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Review

Characterizing Secondary and Atypical Parkinsonisms: Defining Features and Clinical Variability

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Abstract: Parkinsonism is a clinical syndrome characterized by akinesia/bradykinesia, muscle rigidity, resting tremor, and postural instability. Within the group of parkinsonisms is Parkinson's disease, also known as neurodegenerative parkinsonian syndrome. The group of atypical parkinsonisms was established due to the existence of sporadic parkinsonisms that do not share the exact etiology of Parkinson's disease. Additionally, parkinsonisms that arise from causes other than neurodegeneration have been classified as secondary parkinsonisms. With this in mind, given the diversity of etiologies that can trigger parkinsonism, it is crucial to understand the symptomatology and its relationship with the basal ganglia (including damage to the nigrostriatal pathway, neuroinflammation, and neuronal damage). Only then will it be possible to propose appropriate treatments for each variant of parkinsonism.

Keywords: Parkinson's disease; parkinsonism; atypical parkinsonism; secondary parkinsonism; glia; neuroinflammation

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1. Introduction

Parkinsonism or parkinsonian syndrome is a pathophysiological state characterized by akinesia/bradykinesia, muscle rigidity, resting tremor, and postural instability [1]. According to etiological factors, this syndrome can be caused by secondary agents (viruses, lesions, drugs), genetic mutations, idiopathic or sporadic causes. In particular, neurodegenerative parkinsonian syndrome of idiopathic origin, commonly referred to as Par-kinson's disease (PD), is the most frequent in the global population [2]. It is estimated that more than 6.1 million people worldwide suffer from this condition, making it the second most common neurodegenerative disease after Alzheimer's disease [3,4].

Due to sporadic parkinsonian syndromes, meaning they do not share the exact etiology of PD, the term atypical parkinsonian syndrome (AP) has been established [2]. Despite having different etiologies, both PD and AP must be considered progressive disorders that lead to motor, autonomic, emotional, and cognitive dysfunction [5].

In addition to APs, a group of secondary parkinsonisms is not sporadic since these types require a cause other than idiopathic neurodegeneration to develop [6,7]. Due to this variability, it has been proposed that parkinsonism be functionally classified into two groups: The first consists of APs due to their association with striatal dopaminergic deficiency. In contrast, the second group includes parkinsonisms unrelated to dopaminergic deficiency in the striatum, so-called secondary parkinsonism [8]. The most common etiology of secondary parkinsonism is vascular injury or drug-induced parkinsonism, with the latter being the second most common cause of parkinsonism after PD [9].

Neuroinflammation is one of the processes associated with PD; these processes highlight the chronic activation of glial cells, such as microglia and astrocytes [10,11]. Particularly, microglia can release proinflammatory cytokines, such as TNF-α, IL-1β, and IFN-γ, which promote oxidative stress and premature neuronal death.

Microglia become chronically activated due to the accumulation of damaged mitochondria resulting from mutations in the *PINK1* and *PRKN* genes. These mutations impair mitophagy, leading to mitochondrial dysfunction and the release of mitochondrial damage-associated molecular patterns (mtDAMPs), such as mitochondrial DNA and cardiolipin, into the extracellular space [12,13]. The mtDAMPs activate microglia through pattern recognition receptors like Toll-like receptors (e.g., TLR9), prompting the release of proinflammatory cytokines including TNF-α, IL-1β, and IL-6 [10,14].

Furthermore, microglial activation has been observed in α-synuclein aggregates, generating a feedback loop that prolongs inflammation and neurodegeneration. Similarly, astrocytes participate in this inflammatory process, especially those in a reactive state (A1 astrocytes), as they promote neurodegeneration by releasing toxic factors [10,11,15]. This interaction between microglia and astrocytes may be critical in PD and other parkinsonisms, including secondary parkinsonism or APs.

In practice, parkinsonian symptoms manifest in various ways depending on their etiology. Correct diagnosis represents a medical challenge, as differentiating between types of parkinsonisms is crucial to provide appropriate medical care and prevent further harm to the patient. Therefore, the present work aimed to mention the characteristics of the most well-known secondary and APs, such as symptomatology, etiology (affected pathways, neuroinflammatory systems, or genetic aspects), diagnosis, and possible treatments, as well as what is known to date about the role of glia in the etiology of parkinsonism.

2. Secondary Parkinsonism

2.1. Early-Onset Parkinsonism

Early-onset parkinsonism (EOP) is a type of parkinsonism characterized by the presence of motor symptoms similar to idiopathic PD, but occurring at an early age, typically before 40–50 years. Specifically, EOP occurs in 3–5% of all PD cases in Western countries, with increased prevalence in countries like Japan, where it can reach 10–14% [16]. Due to the early onset of EOP, patients may experience disruptions in their professional and reproductive lives, resulting in significant personal and social impact [17]. Additionally, EOP is often divided into two stages: young-onset (over 21 years) and juvenile-onset (under 21 years); generally, the former group is defined as patients with young-onset PD [18].

Since specific studies on EOP are limited, most data on incidence and prevalence come from general research on PD. Isolated from PD, EOP affects approximately 1.43/100,000 individuals annually, all under 55 years of age. For those under 50, the incidence drops to 0.55/100,000 individuals annually, predominantly affecting men [19].

The primary symptomatology of EOP includes bradykinesia and symmetrical rigidity, which show a limited response to levodopa, with bradykinesia being more prominent than tremor [16,17,20]. Additionally, cognitive impairment, social dysfunction, and the occurrence of psychiatric complications, such as anxiety and depression, affect the quality of life [17,21]. Due to secondary causes, patients exhibit more symmetrical symptoms and often lack the resting tremor characteristic of PD [22]. Finally, EOP has a mortality rate of approximately twice that of the general population, similar to that of PD patients [23].

At the genetic level, autosomal recessive mutations in PD-associated genes are highly related to EOP. These include the *PRKN* gene (accounting for up to 77% of juvenile-onset EOP cases) and the *PINK1* gene (accounting for 47% of sporadic cases, with a mean onset of 32 years) [17,24,25]. Patients with mutations in these genes exhibit distinctive characteristics, including dystonia, hyperreflexia, spasticity, and psychiatric symptoms [24].

Patients with mutations in the *FBX07* gene, which encodes the F-Box Protein 7, tend to present with autosomal recessive parkinsonism. This condition often manifests early, even

in childhood, and is classified as EOP with pyramidal tract signs, including spasticity and hyperreflexia, mainly in the lower limbs [17,26].

