HIGH SCHOOL EDITION
Journal of Student Research
Volume 12 Issue 3 (2023)

Progressive Supranuclear Palsy: A Review

Rishima Misra

Dulles High School

ABSTRACT

Progressive Supranuclear Palsy (PSP) is a rare neurodegenerative disease which is caused by 4 repeat tau proteins. PSP has a low diagnosis rate because it is underdiagnosed or misdiagnosed as other common diseases such as Parkinson's Disease (PD). A systematic and comprehensive literature review has been conducted with evidence from various sources in the databases of PubMed, Google Scholar, and JSTOR. A synthesis was conducted based on "Progressive Supranuclear Palsy" in etiology and differential diagnosis was conducted based on "'Parkinson's disease' on the way to progressive supranuclear palsy: a review on PSP-parkinsonism." From the results we can see that there is a lack of research overall for PSP and it is greatly understudied. One area that needs to be focused on is the treatment for disease-modifying symptoms of PSP as mostly only PD medications are used even though both the diseases are vastly different. A systematic literature review has been done on the topic of PSP regarding the current advances. In general, the diagnosis of PSP is lacking as there is misdiagnosis between one of the PSP subtypes, PSP-Parkinsonism (PSP-P), and PD while there is also underdiagnosis as they symptoms of PSP-Richardson's Syndrome is seen as natural aging. The lack of early diagnosis and validated biomarkers makes it difficult to find a treatment for PSP. With the lack of information about PSP it is imperative that systematic research needs to be done so that patients have a favorable course and better standard of living.

Overview

Progressive Supranuclear Palsy (PSP) is a sporadic neurodegenerative disease. It is characterized pathologically by 4 repeat tau protein depositions in various cells [1]. These tau proteins are the most abundant microtubule protein found in the brain. Normally, the tau proteins would naturally build up in the brain and break down before they reached a high level. However, for people with PSP, the tau proteins aren't broken down properly which causes harmful clumps of the protein in the brain. More specifically, a normal brain has similar levels of 3 repeats (3R) and 4 repeats (4R) tau. However, PSP patients have an abnormal amount of 4R-tau which causes problems in the adult brain as there are depositions of tau proteins [1,2]. The amount and location of these clumps differ from patient to patient. This in turn leads to varying symptoms [4]. Some of the leading characteristics of PSP include postural instability, vertical supranuclear gaze palsy, slowness of saccades, and cognitive decline due to nerve cell degeneration in the brain stem [1,3]. We must learn more about this disease as its diagnosis rate is very low. There is underdiagnosis happening which is deadly as many patients are having irreversible symptoms. Historically it was confused with Parkinson's disease and was known as an atypical form of parkinsonism which led to misdiagnosis [1]. In addition, with the current research, we now know that PSP has a range of motor and behavioral symptoms, which invariably leads to underdiagnosis as people get it confused with natural aging. If we don't properly learn about the symptoms, this can lead to not being able to diagnose patients accurately. This in turn can cause us to not be able to prolong the patient's life and not delay the progression of the disease. As PSP progresses there are many irreversible symptoms such as not being able to eat, walk, or communicate Once this disease indication is studied, patients who are suffering deteriorating symptoms in walking, eating, and communication can get medical resources [1]. The medical and economic, and societal burden is underestimated and does not get enough attention.

There are many clinical phenotypes related to PSP pathology, and all these different phenotypes have different symptoms specific to the phenotype. The most common phenotypes are PSP-Richardson's Syndrome (PSP-RS) and PSP-Parkinsonism (PSP-P). The symptoms of PSP-RS include vertical ocular motor dysfunction, early onset postural instability, and falls. The symptoms of PSP-P include a clinical phenotype resembling Parkinson's disease [1,3,4]. Back then, PSP-RS was the only known PSP phenotype, which led to the underdiagnosis of PSP overall as people who may have had a different PSP phenotype weren't diagnosed at all. Patients who had PSP-RS clinical symptoms did not receive medical attention, hence not receiving timely treatment [1]. With the situation related to underdiagnosis, the current incidence and prevalence aren't accurate. However, with more research going into PSP there has been a better understanding of the disease. This has allowed for diagnosis to occur with better accuracy, making the data more reliable.

