Towards the Accurate Early-Stage Differentiation of PSP and PD: Clinical and Molecular Biomarkers

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ABSTRACT:

Background: Parkinson's Disease and Progressive Supranuclear Palsy (PSP) are two separate neurodegenerative disorders that share similar symptoms. As a result, they are easily mistaken for each other, leading to misdiagnoses and ineffective treatments.

Objectives: This study explores different biomarkers and symptoms that are able to effectively distinguish Parkinson's disease from PSP in its early stages.

Methods: PubMed was searched with keywords including "Parkinson's Disease", "Progressive Supranuclear Palsy", "early stages", and "biomarkers," 5 studies were reviewed in this paper. Non-English articles and review articles were excluded.

Results: The studies reveal that differentiation between PD and PSP is feasible through an analysis of a multitude of biomarkers and symptoms, including gait analysis, microRNAs in tear fluid, AI analysis of MRIs, alpha-synuclein misfolding, and subtle abnormalities in eye movement.

Conclusion: All of the stated biomarkers and symptoms are reliable enough to be able to differentiate Parkinson's disease from Progressive Supranuclear Palsy. While each biomarker/symptom by itself cannot accurately distinguish the two disorders, the integration of testing for all the biomarkers and symptoms, can greatly improve the accuracy of the diagnosis.

INTRODUCTION:

Parkinson's disease and PSP, or Progressive Supranuclear Palsy, are two neurodegenerative disorders; they have very similar symptoms to each other and are often mistaken for each other

[1]. Their extremely similar symptoms, with both conditions beginning with rigidity and movement problems, allow for the possibility of an inaccurate diagnosis [1-3].

Parkinson's disease (PD) is a neurodegenerative disorder caused by the misfolding of alpha-synuclein proteins inside the brain [2]. It is a much more gradual disorder that mainly affects the midbrain, particularly the dopaminergic neurons responsible for regulating movement [2]. This early degeneration in the midbrain leads to a loss of dopaminergic neurons and gradual movement problems [2]. Because symptoms develop gradually, they appear stable in the disorder's early stages due to their response to dopamine-increasing medications; however, patients gradually become less and less responsive as the disorder increases in severity [2].

PSP, however, is caused by the misfolding of tau proteins inside the brain [1,3]. It has a rapid progression, and its severity increases at a high rate [3]. It affects various parts of the brain, including the frontal-subcortical circuits, midbrain, and cerebellum, causing instability and movement abnormalities [3]. This resemblance is one of the key reasons PSP is so frequently misdiagnosed as PD [1].

Twenty to thirty percent of PSP cases are initially diagnosed as PD [4]. This becomes a large complication, as the treatments for the two disorders differ significantly: PD patients are generally responsive to dopaminergic drugs and can possibly benefit with treatment methods such as deep brain stimulation. Comparatively, PSP patients show little improvement with these same medications and instead require care focused on speech therapy, swallowing help, and fall therapy [4]. When PSP is diagnosed as PD, patients will spend years on ineffective medications that provide no benefit, delaying the supportive methods that manage the severity of Progressive Supranuclear Palsy. On the other end, if PD is mistaken for PSP, patients are not given dopaminergic therapy that can lower the severity and symptoms of PD. Treating either condition after the misdiagnosis is corrected becomes much harder due to the increased severity of either disease and the gap in time without effective treatment [4].

This study aims to synthesize the discoveries of various research papers to locate biomarkers and symptoms that can distinguish Parkinson's disease from progressive supranuclear palsy. In addition to being reliable, these tests need to be easily accessible and standardized so they can be available to all. People around the world have been wrongly diagnosed, leading to ineffective treatment and increased severity of the actual disorder. By using a combination of movement patterns, microRNAs, and the misfolding of alpha-synucleins, this paper looks into the physical and neurological symptoms and biomarkers that differentiate Parkinson's disease and PSP.

METHODS:

This paper is a narrative review of studies that investigate symptoms and biomarkers that can discern Parkinson's Disease from PSP. PubMed was used to find sources for this paper. The keywords used were "Parkinson's Disease", "Progressive Supranuclear Palsy", "biomarkers", "symptoms", and "early stages". Non-English and review articles were excluded from this study.