It is currently known that the involvement of glial cells, specifically microglia, may play a crucial role in disease progression. Chronic microglial activation can trigger a neuroinflammatory response that damages dopaminergic neurons, accelerating neurodegeneration in young patients. This occurs because *PINK1* and *PRKN* genes affect mitochondrial control and increase susceptibility to microglia-mediated inflammation [27–29]. Thus, this sustained neuroinflammatory response could exacerbate oxidative stress and promote apoptosis of dopaminergic neurons, accelerating neurodegeneration in young patients [14,30]. At the neuroanatomical level, EOP can also be caused secondarily by adverse events such as vascular malformations, hepatic insufficiency, supratentorial tumors or neoplastic lesions [17], basal ganglia lesions, systemic lupus erythematosus [18], obstructive hydrocephalus, and infectious diseases like HIV [22]. Patients with secondary EOP present with symmetrical alterations and lack resting tremor [17,22].

Additionally, sleep disorders are common in individuals with EOP and occur at similar frequencies as in PD. However, insomnia prevalence is higher in EOP. Before motor symptom onset, 24% of EOP patients experienced sleep disorders, compared to 16% in PD. Post-motor symptom sleep disorder incidence was 5.85 cases per 100 person-years in EOP vs. 4.11 in PD. Specifically, the risk of developing post-motor insomnia was 1.73 times higher in EOP [31].

On the other hand, the diagnosis of EOP focuses on early-onset symptoms, genetic mutation identification techniques, and the patient's clinical history. Factors such as family history and genetic mutations increase the risk, making the time of disease onset and genetic testing essential for confirming the diagnosis and differentiating it from other disorders similar to PD [32,33].

The primary treatment for EOP includes levodopa, although its administration is delayed, avoiding levodopa-induced motor complications, such as levodopa-induced dyskinesia in young patients. Other first-line treatments, such as dopamine agonists or *monoamine oxidase* B (MAO-B) inhibitors, focus on alternatives to minimize motor complications [16,32,34].

2.2. Drug-Induced Parkinsonism

Drug-induced parkinsonism (DIP) is a type of parkinsonism caused by the prolonged administration of high doses of drugs that act as agonists on D2 dopamine receptors, differentiating itself from PD by its non-neurodegenerative pharmacological etiology. DIP is considered the second most common type of parkinsonism, only behind PD, but it is the most common type of secondary parkinsonism.

The incidence of DIP varies depending on the type of drug, dosage, and duration of treatment, but studies have identified an estimated incidence of 3.3 to 13.9 per 100,000 people per year [35]. Approximately 24% to 35% of parkinsonism cases are drug-induced [36]. Furthermore, its prevalence is higher in women and individuals over 50 years old, with prevalence rates reaching up to 9.78 per 100,000 people in some populations [6,36–40]. However, it can also affect younger populations depending on the type and duration of medication.

In terms of symptomatology, DIP, like other types of parkinsonism, presents with rigidity, bradykinesia, tremors, and gait disturbances [41]. However, there are significant differences compared to different types of parkinsonism or even PD. In DIP, symptoms are primarily symmetrical (bilateral), while in PD, they typically begin unilaterally. Resting tremors are not as prominent in DIP, and patients tend to develop tardive dyskinesias with prolonged drug use [42].

The etiology of DIP is closely related to the blockade of dopamine receptors in the nigrostriatal system. It has been shown that blocking 65–80% of D2 dopamine receptors in the medium spiny neurons of the striatum results in motor dysfunction leading to parkinsonian symptoms [38,43]. While neuroleptics are the drugs most frequently associated with

this pathology (accounting for 10–60% of cases) [6,36–39], other types of drugs can also trigger this condition, including calcium channel blockers [44], tetrabenazine [36], antiemetics [45], cholinomimetics, antidepressants, antivertigo medications, antiarrhythmics [6], and antiepileptic drugs [46].

However, not all drugs capable of inducing DIP directly affect D2 dopaminergic receptors. For instance, flunarizine and cinnarizine impair dopaminergic function by interfering with the storage and release of dopamine. Additionally, other medications such as selective serotonin reuptake inhibitor (SSRI) antidepressants are associated with a reduction in dopamine levels within the striatum. Furthermore, certain drugs, including calcium channel blockers and some antiepileptics, operate through indirect mechanisms or pathways unrelated to direct dopaminergic signaling [47,48].

The onset of DIP symptoms also varies depending on the type of medication and the method of administration. Peripheral dopamine antagonists typically exhibit a rapid onset of symptoms within 0.1 to 1 week, followed by benzodiazepines (0.5 to 1 week), typical and atypical antipsychotics (0.7 to 3.3 weeks), and benzamides (4 to 5 weeks). In contrast, medications such as antiepileptics and tricyclic antidepressants tend to have a delayed onset, ranging from 9 to 28 weeks, with some cases reported to develop symptoms after two years or more. Drugs that directly block D2 receptors generally cause symptoms more rapidly, whereas those that affect indirect systems, such as the GABAergic or serotonergic pathways, exhibit a longer latency before symptom onset [47]. Additionally, it has been observed that patients with DIP exhibit a limited response to levodopa, a diagnostic marker that helps distinguish this disorder from PD [6].

The diagnosis of DIP involves precise differentiation between this condition and idiopathic PD. One approach is to detect hyposmia, as it is significantly more common in individuals with PD than those with DIP. However, this evaluation must consider factors such as smoking history, concomitant otorhinolaryngological diseases, and cognitive status, as these can affect olfactory assessment [6].

Additionally, various diagnostic tools can be used to diagnose DIP, including neuroimaging techniques such as positron emission tomography (PET) and single-photon emission computed tomography (SPECT), which assess the integrity of the nigrostriatal pathway. In DIP, this pathway remains intact [6]. Another imaging modality that can differentiate DIP from PD is functional magnetic resonance imaging (fMRI). This technique evaluates factors such as regional homogeneity and the amplitude of low-frequency fluctuations, which provide insights into the intrinsic activity patterns of voxels (the three-dimensional equivalent of a pixel) [49]. On the other hand, clinical tests, such as the response to levodopa where a diminished or absent response to the drug is observed [42], or blink rate tests, though with limited sensitivity and specificity, may also be used [50].