It is said that PSP pathology is found in 2-6% of elderly people with no diagnosis of PSP before death. The mean survival time is 6 to 7 years. Most patients are diagnosed 3 years after the appearance of the first symptom when the symptoms have gotten more severe making it easier to identify [3].

There is an estimate that 5 to 17 people are affected by PSP 100,000 people in 2018. The incidence of the disease is 0.14 to 1.9 people per 100,000 in 2018. The median age of onset is 67.2 years (SD 7.3, median 67.0, range 49-86) [1,3]. The disease population is dominated by males (1.6: 1) [5].

If we research this disease more with more understanding, we will be able to detect the disease at an earlier age, which can lead to a timelier treatment given to the patient so that the deterioration isn't as progressing. This in turn can increase the mean survival time and increase the standard of living for the patients. We will be able to prevent irreversible symptoms and improve the quality of life for the patients. This paper will give information about how PSP symptoms differ from the symptoms of other diseases such as Parkinson's and old age.

Subtypes

PSP-RS was the first phenotype of PSP that was found in 1964, which resulted to not much misdiagnosis or underdiagnosis occurring [1]. Some of the symptoms include postural instability, falls, and vertical supranuclear palsy. The mean age of onset in PSP-RS is 62.0 years and the mean duration of the disease is 7.3 years. The male to female ratio in PSP-RS is 1.8:1. PSP-RS patients have overall lower cognitive dysfunction based on standard cognitive scales. They are also linked with early phonological verbal fluency deficit [3].

PSP-P on the other hand has symptoms that are very similar Parkinson's disease such as asymmetric onset, tremor, and moderate initial response to levodopa. It is believed that PSP-P and Parkinson's disease during the first few years may be indistinguishable [1,3]. That itself is very dangerous as a patient may be misdiagnosed with Parkinson's as Parkinson's is a more well-known disease compared to PSP. This can cause the patient to have irreversible symptoms that could have been delayed through therapy if the disease was diagnosed correctly. Although PSP-P and Parkinson's are quite similar, as disease progresses, patients started developing symptoms such as visual hallucinations, drug-induced dyskinesias, and autonomic dysfunctions, which are exclusive symptoms of PSP-P [3]. The mean age of onset for PSP-P is 67.7 years and the mean duration of the disease is 12.8 years. People with PSP-P traditionally live longer than PSP-RS patients. Studies show that even when the severity of the disease is similar, patients with PSP-RS progress significantly faster than patients with PSP-P [3]. Thus, PSP-P patients have longer survival and a more favorable course. One of the symptoms that PSP-P continues to have in the later stages that PSP-RS doesn't are tremors. Apathy supported the diagnosis of PSP-P. PSP-P patients score lower on PSP Rating Scale (PSPRS) compared to PSP-RS on bradyphrenia, disorientation, emotional incontinence, and anxiety/depression [3]. The PSP Rating Scale is composed of 28 items in 6 areas. The scores range from 0 (normal) to 100. The PSP Rating Scale is not a diagnostic tool but is a quantitative measure of disability. It includes all the areas of clinical impairment in the different PSP phenotypes [6]. Moreover, PSP-P patients score lower on Non-Motor Symptoms Scale (NMSS) than PSP-RS patients with sleep/fatigue, mood/cognition, and gastrointestinal tract [3]. The NMSS is composed of 30 items based on a scale to assess a wide range of non-motor symptoms in patients with

Parkinson's disease [7]. PSP-P unlike other PSP phenotypes responds to other levodopa and other dopaminergic drugs. Over the course of the disease, it is possible for PSP-P to evolve into PSP-RS. The clinical differences between PSP-RS and PSP-P are more evident the first two years, but after that they may become similar [1,3].

