A Comprehensive Review and Evaluation of the Diagnostic Methods of a Multiple System Atrophy Diagnosis

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Abstract

Multiple System Atrophy (MSA) is a rare neurodegenerative disorder, characterized by the accumulation of α-synuclein in oligodendrocytes, often misdiagnosed with Parkinson's Disease (PD) due to overlapping symptoms. This study reviews the diagnostic methods used for MSA and discusses their benefits and how they can be improved for future research. Through a comprehensive search of the current literature, utilizing PubMed and Google Scholar, I analyzed and compiled numerous research articles for their relevance and content. Current diagnostic methods include diagnostic criteria, biomarkers, and genetic screening; these methods allow clinicians to identify individuals with MSA from healthy individuals. However, there is not yet substantial research toward concrete guidelines distinguishing MSA from other disorders. While several promising techniques are being studied, they have primarily addressed identifying a movement disorder. Accurately diagnosing MSA does not stop there: studies must also be consistent in measuring data from MSA and PD patients to establish categorical use. Generally, studies have found that MSA symptoms present more severely, but concrete numbers should be developed in order to categorize a patient as MSA, PD, or some other disorder. Should clinicians come across a patient with a movement disorder, data taken from the patient must point to either MSA or PD. Further exploring these methods will help identify variations between MSA and PD in symptoms, disease risk, and disease severity _ all of which will improve upon symptom management and disease treatment. Emphasizing the accurate and distinctive diagnosis of MSA allows individuals to better manage the severe consequences of this devastating disease.

Introduction

Multiple System Atrophy (MSA) is a rare adult-onset neurodegenerative disorder with no known cause or treatment (Overk et al., 2018). The pathological hallmark of MSA is the abnormal accumulation of the α-synuclein protein in oligodendrocytes, which are glial cells that produce myelin in the central nervous system (Overk et al., 2018; Jellinger, 2022). It belongs to a group of neurodegenerative disorders called synucleinopathies, which include Parkinson's Disease (PD) and Dementia with Lewy Bodies (DLB). The symptoms of MSA present similarly to those of other synucleinopathies, in particular, PD; developing concrete guidelines distinguishing MSA is imperative to managing the disease.

MSA is divided into two main categories: the Parkinsonian-type (MSA-P), characterized by motor abnormalities, and the Cerebellar-type (MSA-C), characterized by a lack of coordination (Jellinger, 2022). MSA is often misdiagnosed due to its overlapping symptoms with other disorders, especially Parkinson's Disease (PD). The disorder presents with symptoms of autonomic failure, parkinsonism, and cerebellar dysfunction (Wenning et al., 2022). Autonomic failure occurs when the autonomic system fails to regulate involuntary bodily functions, such as heart rate and blood pressure. Parkinsonism is a condition of rigidity, slow movements, and tremors, commonly associated with PD. Cerebellar dysfunction refers to difficulties in maintaining balance and performing coordinated movements.

MSA affects many regions of the brain, the most significant being the cerebellum (Figure 3), due to its role in movement and balance. The middle cerebellar peduncle is responsible for relaying information from the cerebrum and pons to the cerebellum, as well as for motor skills

and movements. Another major brain region affected by MSA is the brainstem (Figure 2), which includes the midbrain, pons, and medulla. The pons and medulla are more affected by MSA than the midbrain; the pons regulates unconscious processes such as sleeping and breathing and the medulla regulates other autonomic processes such as heart rate, circulation, and blood pressure. The putamen, a structure in the basal ganglia, is also affected by MSA and is responsible for motor control and learning.

Methods of diagnostic criteria, biomarkers, and genetic screening have been investigated to improve the diagnosis of MSA. Diagnostic criteria are crucial in correctly diagnosing MSA because symptoms are very similar to those of other disorders. Different levels of diagnostic certainty allow clinicians to effectively manage disease progression according to severity. Biomarker identification better distinguishes MSA through differences in biomarker presence. This includes biomarkers present in fluids and tissues, such as α-synuclein and metabolite concentrations. Though MSA is a sporadic disease, some familial cases have occurred. Genes that contribute to the disease are being explored; these genes include SNCA, CoQ2, and the MAPT gene. Identifying genetic components allows clinicians to determine those who are at higher risk of developing MSA.