The treatment of DIP is based on discontinuing the offending drug, which improves symptoms in a high percentage of patients. Approximately 70% of patients are estimated to recover within three to six months after stopping the medication [38]. However, in some cases, DIP can unmask underlying PD, complicating treatment and potentially requiring continued use of levodopa or other antiparkinsonian drugs [51]. The prevention of DIP involves strict monitoring of at-risk patients and careful selection of medications, particularly in those more susceptible to developing DIP [52].

2.3. Hyperpyrexia Parkinsonism Syndrome

Hyperpyrexia parkinsonism syndrome (HPx), a type of secondary parkinsonism, also known as malignant dopaminergic syndrome, is a rare but lethal complication that arises during the treatment of PD. Clinically, it is characterized by hyperpyrexia, autonomic dysfunction, and muscle rigidity. Its incidence is estimated to be 0.3% in patients with advanced PD or those on high doses of levodopa [53]. The primary cause triggering this condition is related to changes or discontinuation of parkinsonian medication, primarily levodopa, as well as malfunction of deep brain stimulation devices, whether due to battery depletion or even the suspension of antiparkinsonian treatments during the pre-

implantation period [54]. The most frequent complications in HPx include respiratory failure, seizures, deep vein thrombosis, disseminated intravascular coagulation, and renal failure [55,56]. Treatment typically includes support for vital functions, reinstatement of antiparkinsonian medication, intravenous fluids, and benzodiazepines [57].

2.4. Vascular Parkinsonism

Vascular parkinsonism (VP) is a form of secondary parkinsonism resulting from cerebrovascular disease [58], drugs, infections, or trauma [59]. It is commonly classified into acute/subacute, insidious-onset, and mixed types. The acute/subacute VP subtype arises following a stroke that involves the striatal dopaminergic system, often manifesting asymmetrically, leading to contralateral hemiparkinsonism with acute or subacute onset [60]. Insidious-onset VP is the most frequent and presents with progressive parkinsonism, characterized by more prominent postural instability, gait difficulties, and a lack of response to levodopa. This VP subtype is primarily caused by small vessel disease in the white matter, which results in the narrowing of arterioles and blood–brain barrier damage. The emergence of bilateral motor symptoms in the lower limbs is gradual, possibly due to the involvement of the frontal lobe, striatum, and periventricular regions [60]. Finally, the mixed subtype is an overlapping syndrome of neurodegenerative parkinsonism and comorbid vascular lesions, contributing to postural instability and gait difficulties [59,61].

It is estimated that VP represents approximately 4.4–12% of all parkinsonism cases [62], and some authors suggest it could account for up to 20%, depending on the control of risk factors and socioeconomic conditions [63].

Symptoms related to this form of parkinsonism include urinary incontinence, dementia [61], symmetrical involvement, mainly of the lower limbs [64], and gait disturbances (a clinical aspect that significantly differentiates it from PD). It has been reported that 90% of patients with VP present with disproportionate gait impairment in the early stages, compared to only 7% of PD patients who exhibit such disturbances. Additionally, resting tremor is observed in only 4% of VP patients, compared to 47% of PD patients [62].

Patients with PV not only experience movement disorders but also sleep disturbances [65]. One of the identified symptoms is nocturia and nighttime difficulties associated with getting up to urinate. However, reports indicate that VP exhibits better sleep initiation compared to PD [66].

Risk factors for VP include hypertension, heart diseases, atrial fibrillation, ischemic heart disease, cardiomyopathies, valvular heart disease, orthostatic hypotension, diabetes mellitus, dyslipidemia, obesity, high-fat diets, lack of physical activity, smoking, sleep apnea, excessive alcohol consumption, and genetic factors [61].

Due to the considerable overlap of clinical symptoms with PD, defining VP has been a complex task. Studies using fMRI have not established a clear boundary between the extent of white matter lesions in patients with hypertension and those with VP. However, white matter lesions do not necessarily imply a diagnosis of VP [59]. Therefore, it has been suggested that a temporal relationship must exist between the stroke affecting the basal ganglia and the onset of parkinsonian symptoms or extensive white matter lesions affecting the basal ganglia tracts coexisting with parkinsonism and even dementia [63].

Among strokes, ischemic stroke represents 75–80% of cases. Ischemia induces cell death and dysfunction by promoting the production of proinflammatory mediators, leading to neuroinflammation [67], as well as peripheral leukocyte infiltration, where T cells have the potential to play either neuroprotective or harmful roles in post-stroke neuroinflammation. TH1, TH17, T-helper cells, and IL-17-producing T cells are known to induce secondary neurotoxicity, exacerbating the damage. In contrast, regulatory T cells exert anti-inflammatory and neuroprotective effects by suppressing excessive inflammatory responses [68].

The dopamine transporter imaging technique identifies and differentiates VP from other parkinsonisms, specifically distinguishing PD from VP [59]. The accumulation of

neuromelanin in the substantia nigra, visible in fMRI, may corroborate suspected VP cases associated with damage to the substantia nigra or the nigrostriatal pathway [69].

Among the tentative treatments for VP, it has been speculated that vitamin D may benefit bone mineral density and improve type II muscle fiber atrophy, thus preventing falls. This hypothesis arises from a study involving 92 PD patients and 94 VP patients administered vitamin D (1200 IU of ergocalciferol). After 24 months, a reduction in falls from 34% to 16% was observed in the VP group, along with a significant increase in muscle strength [70].

In the case of strokes, it is known that naringenin reduces the expression of proinflammatory markers in microglia and astrocytes containing iNOS (*inducible nitric oxide synthase*) and COX-2 (*cyclooxygenase-2*) by decreasing NF-kB (nuclear factor kappa B) activity. Additionally, quercetin, apigenin, baicalein, and anthocyanins have been mentioned as inhibitors that limit post-stroke neuroinflammation by affecting the activation of microglia or astrocytes, making these flavonoids potential candidates for the treatment of ischemic stroke [71].

2.5. Viral Parkinsonism

Viral parkinsonism (ViP) is characterized by the onset of parkinsonian symptoms following a viral infection that affects the central nervous system (CNS). These viruses can access the CNS through various routes: peripheral nerves, the blood–brain barrier, and the blood-cerebrospinal fluid barrier, leading to direct neuronal damage or triggering persistent inflammation that indirectly affects the nigrostriatal pathway by inducing inflammatory lesions. Additionally, post-infectious viral parkinsonisms are believed to occur through pathogen-induced autoimmunity [7,72]. This section focuses on three types of viruses that can cause ViP: HIV, dengue (DENV), and SARS-CoV-2 (responsible for COVID-19); however, the latter will have a subsection developed at the end of the HIV- and dengue-induced ViP subtopic.