Differential Diagnosis

PSP-P, a subtype of PSP is often misdiagnosed as Parkinson's disease which is more common and has similar symptoms [8]. It is very difficult to differentiate between PSP-P and Parkinson disease especially in the early stage. The reason PSP and Parkinson's disease are similar is because an area that is damaged in the brain is substantia nigra for PSP patients which is also where Parkinson's disease damage occurs. That is the reason why both diseases can present similar symptoms, but Parkinson's treatments will not work for PSP patients [9]. The clinical differences between PSP-RS and PSP-P are more evident between the initial 2 years [3]. In those first 2 years it is difficult to differentiate between PSP-P and Parkinson's disease. Although after that there is clinical overlap between PSP-RS and PSP-P and 6 years of follow-up, the clinical phenomenology might become very similar [1,3].

PSP-P has symptoms that are shared by both PSP-RS and Parkinson's. However, PSP-P patients demonstrated more symptoms related to speech and difficulty swallowing compared to Parkinson's patients [8]. Patients with PSP-P have more problems moving the eyes, especially looking downwards, compared to patients with Parkinson's [8]. Also, unlike patients with Parkinson's disease, patients with PSP-P are more likely to fall backward rather than forward [8,9].

A way to differentiate between PSP-P and Parkinson's is the onset of cognitive, behavioral, or emotional changes. For cognitive changes, PSP-P patients presented cognitive changes, such as difficulty finding the right words, problems making decisions, disorientation, judgement changes, problem-solving issues, forgetfulness, or irritability, whereas Parkinson's disease patients presented these symptoms at a later stage [9]. And the symptoms are often caught by family members. PSP patients may have outbursts where they will burst into laughter or tears. They could also become more aggressive and out-of-control behavior towards family members. Parkinson's patients do not present these behavioral changes. PSP-P patients tend to present depression, irritability, apathy, and detachment [8,9].

Currently there are no tests or brain imaging techniques to definitively diagnose PSP. An initial diagnosis is based on the patient's medical history and physical and neurological exams. Identifying early gait problems, problems moving the eyes, speech and swallowing abnormalities can help doctors diagnose PSP. Diagnostic imaging can show shrinkage at the top of the brain stem and areas may show degeneration [1,8].

Etiology

PSP is a sporadic disease, and its etiology is yet to be confirmed. There have been hypotheses about whether PSP is caused by environmental factors, or it is genetic, or maybe both [1].

There are a few environmental factors that are thought to increase the occurrences of PSP which include Annona Muricata fruit in Guadeloupe and chemicals which are in geographic clusters [10]. The initial assumptions came from the fact there was a PSP-like disease in Guadeloupe which was associated with the consumption of Annona Muricata [1]. The consumption of plants of the Annonaceae family specifically Annona Muricata which suggests a toxic etiology. Annonaceae has two possible groups of potential toxins, alkaloids and acetogenins. Alkaloids and annonacin, the most abundant acetogenin were toxic and in neurons [10]. Acetogenins are potent mitochondrial poisons, like other poison parkinsonism inducing compounds. Studies show high concentrations of annonacin are present in the fruit or aqueous extracts of the leaves of A. muricata, can cross the blood brain barrier since it was detected in brain parenchyma of rats treated chronically with the molecule. These studies reinforce the concept that consumption of Annonaceae may contribute to the pathogenesis of PSP-like disease in Guadeloupe. There have also

been case studies regarding how exposure to chemicals can be a risk factor for PSP. Surveys show that PSP patients on average have less educational attainment. This can suggest that the cause of PSP may be related to certain occupational factors exposing the patients to different chemicals that aren't necessarily encountered in a typical city occupation.[10]. Another possibility is that people with less education tend to live in areas closer to industrial sites as housing there is cheaper for them, which generate toxins [10]. The largest study regarding pesticides reported well water as a risk factor for PSP [1]. Another geographic cluster is in the suburbs of Northern France. The area was the site of metal-related industry which contaminated the soil in the 20th century. There are current investigations to see which toxins could possibly lead to this geographical cluster [10]. It is difficult to identify and rule out environmental risk factors due to the low numbers of patients that have PSP and are available for recruitment of studies [1,10].