Through my research of these different methods, I explore how the medical field can improve upon them for MSA to be more distinguishable from other neurodegenerative diseases. The purpose of this paper is to outline studies of diagnostic methods of MSA and to evaluate their success and viability through suggestions for future steps. Based on current findings, appropriate diagnostic measures that accurately identify MSA and differentiate it from other diseases should be emphasized to help improve the diagnosis of the disease.

Diagnostic Criteria

Having reliable and valid guidelines for diagnostic criteria is a crucial aspect of correctly diagnosing MSA since MSA presents with symptoms that are very similar to other disorders, especially PD. The first MSA consensus conference regarding MSA diagnosis took place in 1998; then, an autopsy was necessary to confirm the presence of α-synuclein. Since then, there have been two conferences (in 2008 and 2022) that have worked to improve the criteria: biomarker identification through brain imaging, blood, and CSF, and developing levels of diagnosis to keep track of disease progression (Watanabe et al., 2023).

The Movement Disorder Society outlines four levels of diagnostic certainty of MSA: possible prodromal MSA, clinically probable MSA, clinically established MSA, and neuropathologically established MSA (Wenning et al., 2022). The different levels allow clinicians to manage the disease appropriately and pursue an approach best suited for the severity of the disease. The primary features necessary for a clinical MSA diagnosis of any level are the onset of symptoms after 30 years of age and an increase in disease severity over time. The presence of a negative family history is also a factor as MSA is generally a sporadic, not inherited disease, but there have been rare cases of familial MSA (Hara et al., 2007; Soma et al., 2006). More often than not, if there is a history of other family members having the same disorder, it is likely not MSA but rather another neurodegenerative disorder such as PD.

Possible prodromal MSA is an early stage of MSA where symptoms are not fully present, but there are signs of disease development. These signs tend to present as subtler, less severe symptoms than the core clinical features of clinically established MSA. Identifying this stage allows for earlier intervention and management of the disease. Further research is being conducted to develop treatments and slow disease progression (Wenning et al., 2022).

Core clinical features of clinically probable and clinically established MSA include urogenital failure, cardiovascular autonomic failure, parkinsonism, and cerebellar syndrome (Wenning et al., 2022). Urogenital failure refers to bladder control problems, sexual dysfunction, and kidney failure. Cardiovascular autonomic failure is caused by autonomic nervous system dysfunction. Other supportive features of clinically established and clinically probable MSA are the increase in MSA symptoms over time and postural instability. Structural changes in the brain, evaluated through MRIs, also signify MSA. This includes atrophy of the pons (Figure 2a), putamen, middle cerebellar peduncle (Figure 3a), and cerebellum (Figure 2a, Figure 3a). Clinically probable MSA requires fewer symptoms and features to be present than clinically established MSA. These symptoms are more significant than those of possible prodromal MSA but do not yet meet the full criteria for clinically established MSA. Differences include more supportive features, the presence of MRI markers, and greater diagnostic certainty in clinically established MSA compared to clinically probable (Wenning et al., 2022).

Neuropathologically established MSA refers to definitively diagnosing MSA through brain tissue examination postmortem, or after death. Key features involve the abnormal accumulation of the protein α-synuclein in neurons and glial cells and striatonigral and olivopontocerebellar degeneration (Wenning et al., 2022). Striatonigral degeneration decreases basal ganglia size, resulting in rigidity and bradykinesia, or slow movement. Olivopontocerebellar degeneration refers to atrophy of the olivary nucleus, cerebellum, and pons, leading to difficulties with balance and muscle coordination. This postmortem analysis supports the diagnosis of MSA and provides further information on the disease's progression.