The primary symptomatology of ViP includes bradykinesia, rigidity, and gait disturbances. Notably, patients with HIV who develop parkinsonism exhibit early onset and rapid progression of symptoms, along with a limited response to levodopa [72]. In contrast, patients with dengue-induced ViP may experience prominent postural tremors associated with persistent inflammation of nigrostriatal dopaminergic areas. However, the rigidity and bradykinesia symptoms resemble those of idiopathic PD in intensity [73,74].

Epidemiologically, ViP is more common in severe infections, such as those caused by HIV or dengue, as these viruses affect millions of people worldwide. HIV-induced ViP may result from acquired immunodeficiency syndrome (AIDS)-related encephalopathy, which is linked to severe damage to the basal ganglia [72,75]. Additionally, it may be caused by secondary infections related to HIV and the neurotoxic effects of antiretroviral therapy. HIV entry through the blood–brain barrier allows viral proteins (gp120, tat) and inflammatory cytokines to contribute to neurodegeneration through oxidative stress and excitotoxicity. Moreover, antiretroviral drugs, such as protease inhibitors, can exacerbate neuronal damage [76,77]. This specific type of PEV occurs in severely immunosuppressed patients with a thymic CD4 T-cell count of less than 40 cells/mm^3 [78].

On the other hand, dengue-induced ViP typically blocks the IFN pathway, infiltrating the blood–brain barrier through damage caused by proinflammatory cytokines (such as IL-1β and TNF-α). This leads to infection that triggers viral activation of microglia, causing hypercytokinemia and microglial aggregation around dopaminergic neurons, resulting in chronic inflammation and neuronal damage [73,75]. Additionally, viral replication and cell lysis are other factors that may worsen dopaminergic neuronal damage. However, the precise mechanism of dengue-induced ViP is not yet fully understood [73,76]. In reported cases, dengue-associated PEV has emerged after the acute phase of the viral infection, even when medical care was provided [79], and even following dengue encephalitis, developed post-infection [80].

The diagnosis of HIV-induced ViP focuses on the presence of clinical symptoms, supported by imaging studies such as fMRI, which help rule out secondary causes, such as opportunistic infections (toxoplasmosis, cryptococcosis) that may cause basal ganglia lesions. In other cases, PET scans are often used for proper corroboration. Additionally, in patients with HIV-associated dementia, overlapping symptoms may complicate the diagnosis, requiring a more thorough evaluation [75–77].

As with HIV-induced ViP, the diagnosis of dengue-induced ViP relies on clinical symptoms and imaging studies such as fMRI to rule out overlapping symptoms with other neurological manifestations of dengue, such as encephalitis or encephalopathy [73].

In many cases, the response to levodopa is limited, highlighting the importance of treating the underlying viral infection to control symptoms [73].

For the treatment of ViP, specifically HIV-induced ViP, antiretroviral therapy has proven effective in reducing the progression of parkinsonism by controlling the neuroinvasion of the virus and reducing inflammation in the basal ganglia [76]. On the other hand, in dengue-induced ViP, the treatment of choice is levodopa; however, the effectiveness of this treatment varies, being effective in approximately 60% of clinically diagnosed cases. In patients with a limited response to levodopa, it is often associated with more extensive dopaminergic neuronal damage, where treatment may focus on stabilizing dopamine levels and reducing persistent inflammation [73].

Despite these therapies, the long-term prognosis for patients with ViP remains uncertain, especially in those with extensive neuronal damage [73].

Parkinsonism and COVID-19

Coronavirus disease (COVID-19) is an infection caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The infection has been associated with symptoms such as headaches, myalgia, anosmia, ageusia, fatal pneumonia, and neurological disorders, suggesting that COVID-19 may extend beyond the respiratory system [81–83]. Additionally, approximately 64% of patients with COVID-19 experience sleep disorders, including increased sleep duration or insomnia [84].

During the COVID-19 pandemic, a possible relationship between this disease and parkinsonism was observed. Coronaviruses can enter the CNS and affect the structure or function of the basal ganglia, which can lead to inflammatory brain injury or unmask underlying parkinsonism. Additionally, it has been proposed that COVID-19 could trigger α-synuclein aggregation, increasing cellular vulnerability and the degeneration of dopaminergic neurons [81,82,85,86].

COVID-19-related parkinsonism has been reported between 2 and 5 weeks after infection. Dopamine transporter SPECT has shown asymmetric loss of dopaminergic fibers in the nigrostriatal pathway and decreased dopamine transporter density in the left putamen [81,87]. These findings suggest that COVID-19 may be linked to sudden parkinsonism, as the affected patients were neurologically regular before contracting the infection, had no family history of PD or depression, and genetic tests related to PD were negative. Reported symptoms include hypophonia, hyposmia, moderate rigidity, bradykinesia, tremor, and slightly slowed gait. Some patients experienced spontaneous improvement without needing medication, while others responded favorably to levodopa [81,83].

Recent studies have shown that dopaminergic neurons of the midbrain, derived from human pluripotent cells (targets of neurodegeneration in PD), are susceptible to SARS-CoV-2 infection [88]. Furthermore, dopamine transporter scans have revealed a decrease in presynaptic dopamine uptake, suggesting a possible viral invasion of the CNS. This decrease has been reported in the putamen or striatum, indicating nigrostriatal dysfunction, which appears to be more related to the action of cytokines and chemokines than to a direct viral effect on the substantia nigra [89,90].

One of the main entry routes of the virus into the CNS could be through the olfactory pathway. The anatomy of the olfactory bulb, olfactory nerves, and forebrain allows these structures to act as an entry channel, potentially causing inflammation and degenerative

processes [89]. Additionally, proinflammatory cytokines such as TNF-α and IL-1β have been associated with an increased risk of developing PD [91].

3. Atypical Parkinsonism

Atypical parkinsonian syndromes (APs) are heterogeneous progressive neurodegenerative diseases that share clinical characteristics with parkinsonism; however, they are considered distinct clinicopathological disorders [92]. As with PD, the central motor features of parkinsonism must be present in patients with AP, including bradykinesia in combination with resting tremor, rigidity, or both. In this context, the absence or scarcity of tremors may be a focus point in diagnosing AP [93].

