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Progressive Supranuclear Palsy (PSP) and Newer Approaches towards its Treatment

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Abstract:
Progressive supranuclear palsy (PSP) is a relatively rare brain disorder in today's world, primarily stemming from mutations in the microtubule-associated protein tau (MAPT) gene and the tau protein. It manifests into significant difficulties related to walking, balance, eye movements, and later swallowing. Diagnosis of PSP lacks definitive criteria, although ongoing efforts by scientists leverage positron emission tomography (PET) and magnetic resonance imaging (MRI) techniques. Advancements in medical science have led to the emergence of several new or in-progress treatments for PSP, such as O-GlcNAc modification, the ubiquitin proteasome system and microtubule stabilizers. This comprehensive review delves into the intricate details of progressive supranuclear palsy, shedding light on its complexities and potential avenues for treatment.

Keywords: Progressive supranuclear palsy, neurodegeneration, Tau phosphorylation.

Introduction:

In 1963, J.Clifford Richardson and his two colleague Jerzy Olszewski and John Steele first described a rare neurological disorder in which nerve cells got damage and altered the harmonisation of healthy life. They observed symptoms like difficulty in vision and eye movement, eating and maintaining balance while walking and problem while speaking due to the disbalance between the ratio of 3R and 4R tau proteins. They collectively termed this as progressive supranuclear palsy (PSP) also known as Steele Richardson Olszewski Syndrome. 3R and 4R are tau protein isomers, formed from microtubules associated tau protein (MAPT) gene; mutation in this gene hampers the ratio of 3R and 4R tau protein, which is responsible for stabilization of microtubules. Microtubules are the backbone of neurones and when they destabilize, they are unable to maintain proper structure resulting in damaged neurone.

PSP is a rare disease, that occurs during 50's and 6o's. It has various variant each of which shows their unique sign and symptoms. Earlier, neurophysiological markers and MRI were used for the diagnosis of PSP which was not completely reliable and symptomatic treatment was the only option available. Later, a huge boost came in the medical field which led to the development of new diagnostic procedure and medications. In this article, an attempt has been made to highlight the newly developed diagnostic procedures, medications, and drugs under clinical trial along with new treatment strategies for PSP.

Epidemiology:

The prevalence of progressive supranuclear palsy (PSP) stands at approximately 6-7 cases per 1,000 individuals, typically manifesting between the ages of 50 and 60. The average age of onset is reported to be 63 years, with roughly half of affected individuals exhibiting the classic form of PSP. In the United Kingdom, research indicates a higher prevalence, with around 18 cases per 100,000 adults aged 70 to 74 (Coyle *et al.,* 2016).

Conversely, studies in Japan have found a total frequency of 18 instances per 100,000 across all age groups, encompassing various PSP phenotypes beyond PSP-RS (Takigawa *et al.,* 2016). Most individuals with PSP symptoms gradually develop clinical traits characteristic of PSP-RS. Common PSP disorders include primary parkinsonism (PSP-P), corticobasal syndrome, and pure akinesia with gait freezing, now termed PSP with progressive gait freezing (PSP-PGF). Over time, a majority of individuals with PSP syndromes exhibit some or all of the clinical features of PSP-RS (Boxer *et al.,* 2017).

Risk Factors:

Risk factors associated with progressive supranuclear palsy includes genetic risk factors and exogenous risk factors. The H_1 haplotype of the microtubule associated protein tau gene (MAPT gene) and its role in tau protein encoding is the most important genetic risk factor (Baker *et al.,* 1999).

In a study conducted by Höglinger *et al.,* three genetic risk factors have been linked to PSP. EIF2AK3 (Protein transcription is regulated by protein kinase R-like endoplasmic reticulum kinase), MOBP (a component of myelin), and STX6

(helps in vesicular exocytosis), however the importance of these genes are unknown (Höglinger *et al.,* 2011).