These criteria are a great improvement in identifying the presence of a movement disorder. Once MSA is confirmed, it can be managed appropriately and the levels of diagnostic certainty provide a timeline for disease severity and progression. However, the confirmation of MSA itself is a current problem; the criteria at present lack criteria that concretely distinguish MSA from other disorders. Preventing misdiagnosis is key to helping patients battle this disease, and developing proper differentiating techniques is imperative.

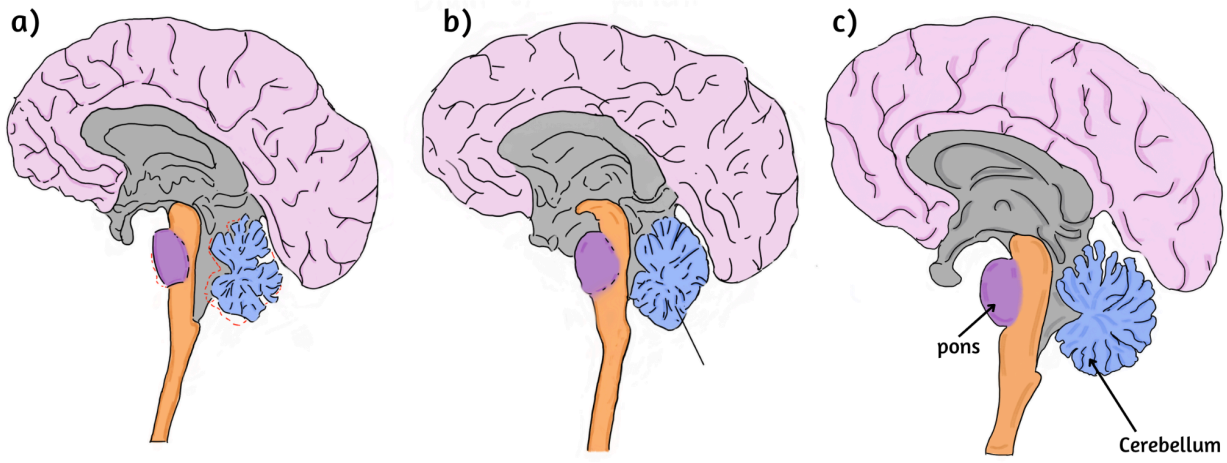

Figure 2. Representation of pons and cerebellum in MSA. The midsagittal view of atrophy in the pons and cerebellum in an MSA patient (a) compared to little atrophy in a PD patient (b), and a healthy brain (c). The red dotted lines compare an MSA pons and cerebellum to a healthy

pons and cerebellum (Butler et al., 2017). (These figures are not drawn to scale and serve purely as image representations).