The genetic causes are mainly from MAPT gene, Leucine-rich repeat kinase 2 (LRRK2) mutation, and R1441H mutation. It can be associated with mutations in the MAPT which is the microtubule-associated protein tau gene that can lead to PSP-pathology and associated to the phenotypes [10,11]. The MAPT gene is located on the 17q21.31 chromosome [4,11]. MAPT mutations were first reported in families in 1998. Since then, more than 60 mutations have been identified which have been characterized by behavioral changes and clinical parkinsonism. The frequency of PSP cases carrying MAPT mutations varies with a range from 0.6% to 14.3%. The mean age at onset in PSP with MAPT mutations is approximately 44.8 years (range of 36-62 years) with a peak in the early 40s [4,11]. In general, for most cases of PSP the mean age of onset is 67.2 years (SD 7.3, median 67.0, range 49-86) [1,3]. Most cases with MAPT mutations have a family history with parkinsonism, dementia, or other neurodegenerative disorders [11]. The H1 MAPT haplotype has been consistently associated with PSP. About 95% of PSP patients have this variant on both copies of chromosome 17, but this is also true for 60% of the world population [10]. This proves that the H1 Haplotype is necessary but not a sufficient cause of PSP [10]. There is another mutation that can be associated with PSP. LRRK2 is considered a very common genetic cause of Parkinson's disease [4,12]. Five LRRK2 mutations in patients presenting a PSP phenotype. The prevalence of autosomal dominant mutations in LRRK2 in PSP can be estimated 0.17-0.34% [12]. The R1441H mutation has been identified in a patient originally diagnosed as typical PD but transitioned to PSP 8 years later [4]. This case indicates that the R1441H mutation has been involved in the PSP-P [4].

PSP is challenging due to the inexplicit pathogenesis, lack of effective medications, poor prognosis, and early diagnosis is difficult. There is data proving that genetics plays a role in PSP and so do environmental factors [4]. However, there is still not enough data to validate the other risk factors that might cause this complex disorder [4]. There are still no definite causes of PSP but there are many hypotheses about it being caused genetically or through environmental factors.

Testing

Unlike other diseases there is no one definite test that can prove that a patient has PSP [1]. However, there are several diagnostic tests that can be taken together as a group that can support a diagnosis. It can be very difficult to differentiate between Parkinson's Disease and PSP as mentioned before due to similar symptoms. The doctor can suspect that a patient has PSP rather than PD if they have tremors, unexplained falls, little or no response to Parkinson's medication, and difficulty moving eyes.

Neuroimaging can only show information for PSP in the advanced stages. Neuroimaging hasn't provided any information about diagnostic or prognostic biomarkers for PSP that can help detect PSP early on [1]. There needs to be more research before setting up standardized measures that could be used for clinical practices.

In MRI scans Midbrain atrophy is the most consistent sign of PSP-RS seen in the structural MRI [1]. Midbrain atrophy is the loss of cells in the midbrain area which is in the brainstem area. PSP patients have reduced midbrain volume [13]. There are multiple ways to measure midbrain atrophy. One of these ways includes a simple visual assessment of the midbrain like the presence of the morphological markers such as the "hummingbird" sign in midsagittal plane, the "Mickey Mouse" sign in axial planes, and "morning glory" signs in axial planes [1]. The

"hummingbird sign" is referred to as significant midbrain atrophy with no pons atrophy [14]. The hummingbird sign is reported to have a sensitivity of almost 100% [14]. The Mickey mouse sign in axial planes is seen as reduction of midline midbrain diameter [15]. The morning glory signs in the axial planes are the loss of the lateral convex margin of midbrain [15]. Quantitative measurement of the midbrain has shown consistently that midbrains are smaller in PSP-RS compared to multiple system atrophy PD [1]. Even though MRI scans can be used to determine the clinical phenotype; they aren't useful as biomarkers [1]. A MR Parkinsonism index was developed which considers the midbrain/pons area ratio and the middle cerebellar peduncle SCP width ratio. This shows excellent sensitivity and specificity values for the differential diagnosis of PSP-RS [1]. Different studies have said that it might be beneficial to look at all the areas that PSP affects rather than just the brainstem through the use of optimal prediction models, or automated machine-learning techniques [1]. It looks like a reasonable approach to assess the pattern of atrophy of different regions rather than considering only specific regions [1]. These data need further validation and studies in all PSP phenotypes before they can be standardized.