Among the exogenous risk factors are the early life (or prenatal) nutritional deprivation, unskilled employment with chemical exposure, residential exposures in working-class or impoverished neighbourhoods, or other characteristics linked to lower educational level. This should be given new and special attention as they are the potential causes of PSP. Another theory suggests the aberrant lipid peroxidation in PSP brain areas is caused by toxins or diets that promote that abnormalities (Odetti *et al.,* 2000).

Signs And Symptoms:

Classical PSP is characterized by a range of signs and symptoms, including severe gait and balance impairment, generalized bradykinesia, dementia, visual impairment, tremor, dysarthria, dysphagia, sleep disturbance, constipation, apraxia, urinary incontinence, and dystonia, among others.

Visual impairment (vertical supranuclear gaze palsy) - More than half of the clinical cases reported show that after 3-4 years of the disease the patients show symptomatic difficulty in eye movement (Davis *et al.,* 1988). Towards the later stage of disease the patient's vertical gaze range decreases, with downgaze usually being poor compared to up gaze. PSP patients often have problems with eyelid movement, such as reduced blink frequency or blepharospasm, which lead to drying out of the eye which can be irritating for the patients (Golbe *et al.,* 1989).

Movement disorder - Gait apraxia, poses a significant challenge in PSP (Progressive Supranuclear Palsy), leading to gait freeze and impaired mobility in patients (Matsuo *et al.,* 1991). Some patients exhibit no rigidity upon autopsy, prompting scientists to designate this variant as PSP-pure akinesia with gait freezing (Williams *et al.,* 2007).

Speech problems - The slowing, softening, or slurring of speech in PSP poses comprehension challenges. Dysarthria is identified in 41% of PSP patients within two years of onset (Davis *et al.,* 1988). Research indicates that Richardson syndrome affects nearly 90% of individuals, while PSP-parkinsonism affects approximately 81%, highlighting the prevalence of this issue (Williams *et al.,* 2005).

Personality, behavioural and cognitive changes - Symptoms include cognitive sluggishness, memory deficits, and personality alterations such as anger, apathy, and mood swings. Behavioural changes like recklessness and impaired judgment also manifest. In over 30% of cases, cognitive or behavioural abnormalities serve as the initial PSP symptom (Williams *et al.,* 2005). Extended response times lasting several minutes, coupled with feelings of melancholy and apathy, can create an impression of global dementia. PSP dementia is discerned from Alzheimer's dementia primarily by the presence of significant anterior impairments in PSP dementia, with minimal anxiety, irritability, aphasia, or wandering behaviour (Litvan *et al.,* 1996).

Sleep Disturbances - In PSP, both primary and secondary insomnia are common concerns. The overall sleep efficiency is only 43%. In a study, a nonspecific condition called sleep-disordered breathing was seen in 55 percent of PSP patients. Only one of the 27 patients with PSP had another nonspecific condition, called restless legs syndrome (Sixel *et al.,* 2009).

Dysphagia - As a result of fluid or small food particles entering the lungs, choking and chest infections occurs. In severe PSP, aspiration pneumonia is a serious problem that can be fatal (Davis *et al.,* 1988). Choking and chest infections occurs as a result of fluid or small food particles entering the lungs. Aspiration pneumonia is a significant concern in severe PSP and can be fatal.

Urinary Incontinence - Urinary bladder problems affect the vast majority of PSP patients, beginning with need to go to urinate and incontinence is the final result of PSP. It was revealed in a report that about 42% of participants developed urine incontinence in 3.5 years of PSP progression [Testa *et al.,* 2001].

Balance and Falls - It is noticed that PSP patients while walking suddenly lose their balance and falls backwards majority of the time.

Pathophysiology:

Progressive supranuclear palsy (PSP) is characterised pathologically by the bilateral loss of neurons in the periaqueductal grey matter, subthalamic nucleus, red nucleus, pretectal, vestibular nuclei and oculomotor nucleus (Litvan *et al.,* 1996). Deeper cortical layers especially around the precentral gyrus, can also be affected to a lesser degree (Hauw *et al.,* 1994). This mainly happens due to polymorphism or mutation in Microtubule Associated Protein Tau (MAPT) gene (Höglinger *et al.,* 2011).

