism cases. |
| Impact on MAPT expression | **Enhanced MAPT expression** | - Particularly affects the 4-repeat-containing transcript. |

**Scope for future research**

MAPT shows a strong association with PSP distinguishing it from other tauopathies. The H1 haplotype (MAPT H1-clade) which is consistently disproportionately high in PSP patients, which has become a hallmark. Currently the precise molecular mechanisms still remain elusive and also findings suggest that H1 haplotype enhances MAPT expression. Also the further exploration of sub-haplotypes within H1 , such as MAPT H1c, has provided with the valuable insights in the disease risk and progression. This genetic information holds promise for personalized medicine, that would impact the early diagnosis, treatment strategies, and the clinical trial structure in PSP[11].

## IMMUNOTHERAPY IN PSP

Three specific antibodies produced by clones of a single B cell aimed at extracellular tau are in various clinical stages. ABBV-8E12 and BIIB092 showed safety in Phase 1 trials but encountered setbacks in Phase 2 due to failed futility analyses. UCB0107 recently disclosed Phase 1 safety outcomes in abstract format, with a Phase 2 trial being contemplated. Furthermore, clinical investigations encompass stem cell therapy and plasma infusion[7].

The potential significance of extracellular tau in the progression of PSP suggests that tau becomes a natural focal point for targeted immunomodulatory therapy. However, it's important to note that the clinical trials are currently in their initial phases. While the safety profile of tau immunotherapy appears promising, its efficacy has yet to be conclusively demonstrated[7].

*TABLE 6. Recently completed and undergoing immunotherapies[7]*

| Compound (alternate name) | Company | Number of patients | Phase | NCT number | Primary outcome measures | Status |
|---|---|---|---|---|---|---|
| **ABBV-8E12** | AbbVie | 142 | Phase 2 extension | NCT03391765 | change is PSP-RS, upto 5 years | Completed |
| | | 378 | Phase 2 | NCT02985879 | Change is PSP-RS , up to 1 year, adverse events | completed |
| | | 3 | Phase 1 extension | NCT03413319 | Adverse events | Completed |
| | | 30 | Phase 1 | NCT02494024 | Safety and tolerability | Completed |
| **BIIB092** | Biogen | 490 | Phase 2 | NCT03068468 | Change is PSP-RS , up to 1 year, adverse events | Terminated |
| | | 47 | Phase 1 extension | NCT02658916 | Adverse events, change is lab abnormalities, vital signs ECGs and physical exams | Terminated |
| | | 48 | Phase 1 | NCT02460094 | Safety and tolerability | Completed |

| | | | | | | |
|---|---|---|---|---|---|---|
| **UCB0107** | UCB Biopharma | 52 healthy males | Phase 1 | NCT03464227 | Adverse events | Completed |
| **Autologous bone marrow-derived stem cells** | MD stem cells | 300 | Not applicable | NCT02795052 | Activities of daily living , upto 1 year | Recruiting |
| **FFP** | University of California | 6 | Phase 1 | NCT02460731 | Drug limiting toxicity | Active, not recruiting |

The headway of the tau pathology as observed in the PSP-RS follows different stages :-

- Early stages involve the neuronal tau accumulation that begins with the clustering of tau in neurons within the subcortical and the brainstem nuclei.
- As disease progresses the astroglial involvement precedes the accretion of tau in the cortical neurons and oligodedroglial cells.

These progressions follows specific spatial sequence as in the tau accumulation initiates in the fronto-parietal regions and then it spreads towards the temporal areas and finally the occipital cortex region[7,8].

**Conclusion and Summary of findings**

**Directions for future research**

*TABLE 6. Immunotherapy and the key focus of the target[7].*

| **Immunotherapy Approach** | **Target** | **Key Focus** |
|---|---|---|
| Monoclonal Antibodies | Extracellular tau | Clearing tau aggregates outside neurons. |
| Intracellular Tau Targeting | Intracellular tau | Directly addressing intraneuronal tau pathology. |
| Active Vaccines | Tau antigens | Stimulating the immune system to produce antibodies against tau. |
| Antibodies Against Tau-Interacting Partners | Tau-interacting proteins | Disrupting interactions that contribute to tau aggregation. |

| | | |
|---|---|---|
| Broad Immunotherapies | Innate immune system | Modulating inflammation or enhancing clearance mechanisms. |

**Immunotherapies currently undergoing trials**

*TABLE 7: Antibodies Targeting Tau in Neurodegenerative Disorders[7]*

| Antibody | Targeted region | Characteristics |
|---|---|---|
| ABBV-8E12 | Extracellular tau (amino acids 25–30) | - Monoclonal antibody aiming at extracellular tau.<br>- Demonstrated blocking of tau uptake into neurons in lab tests.<br>- Reduced insoluble tau levels and brain atrophy in mouse studies.<br>-Behavioral deficits in learning tasks were rescued by CSF delivery. |
| BIIB092 | Extracellular tau (amino acids 15–24) | -Humanized murine monoclonal antibody focusing on N-terminal tau fragments.<br>- Located near the ABBV-8E12 epitope.<br>-Studies suggest the prevalence of N-terminal tau seeds.<br>- Decreased tau fragments in interstitial fluid and CSF.<br>-Selective binding to extracellular tau. |
| UCB0107 | Central tau epitope (adjacent to microtubule-binding repeats) | -Humanized murine monoclonal antibody that targets the central tau part.<br>- Suppressed tau aggregation in lab tests.<br>- Strongly inhibited tau seeding and spread.<br>-Outperformed antibodies targeting N-terminal epitopes. |

The presence of extracellular tau makes it more natural and easy to focus on immunotherapy. However, the efficiency of these therapies remains to be demonstrated through studies. Additionally there are many challenges in developing in tau immunotherapy which includes- the absence of standardized preclinical models and the intricate nature of tauopathies' development. Even the optimal target for the epitope , the ideal region of tau protein that is to be targeted still remains unclear. Some studies suggest that the N-terminal is attractive due to the hypothesized role in the seeding

of tau, also some studies suggest targeting the microtubule-binding repeat(MTBR). The mechanism to target is still under investigation[7].

The use of glial tau as a therapeutic target is also under consideration as microglia are responsible for tau clearance that plays a very important role[7].

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