PSP-P is associated with white matter damage, and it progresses significantly over time [16]. PSP-RS patients show greater degeneration of superior cerebellar peduncle compared to PSP-P and other subtypes. Therefore, diffusion imaging can be used as a means for testing of PSP as a means of differentiating between different phenotypes of PSP [17]. [1,16,17]. However there needs to be more research before this can be used as standardized tests which can be used for practice.

PET (FDG-PET) studies have shown that hypometabolism in midbrain, basal ganglia, thalamus, and frontal lobes in PSP-RS mainly in premotor, precentral, and prefrontal regions and anterior cingulate [1]. The pattern of hypometabolism of 90% specificity and 93% sensitivity to help differentiate between other diseases like PD [1]. There is a lack of standardization in FDEG-PET studies, and this needs to be further researched before it can be used in clinical practice. Tau-PET imaging, a new and promising tool, aims to bind to tau in the brain so it can be used as a diagnostic marker and a marker of efficacy in clinical trials [1]. The first generation of tau-radioligands have been assessed in small cohorts of PSP and show results however more research needs to be done for this to be used [1].

From this we can see that there are many possible diagnostics that can be used to test for PSP. However, due to limited research and studies it is difficult to standardize these methods [1]. It is the utmost priority to research more about these diagnostic markers so that we can detect PSP in the earlier stages and tremendously help the patient's quality of life.

Treatment

There is no disease-modifying treatment for PSP [1]. The current treatments are used to improve symptoms and quality of life in day-to-day activities [1,3]. There are pharmacological and procedural ways to treat PSP. The pharmacologic approach of PSP is based on experience and using drugs that show benefits for patients rather than a controlled, conducted clinical trials [1]. Most of the drugs that are used on the specific patient's symptoms and drugs that are beneficial in other neurodegenerative diseases. Surgical treatment is not an option because PSP patients have no response to dopaminergic drugs, which is required for Deep Brain Stimulation which is a neurosurgical procedure involving the placement of a device called neurostimulator which sends electrical impulses through electrodes to specific targets in the brain [1].

Due to the lack of treatments for PSP patients may use Levodopa which is used in PD even though PSP and PD have many differences. Levodopa is used for rigidity and bradykinesia, and axial symptoms and falls which occurs both in PSP and PD [1]. However, this drug usually doesn't exceed more than a 30% improvement in PSP's initial stages [1]. There is mostly improvement in PSP-P patients, but it isn't long-lasting clinical benefit. PSP-P patients experience a better response to levodopa than PSP-RS. There are known side effects that should be administered with the use of Levodopa include orthostatic symptoms, urinary retention, and constipation. Levodopa induced severe impulse control disorders, psychotic symptoms or Levodopa-induced dyskinesias which are behavioral addictions are extremely rare in PSP and if it occurs there should be alternative diagnoses [1,18]. Dopamine agonists

and Monoamine Oxidase B (MAO-B) inhibitors are considered less effective than Levodopa. Dopamine agonists are used to stimulate parts of the brain affected by dopamine [1,19]. MAO-B is an enzyme in the body that breaks down several chemicals in the brain, including dopamine. An MAO-B inhibitor makes more dopamine available to the brain [1,20]. Amantadine can improve bradykinesia, rigidity, possible freezing, and improve balance in patients. It can be administered alone or as an add-on to Levodopa. High doses of Amantadine (>400mg) are very dangerous may induce insomnia, confusion, gastrointestinal symptoms, and specifically for PSP patients, it can lead to agitation and worsening their disinhibited behavior.