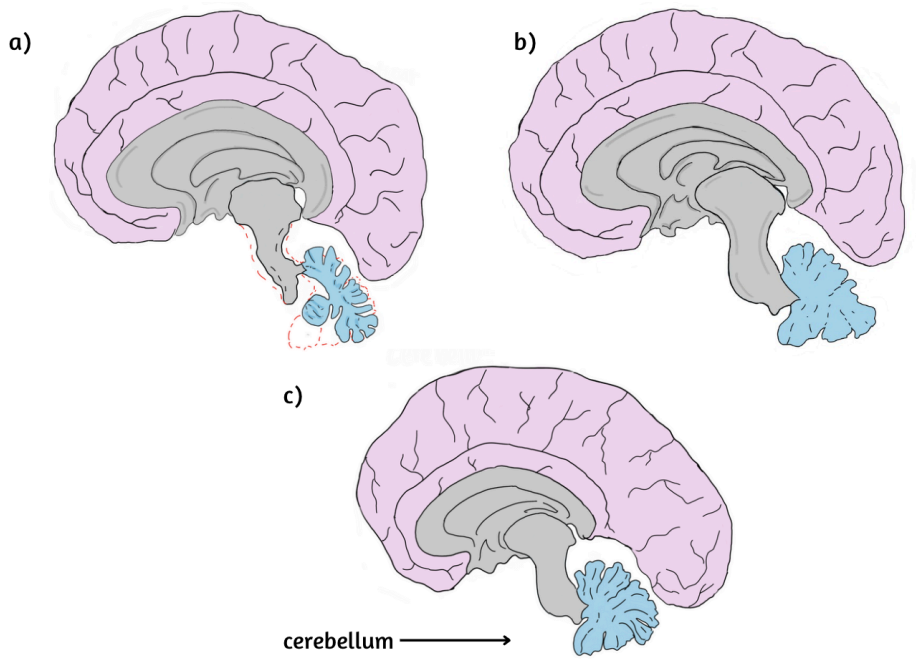

Figure 3. Representation of cerebellum in MSA. The parasagittal view of a closer look at cerebellar atrophy, specifically the middle cerebellar peduncle. The MSA patient (a) is seen to have significantly more atrophy than the PD patient (b), and both are compared to a healthy brain image (c). The red dotted lines indicate the comparison of an MSA cerebellum to a healthy cerebellum and the PD cerebellum is less defined to represent the loss of neural pathways (Butler et al., 2017).

Biomarkers

A biomarker is a molecule found in the body that suggests the presence of a disease. Identifying biomarkers of MSA allows for better diagnosis and differentiation of the disorder. Recent studies have found possibilities in fluids and gut and tissue microbiota (Wan et al., 2023).

A fundamental biomarker is α-synuclein (Wan et al., 2023), a protein, found in neurons and glial cells, that regulates neurotransmitter disease. When there is an abundance of α-synuclein in these cells, glial cytoplasmic inclusions (GCIs) are formed. This accumulation of α-synuclein impairs neuronal cellular functions and leads to neurodegeneration. A-synuclein is especially prominent in dopaminergic neurons, which release the neurotransmitter dopamine (Butler et al., 2017). Dopamine is important in supporting movement and is therefore a crucial aspect of movement disorders like MSA and PD. When the aggregation of α-synuclein impairs neurons, it disrupts dopamine release, causing motor symptoms in those disorders.

A-synuclein aggregates through the process of misfolding, where the protein takes on an abnormal shape. The misfolded forms clump together causing inclusions in the neurons. Protein

misfolding cyclic amplification (PMCA) is a technique that amplifies this misfolding process to detect α-synuclein aggregates in biological fluids (Shahnawaz et al., 2020). A study obtained cerebrospinal fluid (CSF) samples from 94 PD patients, 75 MSA patients, and 56 healthy control subjects. A-synuclein aggregates can be measured through CSF since neurodegeneration causes neurons to release α-synuclein into extracellular spaces of the brain and spinal cord. The study used a dye called thioflavin T (ThT), which tracks the aggregation by binding to the α-synuclein. Once it binds, it displays an intense fluorescence which helps to quantify the aggregation. After α-syn-PMCA, the results showed significantly higher maximum fluorescence in the CSF samples of MSA patients compared to PD patients (Shahnawaz et al., 2020). The study also determined that the α-synuclein aggregates in CSF reflected those in the brain, allowing for a less invasive way to detect the protein. PMCA is a promising technique in quantifying α-synuclein aggregation and using the samples to distinguish between MSA and PD, however, in order for this method to become a common practice, several studies should be conducted in the same manner to develop consistent thresholds of α-synuclein aggregation. Specified and dependable thresholds will allow clinicians a guideline of whether the disease is MSA or PD.