APs are classified into (1) α-synucleinopathies, which include PD and other disorders within the Lewy body spectrum, as well as multiple system atrophy, and (2) tauopathies, which include progressive supranuclear palsy and corticobasal degeneration [92]. Additionally, APs have also been associated with frontotemporal dementia, Alzheimer's disease, and Perry syndrome [94].

3.1. Dementia with Lewy Bodies

Dementia with Lewy bodies (DLB) is a synucleinopathy characterized by the accumulation of aggregated forms of the protein α-synuclein in Lewy bodies within vulnerable neurons and Lewy neurites [95]. It is considered the second most common cause of neurodegenerative dementia, accounting for 4–8% of dementia patients. The incidence rate of DLB is 5.9 per 100,000 people, and the prevalence rate is 52/100,000 individuals [96]. The majority of cases present clinically between 70 and 85 years of age and are more common in men than in women, with approximately 70% of diagnoses occurring in men [97]. The median survival following diagnosis is three to five years [98].

Approximately 85% of DLB patients experience motor difficulties, although resting tremor is less common [99]. It has been established that classical DLB presents unique features such as fluctuating cognitive impairment, parkinsonism, and visual hallucinations [100]. The onset of tremors and motor signs occurs within the first 12 months before the onset of dementia. It is accompanied by fluctuations in alertness and attention, as well as recurrent visual hallucinations [2].

Parkinson's disease dementia (PDD) and DLB share similar clinical features, as both include dementia, cognitive fluctuations, and visual hallucinations in the context of parkinsonism. However, there is a critical difference in their diagnosis: DLB is diagnosed when cognitive impairment precedes parkinsonian motor signs, whereas in PDD, dementia develops after a well-established diagnosis of PD [101].

The diagnosis of DLB remains a challenge; it is estimated that only 33% of cases are correctly diagnosed. However, early diagnosis is crucial for managing DLB. Structural imaging techniques, such as fMRI and computed tomography, aid in conducting studies that help rule out cerebrovascular diseases or intracerebral space-occupying lesions. Additionally, cortical thickness measurement through fMRI has shown that DLB patients experience less volume loss in the temporal lobe, amygdala, and hippocampus compared to Alzheimer's disease [102]. Moreover, SPECT has suggested that impaired dopamine transporter binding in the striatum may indicate different pathological processes in DLB [103]. Additionally, sleep disorders appear to be more common in DLB compared to Alzheimer's disease. These include rapid eye movement sleep behavior disorder and excessive daytime sleepiness [104].

Another essential aspect reported in DLB is the increased parenchymal infiltration of T cells near α-synuclein pathology, suggesting that the recruitment of these cells is a feature of the disease's pathophysiology. The interaction between infiltrated peripheral T cells and microglia may play a role in neuroinflammation and neurodegeneration in DLB. One hypothesis is that T cells expressing CXCR4 (C-X-C chemokine receptor 4) accumulate in perivascular spaces surrounded by endothelial cells expressing CXCL12 (C-X-C motif

chemokine ligand 12), which could be involved in the migration of T cells across the blood–brain barrier and their infiltration into the parenchyma [105].

The treatment of DLB patients is complex, as it is based solely on symptomatic management. For cognitive decline, *acetylcholinesterase* inhibitors, such as galantamine, donepezil, and memantine, are commonly used, which may also help control hallucinations [97]. For motor symptoms, drugs such as levodopa, amantadine, rotigotine, and selegiline are employed. Levodopa has been reported to improve motor function and tremors; however, the dose should be kept low (319 mg/day) to avoid worsening hallucinations [106].

3.2. Multiple System Atrophy

Multiple system atrophy (MSA) is a rare neurodegenerative disease characterized by the aggregation of α-synuclein in the cytoplasm of oligodendrocytes and neurons, leading to neuronal loss and gliosis in various areas of the CNS, such as the striatonigral and olivopontocerebellar structures [107,108]. The incidence rate of MSA is 3–4 per 100,000 individuals [108], primarily affecting adults over 30 years of age [109], both sexes are equally affected [110]. MSA is often considered the most aggressive synucleinopathy due to its rapid progression, as it can cause severe disability within 5 to 6 years and later death, on average ten years after symptom onset [111].

MSA spectrum disorders are divided into two categories: parkinsonian and cerebellar [108]. Bradykinesia, rigidity, and postural instability are found in the parkinsonian category [112], accompanied by symptoms such as urinary incontinence, erectile dysfunction, and orthostatic hypotension [96]. Additionally, various respiratory disorders may occur during sleep, such as obstructive sleep apnea, central apnea (the first symptom of MSA), and nocturnal stridor (a severe condition). Other disorders include rapid eye movement sleep behavior disorder and excessive daytime sleepiness [104].

Neuropathological features are primarily localized in subcortical structures (the pons, putamen, brainstem, and cerebellum), making abnormalities detected by fMRI a potential criterion for MSA diagnosis [113]. Additionally, CD3+, CD4+, and CD8+ T cells and increased levels of proinflammatory cytokines (IL-2, IL-13) have been detected in MSA brains, promoting oligodendrocyte dysfunction. Thus, reducing microglial activation could be a promising future strategy for modifying disease progression [114].

The diagnosis of MSA is not straightforward, with postmortem accuracy rates of 62–79% and delayed diagnosis, with an average of 3.8 years between symptom onset and medical diagnosis [110]. This diagnosis is primarily clinical and is based on the most recent consensus criteria, which establish three levels of diagnostic certainty: definite (postmortem histopathological verification), probable (requiring autonomic failure and parkinsonism that responds poorly to levodopa), and possible (parkinsonism with at least one symptom suggesting autonomic dysfunction, such as urinary urgency) [115].

Therapeutic goals have focused on combating pathological oligomers, improving synaptic function, restoring proteostasis, inhibiting neuroinflammation, and providing neuroprotection against neuronal death. However, the results of disease-modifying therapies have not been favorable, leaving symptomatic treatment as the only option [111,116].

Among symptomatic treatments, managing parkinsonism includes the use of levodopa in combination with a peripheral *decarboxylase* inhibitor such as carbidopa or benserazide. Favorable response rates to levodopa are more frequent in parkinsonian-type MSA compared to cerebellar-type MSA. For dystonia, botulinum toxin type A has been reported to offer favorable results for patients [117].