There is no specific treatment for cognitive impairment for PSP patients. Acetylcholinesterase inhibitors, which are used for Alzheimer's disease to help with cognitive functions, behaviors, and daily activities, are not used because it has been shown that they can exacerbate motor symptoms [1,21]. Treating depression and apathy that these patients very commonly have is a challenge too. Most of the time, depression and anxiety and emotional incontinence are treated with selective serotonin reuptake inhibitors (SSRIs) which are effective and are preferred over tricyclic antidepressants (TCAs). Given the lack of effective treatments it is important not to harm, e.g., to assess all concomitant medication that may worsen such PSP 75 symptoms that are important for quality of life, with a doubtful benefit on the symptoms that these drugs are given for, including here dopaminergic medication [1].

In view of the lack of any effective long-term treatment, supportive care, including physiotherapy, fall prevention programs, occupational therapy and speech therapy with swallowing training should be implemented in patients' everyday life. Dependency is expected in later stages in which then safety and comfort for the patients and the caregivers should be priorities.

Conclusion

With the lack of information about PSP it is imperative that research needs to be done to find a treatment. The current situation of PSP is a lack of research on the etiology, treatment, and testing of the disease. Without early diagnosis and validated biomarkers, it is very difficult to find a treatment for this sporadic disease so the priority must be finding a treatment. Even though, PSP and Parkinson's are vastly different in the symptoms PSP patients are still taking medication that is used for PD. This shows the huge disparity and the urgency of research needed for PSP.

References

Giagkou, N, Höglinger, GU, Stamelou, M. Progressive supranuclear palsy. Int Rev Neurobiol. 2019;149:49–86.

(n.d.). *Progressive Supranuclear Palsy*. Physiopedia. Retrieved March 18, 2023, from https://www.physiopedia.com/Progressive_Supranuclear_Palsy

Necpál, J., Borsek, M. & Jeleňová, B. "Parkinson's disease" on the way to progressive supranuclear palsy: a review on PSP-parkinsonism. Neurol Sci 42, 4927–4936 (2021). https://doi.org/10.1007/s10072-021-05601-8

Wen, Y., Zhou, Y., Jiao, B., & Shen, L. (2021). Genetics of Progressive Supranuclear Palsy: A Review. *Journal of Parkinson's Disease*, *11*, 93–105. https://doi.org/10.3233

Mahale RR, Krishnan S, Divya KP, Jisha VT, Kishore A. Gender differences in progressive supranuclear palsy. Acta Neurol Belg. 2022 Apr;122(2):357-362. doi: 10.1007/s13760-021-01599-0. Epub 2021 Feb 17. PMID: 33595832.

Golbe, L. I., & Ohman-Strickland, P. A. (2007). A clinical rating scale for progressive supranuclear palsy. *Brain*, *130*, 1552-1565. https://doi.org/0.1093

Ray Chaudhuri, K., Martinez-Martin, P., Brown, R. G., Sethi, K., Stocchi, F., Odin, P., Ondo, W., Abe, K., MacPhee, G., MacMahon, D., Barone, P., Rabey, M., Forbes, A., Breen, K., Tluk, S., Naidu, Y., Olanow, W., Williams, A. J., Thomas, S., . . . Schapira, A. H. (2007). The Metric Properties of a Novel Non-Motor Symptoms Scale for Parkinson's Disease: Results from an International Pilot Study. *Movement Disorders*, *22*(13), 1901-1911. https://doi.org/10.1002/mds.21596 (n.d.).

Progressive Supranuclear Palsy. John Hopkins Medicine. Retrieved March 19, 2023, from https://www.hopkinsmedicine.org/health/conditions-and-diseases/progressive-supranuclearpalsy#:~:text=Progressive%20supranuclear%20palsy%20is%20rare,significantly%20than%20with%20Parkinson%20disease (2019, October 19).