On chromosome number seventeen, two haplotypes MAPT gene resides, they are haplotype H1 and H2 respectively, and the sub haplotype of H1 tau protein encoded with 16 exon, is currently the most prominent genetic risk factor (Neve *et al.,* 1968). The first (E1), fourth (E4), seventh (E7) ninth (E9), eleventh (E11), twelfth (E12), and the thirteenth exon (E13) also undergo constitutive splicing, while alternative splicing occur to the other exons. The five untranslated sequences of MAPT mRNA are encoded by E0 and E1, while the three untranslated segment is encoded by E14. The promoter containing E0 exon is subjected to undergo transcribed process but the translated process does occur. E1 contains the ATG translation

start codon. Only peripheral tissue transcribes E4a, E6, and E8. Alternative splicing of E2, E3, and E10 produces the six human brain tau isoforms (Andreadis *et al.,* 2006). The tau protein has six alternatively spliced isoforms, it depends on the presence or absence of N1, N2 at the N terminus which is 29 amino acid and 59 amino acid respectively and at the microtubule-binding domain presence or absence of 31 amino acid repeats. The microtubule-binding domain is a protein that binds to microtubules containing either three (3R) or four (4R), 31-amino-acid repetitions. In healthy brain 3R:4R are same but the concentration of 4R become higher and the ratio of 3R:4R become disbalanced in the disease condition (Goedert *et al.,* 2004, Williams *et al.,* 2006).

Tau aids tubulin assembly, stabilizes polymerized microtubules, and nucleates microtubules, and tau has been shown to regulate microtubule dynamics. In neurite outgrowth, tau is involved. Tau expression also cause lengthy cytoplasmic extensions in non-neuronal Sf9 cells, as well as microtubule bundling and stabilization in other non-neuronal cells (Avila *et al.,* 2004).

The role of Tau proteins as a microtubule stabiliser, as well as some of the processes in which it is implicated, can be affected by changes in its amount or structure. Different subcellular structure like mitochondria can also be organized and localized by microtubular organisation (Nangaku *et al.,* 1994).

Hyper-phosphorylation of tau proteins cannot bind with microtubules but bind with each other and form hyperphosphorylated tau, this hyper-phosphorylated tau related disease is known as tauopathy and is mainly found in glia of the brain (Avila *et al.,* 2004).

Patients with PSP develop an abnormal formations in their brain known as neurofibrillary tangles (NFT). The tau protein becomes hyper-phosphorylated in the disease condition and combines with each other to create tau tangles which when combines with each other produces paired helical filament progressively forming NFT (Grundke *et al.,* 1986). It is reported that dementia is exponentially increased with the formation of NFT.

Tau transmission:

Tau species are passed from one neuron to the another. Tau transmission may follow a proximity-dependent pattern within the same brain area. Exocytosis or vesicles such as exosomes produced from multi-vesicular bodies (MVBs) that can fuse with and convey their contents into destination neurons may be used by donor neurons to release tau seeds. Endocytosis or receptor-mediated endocytosis can be used to ingest extracellular tau seeds by recipient neurons. There are two putative routes for tau disease to spread trans-synoptically. First, presynaptic neuron degeneration might result in presynaptic membrane leakage, allowing presynaptic tau seeds to permeate across the synaptic cleft. Second, tau seeds can be released via exocytosis, exosomes, or synaptic vesicles from the presynaptic terminal (SVs). Tau seeds can be picked up by postsynaptic neurons and cause tau aggregation once they have been released (Wang *et al.,* 2016).