There are three main forms of α-synuclein: total α-syn (t-α-syn), phosphorylated α-syn (p-syn), and α-syn oligomers (o-α-syn) (Wan et al., 2023). T-α-syn refers to all of the forms of α-synuclein and gives an overall measure of its abundance. P-syn is a type of α-synuclein that has been phosphorylated and is most closely associated with disease progression. O-α-syn is an aggregated form of α-synuclein that is highly toxic and plays a large part in disease mechanisms. Many studies have measured t-α-syn levels in cerebrospinal fluid (CSF). While some of them found no difference in levels between healthy controls and MSA patients, the majority of the studies found lower levels in MSA patients compared to those of healthy controls (Wan et al., 2023). However, not much of a difference was found between the t-α-syn levels in MSA patients versus patients with other neurodegenerative disorders. Several studies have researched the value of phosphorylated α-syn as a biomarker. Measuring p-syn levels in CSF and red blood cells revealed elevated levels of p-syn in MSA patients than in PD patients and healthy controls (Abdul-Rahman et al., 2024; Foulds et al., 2012; Li et al., 2020). The third form, o-α-syn, is a more reliable biomarker in red blood cells and brain samples than CSF. Increased levels of o-α-syn were found in MSA patients compared to healthy controls, and widespread accumulation of o-α-syn in brain samples was greater in MSA patients than PD patients (Sekiya et al., 2019; Wan et al., 2023). Based on these findings, p-syn seems to be the most promising in diagnosing MSA and differentiating between other neurodegenerative disorders. Similar to the previous study (Shahnawaz et al., 2020), consistent categories evaluating the use of these types of α-synuclein are necessary.

A-synuclein is also present in organs and tissues such as salivary glands, skin, and the gastrointestinal tract. Many studies have shown that p-syn levels can be measured through skin biopsies as well. The majority of the results show that p-syn is detected in the skin biopsies of MSA patients but not in healthy controls (Donadio et al., 2023; Doppler et al., 2015; Wan et al., 2023). Skin biopsies should be further explored and utilized more, as they are a valid and non-invasive way to test for MSA.

One study researched biomarkers that displayed the level of disease severity in MSA-C patients (Takado et al., 2011). Proton magnetic resonance imaging, a technique used to measure metabolite concentrations, was used to image brain regions affected by MSA. The study measured concentrations of N-acetyl aspartate (NAA) and myo-inositol (MI). NAA is a

metabolite involved in axon-glial signaling and reflects the health of neurons. MI is a sugar in the brain that is an indicator of how glial cells respond to injury of the nervous system. The study measured metabolite concentrations in the pons and the medulla of 12 patients with MSA-C and 12 healthy control subjects. The results showed significantly higher mean concentration levels of MI in MSA-C patients than in healthy control subjects in the pons ($P<0.05$) and medulla ($P<0.05$). Lower mean concentration levels of NAA were found in MSA-C patients compared to health control subjects in the pons ($P<0.05$) and medulla ($P<0.05$) (Takado et al., 2011). The study confirmed the role of NAA and MI as biomarkers for clinical severity of MSA. However, it was odd that the cerebellum was not included in the study seeing as it plays a major role in MSA and has been the main focus in other studies. In the future, it would also be beneficial to include MSA-P and PD patients to study the extent to which these biomarkers can be used as distinguishing factors.

Genetic Screening

MSA is a sporadic disease that occurs randomly and without any distinguishable pattern. While it is rare for MSA to run in families, there may be possible genes that contribute to the disease. Understanding and identifying the genetic components of MSA can help better diagnose those who are at risk and develop future treatments.