3.3. Progressive Supranuclear Palsy

Progressive supranuclear palsy (PSP) is a tauopathy characterized by aggregates of four-repeat tau isoforms in astrocytes, oligodendrocytes, and neurons. The neuropathological features of PSP include neurofibrillary tangles, neuropil threads, tufted astrocytes, coiled oligodendroglial bodies, neuronal loss, and gliosis in subcortical structures (basal ganglia, subthalamic nucleus, brainstem, and even cerebellar structures) [118]. PSP has a prevalence

rate of approximately 5 per 100,000 people, with an average onset around 63 years of age and an average disease duration of seven years. The survival time after diagnosis is approximately 2.9 years. The annual incidence is estimated at 5.3 per 100,000 individuals globally, with annual incidence rates ranging from 0.17 to 3.9 per 100,000 individuals for men and from 0.1 to 0.8 per 100,000 individuals for women. Approximately 5–6% of people with parkinsonism are diagnosed with this tauopathy [93,96,119–122].

PSP can present with either Richardson's syndrome or parkinsonism, characterized by axial and symmetric orientation, akinetic-rigid features, resistance to levodopa, early postural instability, and vertical supranuclear gaze palsy [93,96,119].

One of the critical features of PSP is early gait dysfunction and postural instability. Visual symptoms, such as blurred vision, photosensitivity, diplopia, and difficulty reading, are also distinguishing signs. Additionally, PSP can cause mood disturbances and cognitive decline and can even be associated with dementia [93]. A relevant symptom of PSP is oropharyngeal dysphagia, which typically occurs 3–4 years after disease onset. Early onset of dysphagia is associated with reduced survival, and patients have been observed to exhibit interrupted lingual movements, upper esophageal sphincter dysfunction, and esophageal dysmotility [123]. On the other hand, approximately half of PSP patients experience sleep disturbances, including excessive daytime sleepiness, nighttime insomnia, total sleep reduction, restless legs syndrome, and sleep fragmentation. These disturbances have been interpreted as a factor that increases PSP mortality by up to fourfold [124].

Neuroinflammation may contribute to neurodegeneration in PSP, although it is unclear whether it is a cause or an effect. Within the neuroinflammatory profile, IL-6 has been associated with disease severity, while elevated IL-2 levels in PSP have been linked to dysfunctional peripheral inflammation [125].

By the time PSP is diagnosed, three years have often passed since the first symptom (half of the disease duration). Differentiating PSP from PD is usually not difficult, as PSP presents with symmetrical limb signs, no tremor, and more pronounced rigidity in the trunk and neck, the opposite of what occurs in PD [126]. Although fMRI can assist in diagnosing PSP by showing midbrain and superior cerebellar peduncle atrophy, its accuracy is limited. However, advanced neuroimaging techniques, such as volumetric and morphometric analysis of the basal ganglia, brainstem, cerebellum, and diffusion imaging, have shown moderate to high accuracy in differentiating PSP [127,128].

Parkinsonism in PSP can present with asymmetric or symmetric bradykinesia, tremor, and rigidity. It may initially respond to levodopa with slower progression than in those with Richardson's syndrome [129]. Statins have been reported to be associated with less severe motor symptoms without influencing cognitive or behavioral symptoms [130]. Treatment primarily focuses on symptomatic management and physical and occupational therapy [131].

3.4. Corticobasal Degeneration

Corticobasal degeneration (CBD) is an extremely rare and sporadic neurodegenerative disease. It is characterized by neuronal and glial pathological lesions containing abnormally hyperphosphorylated four-repeat tau protein [132]. The average age of onset is 40–70 years, with an average survival rate of seven years for men and nine years for women, with an incidence rate of 0.6–0.9 per 100,000 individuals [108,132,133], showing a slight female predominance [134].

CBD accounts for 4–6% of APs. Its main feature is asymmetry or unilaterality [132], presenting symptoms such as myoclonus, limb apraxia [135], akinesia, rigidity, executive dysfunction, behavioral or personality changes, dystonia, cortical sensory loss, language deficits, and frontal dementia. CBD is resistant to levodopa and has early-onset postural instability [93,96,135].

Additionally, patients often exhibit insomnia, restless legs syndrome, agrypnia excitata, reversal of the sleep–wake pattern, and periodic limb movements [124].

CBD and PSP have a significant overlap in terms of atypical parkinsonism and tauopathy. Forty-two percent of pathologically diagnosed CBD cases clinically presented as PSP, making the diagnostic techniques for both conditions similar. Patients with CBD often show midbrain and frontotemporal lobe atrophy [136].

4. Discussion

Idiopathic PD is the second most common neurodegenerative disease and the leading cause of parkinsonism. Currently, the characteristics of this disease go beyond motor symptoms, presenting cognitive, digestive, and even olfactory impairments [137,138]. Identifying PD should not be exclusively limited to parkinsonism due to the appearance of other non-motor symptoms that may lead to its proper identification. Therefore, it is necessary to precisely determine whether it is this pathology or another motor-focused condition, such as different types of parkinsonism [137,139].

Parkinsonism should not be confused with PD since it is a clinical condition characterized by motor problems such as bradykinesia, muscle rigidity, postural instability, and resting tremor [1,140]. In a scenario where this clinical condition is a characteristic of PD, it should be noted that it would not be exclusive to the disease, as other types of diseases can develop parkinsonism as one of their main features, the so-called parkinsonian syndromes [9].

Correctly differentiating between PD and the different types of parkinsonism plays a crucial role in clinical aspects. As mentioned in this work, there are two main categories of parkinsonism beyond the classic understanding: secondary parkinsonism and APs [9,140,141]. In the former, several syndromes can be subclassified depending on the etiology, but they consistently involve damage to the basal ganglia (specifically, the striatum). Moreover, it is the type of parkinsonism with the highest incidence; however, its diagnosis and treatment often require more than levodopa indicators or surgical procedures typical of PD, such as deep brain stimulation [9,141].

On the other hand, APs demonstrate a heterogeneity of impairments in the implicated structures, resulting in different affected sites. They also present multiple symptoms and severities compared to secondary parkinsonism, that is, beyond motor symptoms. Understanding these differences is crucial for proper clinical management [140,142].

Therefore, this work aimed to gather the main characteristics of the most well-known secondary and APs, including their definition, predominant symptomatology (summarized in Table 1), sociodemographic aspects, etiology, diagnosis, and symptomatic medical treatment.

Due to the wide variety of secondary and atypical parkinsonisms, some stand out for their incidence. For example, DIP and VP are the most common types of parkinsonism, as, based on the current statistics, they account for about 24–35% of the cases of DIP and between 4.4–12% in the case of VP among all parkinsonisms. Therefore, these parkinsonisms are the most prevalent types after PD [35,36,62].