Diagnosis:

Neurophysiological Markers – In PSP, the initial major clinical symptom manifests as difficulty in vertical eye movement, which can be demonstrated using electro-oculogram, a subtype of electromyogram (Vidailhet *et al.,* 1994). Furthermore, the blink rate and spontaneous blink rate are decreased in PSP compared to a healthy condition (Karson *et al.,* 1984). Additionally, damage to the reticulospinal system in PSP results in a decrease in the auditory startle reflex (Vidailhet *et al.,* 1992).

Bio-fluids - PSP patents have low or normal phosphorylated tau and total tau in the cerebrospinal fluid (CSF) compared to healthy individuals (Wagshal *et al.,* 2015). According to a study, patients with PSP have 2–5 times higher neurofilament light chain (NLC) contents in their CSF (Scherling *et al.,* 2014). Neurofilament light chain concentrations in the blood can be properly tested, and individuals with PSP-RS show higher plasma NLC concentrations than healthy individuals of same age and individuals with Parkinson's disease (Hansson *et al.,* 2017). As determined by clinical and MRI assessments, by baseline plasma NLC concentrations predicted illness development over the course of a year (Rojas *et al.,* 2016).

Positron Emission Tomography – Scientist developed tau protein detector that bind with these tau protein and act like a tracer including 18F-5105, 18FFDDNP, 18F-THK523, 11C-PBB3, and others (Villemagne *et al.,* 2015). The most thoroughly investigated tau tracer to date is 18F-Flortaucipir (previously AV-1451 and T807) which can binds with PHF in 3R/4R neurons (Marquié *et al.,* 2015). PET tracer (11C-(R) PK11195) can also give information about the inflammation related to neurodegeneration targeting the activated microglia in PSP and other disorders (Coughlin *et al.,* 2020).

Magnetic Resonance Imaging (MRI) - The well-known anatomical neuroimaging biomarkers in PSP are 'hummingbird sign' (Kato *et al.,* 2003), 'morning glory (Adachi *et al.,* 2004) or Mickey-Mouse (Massey *et al.,* 2012) all of which result from midbrain atrophy.

Symptomatic Treatment:

Several research have led to the discovery of a number of treatment for PSP. Some of the symptomatic treatment associated with PSP includes administration on levodopa in stiffness and bradykinesia. A study on eighty two individuals found that carbidopa/levodopa helped

approximately 10-25 % people mildly to moderately (Nieforth *et al.*,1993). In a double-blind study on twenty one patients it was reported that after using coenzyme Q-10 which is a mitochondrial nutrient; patients showed significant level of improvement (Stamelou *et al.,* 2008). Furthermore, a study showed the efficiency of Botulinum toxin, that can be useful in blepharospasm in PSP patients, and its variant (Piccione *et al.,* 1997).

The use of weighted walkers can assist patients achieve a more stable posture and safer movement. Speech therapy can assist with communication, speaking, eating and swallowing. When there is a problem in swallowing liquids, a modified barium swallow examination can be useful in determining the extent of the problem and provide appropriate compensatory procedures or diets. Occupational therapists can do home safety inspections. Social workers and palliative care consultants can also help with stress management (Wiblin *et al.,* 2017).

Dry eyes can be treated using ophthalmic lubricants. Sunglasses can help with photosensitivity as well. Prism glasses can help with double vision caused by poor convergence, but if they aren't effective, alternating eye patches can be used instead (Coughlin *et al.,* 2020).

Potential Therapeutic Targets

Modulation of MAPT gene - *In vitro* and *in vivo* studies indicated that MAPT antisense oligo-nucleotides (AON) could reduce human tau protein concentrations (DeVos *et al .,* 2017). In healthy condition a RNA have a hairpin like structure which monitors and controls the splicing of Exon 10 but in the disease condition the genetically mutated variants of MAPT gene destabilise the RNA and alter the harmony in splicing of Exon 10 which increase the production of 4-repeat tau. The use of AON or splicing modulators to normalise the 3-repeat:4-repeat tau ratio could possibly be a viable therapeutic option. AON's are small compounds that have been developed as it can stabilise the RNA hairpin structure and can maintain the ratio of 3-repeat:4-repeat tau by decreasing the synthesis of 4-repeat tau, antisense oligo-nucleotides (Schoch *et al.,* 2016).