The SNCA gene is one of the more prominent genes concerning MSA and is responsible for encoding the α-synuclein protein (Tseng et al., 2023). Studies have been conducted to evaluate mutations in the SNCA gene. The variants of SNCA can lead to α-synuclein aggregation and therefore cause the neurodegeneration and symptoms characteristic of MSA. Many variants have been present in European populations with MSA, but not in Asian ones (Katzeff et al., 2019; Sailer et al., 2016; Sun, Xiang, et al., 2015). A study of the rs11931074 variant of SNCA noted a strong association with MSA in Caucasian subjects, but none in Korean subjects (Sun, Xiang, et al., 2015). The study further evaluated these findings within 96 Chinese MSA patients and 120 healthy controls and came to the same conclusion as the study with the Korean participants. One European sample study evaluated 32 different SNCA mutations in 239 living MSA patients and 617 controls recruited from the UK, France, and Germany (Al-Chalabi et al., 2009). The controls consisted of the spouses of MSA patients in the UK and from DNA banks in France and Germany. The study found two mutations with the strongest association with MSA: rs3822086 and rs3775444 (Al-Chalabi et al., 2009). A replication study consisting of 78 MSA blood samples from a pathologically proven MSA brain bank confirmed these results. A further contradiction is presented by a genome-wide association study of 918 MSA patients of European descent and 3,864 health controls (Sailer et al., 2016). The patients were either clinically diagnosed with possible or probable MSA, or pathologically diagnosed with definite MSA. Even though this was a study of a European sample, no association between the SNCA gene and MSA was found. Testing of the SNCA gene is currently a disputed identifying factor of MSA within European populations and requires further research, and should also be further explored within other ethnicities.

The gene coenzyme Q2 (CoQ2) creates coenzyme Q10 (CoQ10), which is essential for proper mitochondrial function and energy production (Tseng et al., 2023). Mitochondrial dysfunction contributes to neurodegeneration in MSA. Mitochondria are located in cells and are essential for producing energy to support bodily processes. Impaired mitochondrial function can result in oxidative stress and lower energy production, causing damage to neurons. Studies have found decreased levels of CoQ10 in MSA patients, thus possibly explaining the mitochondrial dysfunction. One study of an Italian population sample evaluated seven MSA-P

patients, seven MSA-C patients, and six healthy control subjects through skin biopsies and DNA extractions from blood cells (Monzio Compagnoni et al., 2018). The results showed reduced CoQ10 in fibroblast cells of both MSA-C and MSA-P patients. While the cause of these reduced levels is unclear, mutations of the CoQ2 gene may be a contributing factor. Another study of a Japanese sample, with 133 MSA patients and 200 healthy controls, found an association between another variant of CoQ2, L25V, and MSA (Sun, Ohta, et al., 2016). Additionally, a study of Japanese, North American, and European populations identified other variants associated with MSA, among them the V343A variant commonly found in Japanese MSA patients (Multiple-System Atrophy Research Collaboration, 2015).

However, studies have also contradicted the association of CoQ2 with MSA (Chen et al., 2015; Katzeff et al., 2019; Sailer et al., 2016). One study of a Chinese population sample of 312 MSA patients, found no association between the variant Val393Ala of CoQ2 and MSA (Chen et al., 2015). The genome-wide association study that found no relation between SNCA and MSA consequently found no relation between CoQ2 and MSA in the European sample (Sailer et al., 2016). A vital factor to note among all these studies is the different variants of CoQ2 that were evaluated. To solidify these findings, researchers should study specific variants of CoQ2 across different ethnic populations in the future.

Tauopathies are neurodegenerative disorders, such as Alzheimer's disease, that involve the abnormal accumulation of tau within the brain. The microtubule-associated protein tau (MAPT) gene, is responsible for making the tau protein, essential in stabilizing cell structures and managing intracellular transportation (Tseng et al., 2023). While MSA is classified as a synucleinopathy because of its abnormal accumulation of α-synuclein, studies have found the MAPT gene to be in possible association with MSA. This is likely because the tau protein can interact with α-synuclein and can worsen disease progression by doing so. Tau is present in GCIs of MSA patients and is found to be at higher levels in the CSF of MSA patients than in PD patients.