On the other hand, we are focusing on the types of APs, DLB, and MSA, which rank as the most prevalent. DLB, the second most common cause of neurodegenerative dementia, presents in 4–8% of patients and has an incidence of 5.9 per 100,000 inhabitants, while MSA shows an incidence of 0.7–3 per 100,000 inhabitants [96,108].

Although other types of secondary parkinsonism, such as EOP or ViP, as well as other types of APs, represent a growing concern among the population and a clinical challenge to address, specific disease markers should be considered for their diagnosis and prognosis [137].

When considering possible diagnostic tools, one of the primary markers that can be present in both secondary and APs is the response to levodopa. This drug is essential for the precise diagnosis of idiopathic PD since most patients tend to show improvements with this medication. In contrast, other types of parkinsonism, such as DIP, respond less efficiently to levodopa, or in VP, where the response to levodopa is variable and often limited, which is usually an indication in the diagnosis of these pathologies [6,48,59].

It should be noted that due to the type of neurodegenerative damage caused by PIT, the response to levodopa is an uncommon indicator. Although the drug response to the disease will be positive, what truly highlights this type of parkinsonism is the age at onset. In other words, it can be considered a type of parkinsonism with a response to levodopa similar to idiopathic PD, but its differentiation lies in the early onset [33,143].

Likewise, levodopa can have variable responses depending on the type of atypical parkinsonism present. For example, in DLB, levodopa can improve motor function and tremors, but the dosage must be limited to avoid aggravating the situation. Similarly, MSA also presents a limited response, and a clinical approach must be considered to treat the autonomic and neurological symptoms that usually accompany this disease [106,111,142]. Although APs may share sporadic origins similar to PD, their response to levodopa differs, as the more aggressive progression is fundamental to differentiating and optimizing diagnosis, prognosis, and treatment [2,139].

In terms of quality of life, such as mortality and disease progression, APs tend to have a faster course and higher mortality compared to secondary parkinsonism. For example, MSA is particularly aggressive, leading to disability within 5 to 6 years and later death. The PSP, another type of atypical parkinsonism, has a median survival of 7 years after diagnosis [111,119]. In contrast, secondary parkinsonism, such as DIP and VP, tend to have a better prognosis. In the case of DIP, discontinuing the triggering drug leads to symptom improvement in approximately 70% of patients within the first six months; while VP may be more resistant to treatment, its progression is generally slower than that of APs [38,63].

Although the causes of the secondary parkinsonism mentioned here are diverse, they all share a common pathophysiological mechanism: dysfunction of the nigrostriatal pathway, primarily involving the substantia nigra and the basal ganglia. In the case of DIP, this dysfunction is caused by D2 receptor antagonists in the striatum, which disinhibit GABAergic neurons in the thalamocortical projection and facilitate inhibition in the globus pallidus/substantia nigra reticulata. This mechanism is similar to that observed in PD, where the neurodegeneration of dopaminergic neurons in the substantia nigra pars compacta produces motor symptoms [144].

In the case of strokes, for the nigrostriatal pathway to be affected, the damage must be localized in the basal ganglia or be extensive enough to impact this structure. Additionally, the onset of symptoms must temporally coincide with the damage [63]. On the other hand, in the mentioned cases of ViP, it is observed that they are related to severe damage to the basal ganglia caused by viral infiltration [72]. This infiltration triggers an inflammatory response, where inflammatory cytokines contribute to neurodegeneration [73]. As a consequence, the dopaminergic system of the nigrostriatal pathway is also affected, leading to neuronal damage, loss of dopaminergic fibers, and decreased dopamine transporter density [73,75,81,87].

Secondary parkinsonism can arise from various factors not fully covered in this review. However, based on the literature used, we can identify a common denominator: these disorders always emerge when the nigrostriatal dopaminergic pathway is compromised, whether at the level of neurons, receptors, transporters, or dopaminergic fibers. This matches the indication that these syndromes are not necessarily only related to dopamine deficiency [8].

On the other hand, in the classification of parkinsonian syndromes, those that arise sporadically, with unknown causes and a pathological mechanism different from PD, are included [2]. We refer to APs, which encompass tau and synucleinopathies [92]. Unlike secondary parkinsonism, APs present neurodegeneration in subcortical structures such as the putamen, brainstem, cerebellum, and basal ganglia, among other affected areas [109,113,118]. This damage not only causes motor alterations but also cognitive impairment, closely linking these syndromes to dementia [93,136]. Understanding the main diagnostic methods as well as the treatments for most secondary parkinsonisms and APs becomes a critical tool in clinical practice (this information is summarized in Table 1).

Table 1. Symptoms identified in each of the parkinsonisms. EOP, early-onset parkinsonism; DIP, drug-induced parkinsonism; VP, vascular parkinsonism; ViP, viral parkinsonism; HIV, human immunodeficiency virus; AP, atypical parkinsonism; DLB, dementia with Lewy bodies; MA, multiple system atrophy; PSP, progressive supranuclear palsy; CBD, cortico-basal degeneration.