RESULTS:

Table 1. Summary of studies about symptoms and biomarkers that can differentiate Parkinson's Disease and PSP

Author(s)	**Symptom Or Biomarker Being Studied**	**Methods**	**Key Takeaways**	**Relevance**
Amboni M, Ricciardi C, Picillo M, et al [5]	Gait patterns	Patients are tested by walking on a 10m path and standing on a force plate.	Patients with PSP were found to have a poorer gait pattern compared to patients with PD.	Provides a symptom that can be used to differentiate the two disorders in its incipient stage.
Demleitner AF, Gomes LC, Wenz L, et al. [6]	MicroRNAs in tear fluid	Tear fluid was collected from patients of many different Parkisonian disorders, and the RNA was isolated.	There were specific mRNAs found in tear fluid that were exclusive only to one disorder.	Provides a biomarker and a vast amount of microRNAs that are exclusive for differentiating PD from PSP with almost complete certainty.
Marquand AF, Filippone M, Ashburner J, et al [7]	MRI atrophy patterns in the brain	A normal MRI was taken, and advanced machine learning was used to differentiate between the disorders.	The midbrain/brain stem region was best to differentiate between the disorders. The AI model was able to detect the differences.	Provides a cheaper way to differentiate PSP from PD
Fairfoul G, McGuire LI, Pal S, et al [8]	Folding of alpha-synucleins	A large amount of recombinant alpha-synucleins were added into	PD patients had a positive result, while PSP patients had a negative	Able to distinguish Parkinson's from PSP in early stages

		the CSF, so that if there were misfolded proteins, it would aggregate the recombinant ones too.	result	
Pinkhardt EH, Jürgens R, Becker W, Valdarno F, Ludolph AC, Kassubek J. [9]	Study Of Eye Movements	Video-Ocula graphy, Smooth Pursuit, and saccade velocity	Patients of PSP had a slower saccade velocity than PD patients	Eye movement is a symptom that can also be detected in the incipient stages of both disorders.

As shown in table 1, the studies in this review paper highlight the different symptoms and biomarkers that can be used to differentiate two similar disorders, PD and PSP, in their early stages.

The first study focuses on a simpler function, which is that of gait. In the first study, a BTS Bioengineering System was used to capture extremely specific tendencies in gait [5]. There were two phases, a standing and a walking phase [5]. The standing phase was assessed on a force plate, while the walking phase was completed on a 10 m path, with the first phase having the patient normally walk and the second phase requiring the patient to walk while performing simple math calculations [5]. Most of the distinguishing features were prevalent in the second part of the walking phase. Patients with PSP showed poorer gait patterns compared to patients with PD, exhibiting a lower velocity, cadence, step, and cycle length but an increased cycle duration and swing duration variability; however, the step width was greatly increased during the second task only with PSP patients [5].

In the second study, the scientists investigated microRNAs in tear fluid as a possible biomarker to differentiate many Parkinsonian disorders. Tear fluid was collected from the patients, and the RNA was isolated [6]. After all the data was collected, it was found out that there were multiple biomarkers that were completely exclusive to a specific disorder [6]. In addition, the amount of tear fluid was much lower for PD patients, hinting at the possibility that PD can possibly have an effect on the amount of tear output [6]. PD also has the most exclusive miRNAs, providing a stronger way to deduce if a person has PD or not [6]. However, these results were preliminary and still need further research to be completely robust.

The third study utilized machine learning to differentiate between Parkinson's, PSP, and other neurodegenerative disorders. A normal MRI scan was conducted for every patient to supply pictures to the model [7]. Though the machine learning model focused on a variety of features visible through the MRI, it mainly focused on atrophy patterns. In general, the subcortical motor network was the most accurate for differentiating disease processes. The midbrain/brainstem, cerebellum, and basal ganglia were all useful for predicting PSP while only the midbrain/brainstem region was useful for Parkinson's disease [7].

The fourth study examines the misfolding of alpha-synucleins in the cerebrospinal fluid. Real-Time Quaking Induced Conversion, Or RT-QuIC, was used [8]. A CSF sample from patients with varying neurodegenerative disorders was mixed with alpha-synucleins with a native thioflavin-T dye, which fluoresces when bound to misfolding alpha-synucleins [8]. The seeding activity is measured, as alpha-synucleins that are misfolded lead to the misfolding of other unaggregated alpha-synucleins. [8] Through the experiment, it was found that PD patients had a high amount of seeding activity, however, PSP patients had no seeding activity [8]. PSP is a Tauopathy, and the disorder is caused by the misfolding of Tau proteins, not alpha-synucleins [8]. Therefore, the misfolding of alpha-synucleins only occurs in people with PD and not in PSP; as a result, the detection of the misfolding of alpha-synucleins can definitively distinguish PD from PSP.

The fifth study focuses on the difference in eye movements between patients with PSP and patients with PD. The patients went under VOG, or video oculography, which is an eye-tracking method that detects eye movement at an extremely precise scale [9]. They studied saccades, which are quick eye movements, and smooth pursuit, which is slow and gradual eye movements, between patients of both diseases [9]. It was inferred through the experiment that PSP patients have a much slower saccade velocity compared to PD patients [9]. The differences in saccade velocity were increased in vertical movements especially [9]. Smooth pursuit was slightly slower in PSP patients but not enough to be completely distinguishable without a percentage of error [9]. All of these findings present a variety of reliable biomarkers that can differentiate the two otherwise similar disorders.

DISCUSSION:

This review highlights biomarkers that are detectable in early stages of neurodegenerative diseases so that the two disorders, PSP and Parkinson's disease, can be differentiated. These biomarkers vary from movement patterns and microRNAs to misfolded proteins. By finding ways to differentiate the disorders early on, physicians can tailor treatments earlier to address each disease uniquely.