The MAPT gene has two main haplotypes, H1 and H2. Haplotypes are a group of genes that are passed down from a single parent and can be used to understand how traits and diseases are inherited. The H1 haplotype is more commonly associated with a higher risk of developing a neurodegenerative disease, whereas the H2 haplotype tends to decrease disease risk through a protective effect. One study researched the haplotypes and sub-haplotypes of the MAPT gene through 213 Caucasian MSA patients of European descent and 1312 healthy control subjects (Labbé et al., 2016). Of the 213 MSA patients, 127 were pathologically confirmed, and 86 were clinically diagnosed. The pathologically confirmed cases were taken from a brain bank, and the clinically diagnosed cases, 78 probable MSA and eight possible MSA, were living individuals. DNA was extracted from white blood cells and brain tissue to assess six MAPT haplotype variants. The results showed a significantly increased risk for the H1J and H1x haplotypes and a protective effect for the H2 and H1E haplotypes. When evaluating the MSA patients, it was found that the H2 haplotype occurred less frequently in those with MSA-C, indicating greater disease risk. This implies that there are different risk associations for MSA-C and MSA-P concerning the MAPT gene. To corroborate these findings, the association between the MAPT gene and MSA should be further explored among other ethnic populations.

Testing for these genes is necessary to assess the risk of MSA and plan accordingly. For genetic testing to be used widely in identifying MSA, consistency in the methods and results of studies is essential. In many studies, DNA was obtained through blood and brain tissue,

indicating that future studies would benefit from DNA extraction from these areas. There was more variation in whether the DNA was taken while the individuals were living or postmortem, as well as the stage and type of MSA. The studies involved MSA patients of possible MSA, probable MSA, pathologically proven MSA, clinically diagnosed MSA, etc. Taking into account whether the MSA was of the cerebellar type or Parkinsonian also affects whether or not specific genes may be present. Additionally, ethnicity plays a significant role in the presence of specific genes; studies of different ethnic populations revealed differences in findings of whether specific genes were associated with MSA or not. Additionally, these studies examined various mutations and variants of the genes. In order to fully evaluate the extent to which these genes are present across various ethnic populations, consistent variants should be studied.

Conclusion

An accurate clinical diagnosis of MSA is necessary for early intervention and appropriate disease management. The overlapping symptoms between MSA and other neurodegenerative disorders, especially PD, contribute to the complications and delay in diagnosis. In this paper, I reviewed the different methods that have been used in an attempt to diagnose MSA and distinguish it from other disorders accurately. This paper contributes to the evaluation of diagnostic criteria and the reliability and validity of certain biomarkers and genetic markers.

Many studies have focused solely on differentiating MSA patients from healthy control subjects to identify signs of the disease. While these findings help give rise to the fact that a movement disorder is present, most are the same symptoms shared with other neurodegenerative diseases. The key is in researching the severity of these symptoms; in most studies, it has been found that MSA patients tend to present with more severe levels of the same symptoms that PD patients have. For example, atrophy in the cerebellum occurs in both MSA and PD but occurs at greater levels in MSA patients, and α-synuclein aggregates are far more prominent in the CSF of MSA patients than that of PD patients. However, these findings alone are insufficient; several studies must evaluate symptoms in the same manner to develop consistent categories differentiating between MSA and PD so that the symptoms can be effectively categorized. Once these classifications are finalized, the diagnostic criteria of MSA can be updated to increase diagnostic accuracy.

Reliable methods of diagnosing MSA from PD are essential because each disease progresses and is managed differently. MSA progresses at a greater rate than PD, as autonomic dysfunction can develop within a year, and symptoms tend to manifest earlier and more severely (Burns et al., 2020). This also affects life expectancy: after symptoms begin, individuals with MSA have about six to nine years left, depending on severity, and those with PD have about fourteen to sixteen years left. Additionally, treatment options and symptom management are different. For example, those with PD often respond to a treatment called levodopa, used to treat bradykinesia, while most MSA patients have poor levodopa responsiveness (Osaki et al., 2002; Wenning et al., 2022). Effectively managing MSA disease progression, to help individuals who are suffering, requires an accurate and distinct diagnosis, only possible through the improvement of current resources and methods.

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