Parkinsonism	Diagnostic Method	Treatments
EOP	Identification of genetic mutations [17,24,25], clinical history of early onset, bradykinesia, and symmetric rigidity without prominent tremor [17,19,22].	Levodopa (limited administration to avoid dyskinesias), dopaminergic agonists (pramipexole or ropinirole), MAO-B inhibitors (rasagiline, selegiline) [19,32,34].
DIP	Review of recent medications, evaluation of bilateral parkinsonian symptoms, PET/SPECT imaging for nigrostriatal pathways, limited response to levodopa [6,9,41].	Discontinuation of the causative drug, levodopa in cases where underlying PD is unmasked, close monitoring of patients using neuroleptics [6,9,38].
VP	Magnetic resonance imaging for microinfarcts and lesions in basal ganglia, temporal relationship between vascular event and symptoms, evaluation of dopaminergic transporters (SPECT imaging) [9,60,61].	Control of cardiovascular risk factors (hypertension, diabetes), vitamin D supplementation, anti-inflammatory flavonoids (quercetin, naringenin) [60,63,70].
ViP	Parkinsonian clinical symptoms following infections (HIV, dengue, SARS-CoV-2), fMRI or PET techniques to rule out other causes, history of opportunistic infections or immunosuppression [73,75,76,81,83].	Antiretroviral therapy (in cases of HIV), levodopa for symptomatic management (variable response), control of persistent inflammation [73,75,76,81,83].
DLB	Analysis of dopamine transporter (PET/SPECT), magnetic resonance imaging for temporal and hippocampal regions, study of sleep patterns and cognitive fluctuations [95,135].	*Acetylcholinesterase* inhibitors (donepezil, galantamine), low doses of levodopa to avoid hallucinations, NMDA antagonists (memantine) for cognitive impairment [95,98,99].
MSA	Clinical diagnosis based on autonomic insufficiency, magnetic resonance imaging for brain atrophies, autonomic function tests such as orthostatic hypotension [108,109].	Levodopa combined with carbidopa or benserazide, botulinum toxin type A for dystonia, management of specific autonomic and respiratory symptoms [104,109,110].
PSP	Advanced imaging: morphometric analysis of basal ganglia, magnetic resonance imaging for mesencephalic atrophies, differentiation of PD through eye movement studies [119,120].	Levodopa for initial symptoms (limited effects with progression), occupational therapy and physiotherapy, statins to mitigate motor symptoms [119,122,123].
CBD	Imaging analysis for mesencephalic and frontal atrophy, clinical evaluation of asymmetric symptoms, exclusion of similar neurodegenerative diseases [119,120,129].	Botulinum toxin type A for focal dystonia, functional support and occupational therapies, management of insomnia and abnormal sleep patterns [129,132,145].

A relevant observation in this review is the close relationship between APs and neuroinflammation, as it plays a crucial role in the observed neurodegeneration. In the case of DLB, increased parenchymal infiltration of T cells has been reported, and interaction with

microglia has been proposed as a critical factor in neuroinflammation and neurodegeneration [105]. Meanwhile, in MSA, T cells and increased proinflammatory cytokines have been detected, promoting oligodendrocyte dysfunction, which leads to neurodegeneration [114]. In PSP, the neuroinflammatory profile has been linked to IL-6 and IL-2 cytokines [125]. This suggests that APs tend to have an inadequate response to microglia, which aligns with the findings of [145,146], who consider proinflammatory microglia detrimental in neuroinflammatory processes.

Although, according to our review, neuroinflammation also appears to play a role in secondary parkinsonism, this relationship is not as direct and only manifests in some of the subtypes mentioned. In the case of VP, microglia-mediated neuroinflammation is highly relevant due to cerebrovascular damage. It has even been reported that T cells can exert both neurotoxicity and neuroprotection, depending on whether proinflammatory or restorative [68]. In the case of ViP, the infiltrating virus causes microglial activation, leading to chronic inflammation and neuronal damage [73,91,147]. This suggests that parkinsonism caused by external agents directly affecting neural tissue will also need to contend with microglia and its neuroinflammatory system.

This intriguing relationship between neuroinflammation and the worsening of parkinsonism has recently attracted the attention of researchers, who are proposing potential therapeutic targets in animal models to reduce microglial activation and slow disease progression. Some strategies include neuroprotective approaches to modulate dopaminergic degeneration [148,149], reducing microglial cells [150], and even proposing drugs that regulate neuroinflammation via the gut microbiome [151], as well as studying possible microRNA suppressors of neuroinflammation [152].

Although these studies have not yet advanced to the clinical phase, they demonstrate a growing interest in the search for new treatment pathways to combat parkinsonism. However, it should also be recognized that parkinsonian syndromes are difficult to differentiate, so it would be necessary to develop a tool that systematically analyzes the symptoms and specific characteristics of each one to avoid confusion with PD and ensure appropriate treatment according to the syndrome. Additionally, a table (Table 2) that shows the critical symptomatology in the types of parkinsonism mentioned in the text was proposed.

Table 2. Symptoms identified in each of the parkinsonisms. DIP, drug-induced parkinsonism; VP, vascular parkinsonism; ViP, viral parkinsonism; HIV, human immunodeficiency virus; AP, atypical parkinsonism; DLB, dementia with Lewy bodies; MA, multiple system atrophy; PSP, progressive supranuclear palsy; CBD, cortico-basal degeneration.

Symptoms	EOP	DIP	VP	ViP			AP			
				HIV	Dengue	COVID-19	DLB	MSA	PSP	CBD
Akinesia/Bradykinesia	x	x	x	x	x	x	x	x		x
Muscle rigidity	x	x	x	x	x	x	x	x	x	x
Resting tremor	x	x	x	x	x	x	x	x	x	x
Postural instability	x	x	x	x				x		
Dystonia	x		x	x	x	x		x		x
Gait disturbances		x	x			x	x	x	x	x
Cognitive impairment			x						x	
Sexual dysfunction	x							x		
Symmetric alterations									x	x
Hyperreflexia (lower limbs)								x	x	
Psychiatric symptoms	x	x		x	x	x			x	x
Antisymmetric alterations					x	x				
Oromandibular dyskinesia								x	x	
Hyposmia	x						x	x		
Urinary incontinence	x	x	x		x		x		x	x
Dementia								x		

Table 2. *Cont.*

Symptoms	EOP	DIP	VP	ViP			AP			
				HIV	Dengue	COVID-19	DLB	MSA	PSP	CBD
Speech difficulty	x							x	x	
Visual hallucinations	x			x		x				
Ataxia	x						x	x		
Psychosocial disorders	x	x				x				
Disequilibrium/Confusion		x				x	x			
Spasms	x		x					x	x	
Hypophonia	x		x				x			x
Visual symptoms								x	x	x
Hyperthermia			x							
References	[17,18, 24,31, 153]	[6,39,41, 46,154]	[62,155–157]	[76–78]	[74,79,158, 159]	[83]	[97,160]	[110, 161]	[126, 129,162]	[134, 163]

5. Conclusions

PD is the second most common neurodegenerative disease in the world and a subtype of parkinsonism. However, differentiating between PD and other parkinsonian syndromes is not an easy task, and differential diagnoses sometimes fail, making it necessary to create a robust instrument that allows for an accurate diagnosis between the different types of parkinsonism.

It is important to emphasize that, due to the multiple etiologies of parkinsonism, the symptomatology of each condition is distinct and plays a crucial role in the correct diagnosis of the disease, allowing for a better understanding of the clinical severity. Additionally, the relationship between the syndrome's progression and neurodegeneration must be considered to explore potential clinical treatment options that can help improve the well-being of affected patients.

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