Through the first study, it was identified that a symptom of PSP is a much slower and less smooth walking pattern compared to Parkinson's disease [5]. Though PSP patients had a slower gait pattern than PD patients when walking normally, the difference was much more amplified when patients were multitasking [5]. This hints that PSP patients have more trouble multitasking, most likely due to the degeneration of fronto-subcortical circuits in the prefrontal cortex in the frontal lobe, which participates in planning and switching between tasks. Step widths for PSP patients during multitasking were greatly increased, while the step widths for PD patients were around the same with and without multitasking [5]. This is most likely due to the instability in movement for PSP patients, which has to be balanced by an increased step width. These takeaways infer that people with PSP have an extremely erratic gait pattern compared to PD patients.

As mentioned before, there are a variety of symptoms and biomarkers in different domains that can effectively distinguish progressive supranuclear palsy and Parkinson's disease. MicroRNA profiling in tear fluid presents a non-invasive biomarker that offers extremely strong statistical evidence for discriminating between PSP and PD [6]. The results showed at least 35 miRNAs exclusive to PSP, and 54 to PD [6]. This is quite shocking, as tear fluid is typically thought to have a smaller connection to neurological disorders compared to other fluids such as cerebrospinal fluid or blood. It is extremely possible that tear fluid has a stronger connection to the brain and the nervous system than we thought. In addition, patients with PD had a reduced tear volume while patients with PD had a normal tear volume. This evidence hints at the possibility that the misfolding of alpha-synucleins in PD may have an effect on the amount of tear output. However, these results were preliminary and still require further research to be confirmed given the small number of patients and tests.

MRIs, though able to detect small nuances between PD and PSP, are usually not able to visualize changes that can be seen by the human eye in the early stages of disease, leading to possible misinterpretations. The machine learning model in Marquand et al.'s study focused on atrophy patterns in the brain specifically [7]. One important takeaway is that though both had atrophy patterns in the subcortical motor network, PSP was identified via changes in the cerebellum and basal ganglia while Parkinson's disease was identified via patterns in the midbrain [7]. This adds to the model's credibility, as it has been proven that Parkinson's disease first originates around the midbrain and PSP originates from the cerebellum and basal ganglia [7]. The model in this study is also able to differentiate the two disorders with a higher accuracy in their early stages

compared to normal MRI interpretation; as such, machine learning models should be further explored for their use in MRI interpretation with possible implementation into hospitals in the future [7]. In the future, this test can be expanded with more focused brain scanning, allowing for the machine learning model to detect exact biomarkers or structural changes [7]. Importantly, these results should be interpreted with caution given the relatively small sample size, and future studies should look to scale up the sample size as possible.

The main difference between PSP and PD is how they are caused: PD is caused by the misfolding of alpha-synucleins in the cerebrospinal fluid while PSP is a tauopathy caused by the misfolding of tau proteins. Fairfoul G et al. used RTQuIC, or Real Time Quaking-Induced Conversion, to take a sample of cerebrospinal fluid from patients and mix it with unaggregated alpha-synucleins to see if there is more misfolding, as misfolded alpha-synucleins cause other normal alpha-synucleins to also misfold [8]. This produced a binary result and was extremely definitive. Unfortunately, the results can only be observed through a Thioflavin-T dye, which fluoresces when it sticks to misfolded proteins [8]. This leads to qualitative data rather than quantitative data.

Eye movement is also a symptom that can distinguish PD and PSP. The study by Pinkhardt et al. used video-oculography, or VOG, to capture subtle anomalies in eye movement [9]. Pinkhardt EH et al. tested saccade movements (quick movements) and smooth pursuit, or slow eye movements [9]. Eye movement was much poorer in PSP patients compared to PD patients, especially in saccade movements [9]. However, there was no correlation between the speed of saccades and how long the patient had either disease [9]. This offers the idea that the lowering of saccade velocity does not gradually decline but rather occurs in the early stages of the disease and is not affected by the severity of the disease. This makes it an extremely valuable biomarker as it is a very stable indicator of both diseases.

There have been countless people who were initially misdiagnosed with Parkinson's disease before eventually receiving a diagnosis of PSP. Unfortunately, by the time they were diagnosed with PSP, the disease had severely progressed. By using reliable biomarkers to distinguish PD and PSP symptoms, more individuals can receive the appropriate diagnosis at an earlier stage, allowing for appropriate treatments to be started immediately. While individually none of these biomarkers can completely distinguish Parkinson's disease and progressive supranuclear palsy with full confidence, a combination of the biomarkers can provide a more accurate distinction between the two disorders.

As technology expands, advancements and the increased detection of early biomarkers shows that distinguishing between PSP and PD is becoming more achievable, and the refinement of these methods can improve the lives of countless patients.

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