Modulation of tau gene in post translational modification –

- **O-GlcNAc modification** - O-GlcNAc modification involves attaching oligosaccharides to proteins, termed glycosylation. N-glycosylation binds sugars to asparagine, while O-glycosylation binds to threonine. Deglycosylation of tau tangles enhances microtubule accessibility (Wang *et al.,* 1996). O-GlcNAcylation reduces tau phosphorylation, acting as competitive inhibition. Targeting O-GlcNAcylation with enzyme inhibitors mitigates neurodegeneration in mice ((Yuzwa *et al.,* 2008; Yuzwa *et al.,* 2012).
- **Tau phosphorylation –** Phosphorylation occurs when a phosphate group esterifies amino acids like tyrosine (Y), serine (S), and threonine (T) in proteins. It's a prevalent tau post-translational modification. Hyper-phosphorylation of tau disrupts microtubule binding, destabilizing the neuron cytoskeleton (Martin *et al.,* 2011). Scientists target tau's phosphorylation sites, seeking ways to mitigate its effects, but clinical trials with GSK-3 inhibitors have shown limited efficacy (Tolosa *et al .,* 2014). (ClinicalTrials.gov, number NCT00703677).
- **Acetylation –** Another potential therapeutic target is acetylation of insoluble tau protein which make them soluble. This hyperphosphorylation in the brain can be decreased and scientist are targeting this pathway to develop new drug (Min *et al.,* 2015).
- **Ubiquitin proteasome system -** Ubiquitin binding signals the ubiquitin-proteasome system (UPS) to degrade specific proteins in the cytosol. Studies with transgenic mice indicate lithium's ability to enhance mutant tau ubiquitination, reducing its overexpression. Ubiquitination, particularly in PHF, escalates with PHF formation, as observed in studies (Martin et al., 2011).

Microtubule stabilizers - Davunetide is a neuropeptide with neuroprotective and microtubule-stabilizing characteristics that has shown promising results in animal models. However, clinical trial performed in over 300 patients did not show clinical efficacy (Boxer *et al.,* 2017). TPI287 is a taxane derivative that stabilises microtubules, crosses the blood-brain barrier, and has the potential to reduce cancer cell proliferation (Fitzgerald *et al.,* 2012). On higher dose TI287 does not show any activity and show adverse effect like anaphylactoid. Epothilone D, which is in the early stage of development can stabilize the microtubule formation (Zhang *et al.,* 2012).

Inhibition of TAU propagation – Various studies have shown evidences that paired helical filament and neurofibrillary tangles can move from one neuron to another neuron like a prion. So, researchers are developing anti-tau antibody to target the tau propagation from one neuron to another. In studies with tau transgenic mice models, scientist reported that anti-tau monoclonal antibodies create passive immunisation in the animal model and increase the cognitive and motor function and decrease the tauopathy. Specific antibodies can target certain three-dimensional conformations of tau that appear to be particularly pathogenic (Boxer *et al.,* 2017). BMS-986168 and Abb-8E12 are monoclonal antibodies and can bind

with the N-terminal of tau protein. AADvac1 and ACI-35 are tau vaccines that have entered the human clinical trials (Pedersen *et al.,* 2015).

Conclusion:

There are several signs and symptoms that can be observed throughout the progression of the disease but currently there are no proper diagnostic criteria for PSP at the initial stage. At the later stage PSP can be diagnosed and detected but it gets too late to fully cure as the neurons get damaged; with the help of treatment, we can assist the patient to control the symptoms. The novel experimental medications for treating PSP have entered clinical trials successfully in the previous decade. The evaluation of new treatment and diagnosis of PSP have been both benefited by the description of several interesting biomarkers. There are several scheduled clinical trials, indicating the possibility of PSP medicines that may work.

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