Do I Have Parkinson's or Progressive Supranuclear Palsy (PSP)? Parkinson's Disease. Retrieved March 19, 2023, from https://parkinsonsdisease.net/answers/progressive-supranuclear-palsy-psp

Boeve, B. F., Book, E. S., Breslow, D., Brittingham, N., Cianci, H., Edmunson, J. E., Gentry, T., Golbe, L. I., Imke, S. C., Robins Kapust, L., McFarland, I., Melen, O., Resnick, W. M., Spencer Scott, P., & Purcell Verdun, L. (2020). *A RESOURCE FOR PEOPLE LIVING WITH PRIME OF LIFE NEURODEGENERATIVE DISEASE* (2020th ed., pp. 21-23). CurePSP. https://www.psp.org/wp-content/uploads/2020/03/2020-GUIDEBOOK_web.pdf

Borroni B, Agosti C, Magnani E, Di Luca M, Padovani A. Genetic bases of Progressive Supranuclear Palsy: the MAPT tau disease. Curr Med Chem. 2011;18(17):2655-60. doi: 10.2174/092986711795933722. PMID: 21568901.

Susanne Herbst, Patrick A. Lewis, Huw R. Morris; The emerging role of LRRK2 in tauopathies. *Clin Sci (Lond)* 15 July 2022; 136 (13): 1071–1079. doi: https://doi.org/10.1042/CS20220067

Virhammar J, Blohmé H, Nyholm D, Georgiopoulos C, Fällmar D. Midbrain area and the hummingbird sign from brain MRI in progressive supranuclear palsy and idiopathic normal pressure hydrocephalus. J Neuroimaging. 2022 Jan;32(1):90-96. doi: 10.1111/jon.12932. Epub 2021 Sep 14. PMID: 34520581.

Sonthalia N, Ray S.The Hummingbird sign: a diagnostic clue for Steele-Richardson-Olszweski syndrome Case Reports 2012;2012:bcr2012006263.

Jones J, Worsley C, Bell D, et al. Progressive supranuclear palsy. Reference article, Radiopaedia.org (Accessed on 26 Mar 2023) https://doi.org/10.53347/rID-1924

Caso F, Agosta F, Ječmenica-Lukić M, Petrović I, Meani A, Kostic VS, Filippi M. Progression of white matter damage in progressive supranuclear palsy with predominant parkinsonism. Parkinsonism Relat Disord. 2018 Apr;49:95-99. doi: 10.1016/j.parkreldis.2018.01.001. Epub 2018 Jan 4. PMID: 29336906.

Whitwell JL, Tosakulwong N, Clark HM, Ali F, Botha H, Weigand SD, Sintini I, Machulda MM, Schwarz CG, Reid RI, Jack CR Jr, Ahlskog JE, Josephs KA. Diffusion tensor imaging analysis in three progressive supranuclear palsy variants. J Neurol. 2021 Sep;268(9):3409-3420. doi: 10.1007/s00415-020-10360-1. Epub 2021 Mar 12. PMID: 33710456; PMCID: PMC8363518.

Voon V, Napier TC, Frank MJ, Sgambato-Faure V, Grace AA, Rodriguez-Oroz M, Obeso J, Bezard E, Fernagut PO. Impulse control disorders and levodopa-induced dyskinesias in Parkinson's disease: an update. Lancet Neurol. 2017 Mar;16(3):238-250. doi: 10.1016/S1474-4422(17)30004-2. Epub 2017 Feb 15. PMID: 28229895.

Parkinson's Foundation (n.d.). *Dopamine Agonists*. Retrieved April 1, 2023, from https://www.parkinson.org/living-with-parkinsons/treatment/prescription-medications/dopamine-antagonists

Parkinson's Foundation (n.d.). *MAO-B Inhibitors*. Retrieved April 1, 2023, from https://www.parkinson.org/living-with-parkinsons/treatment/prescription-medications/mao-b-inhibitors

Winslow BT, Onysko MK, Stob CM, Hazlewood KA. Treatment of Alzheimer disease. Am Fam Physician. 2011 Jun 15;83(12):1403-12. Erratum in: Am Fam Physician. 2014 Aug 15;90(4):209. PMID: 21671540.

.