Differential Diagnosis of Parkinson’s Disease and Atypical Parkinsonian Syndromes
Parkinson Hastalığı ve Atipik Parkinson Sendromlarının Ayırıcı Tanısı

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ABSTRACT
Clinical diagnosis of Parkinson’s disease demonstrates classical presentation of symptoms that are often misdiagnosed as Parkinsonian syndromes predominately in the initial stages of the disease. Innovative clinical trials for the differential diagnosis between the two overlapping illnesses incorporate neuroimaging, pharmalogical medications, deep brain stimulation and cerebrospinal biomarkers. At present, therapeutic options are applicable in reducing symptomatology while delaying the onset of the disease. In this article, Parkinson’s disease and atypical parkinsonian syndromes are comprehensively discussed in relations to symptoms, etiology, diagnosis and treatment.

Key words: Parkinson’s, atypical parkinsonian syndromes, dopamine, dementia.

ÖZET

Anahtar kelimeler: Parkinson, atipik parkinsonyan sendromlar, dopamin, demans.
Introduction

Destruction of neurons in the substantia nigra cultivates an insidious incurable neurodegenerative movement disorder called Parkinson’s Disease (PD). PD causes a number of clinical manifestations both motor and nonmotor typically after 60-80% of dopamine loss occurs in the terminals of the striatum. Pathologically, PD demonstrates an unusual presence of subcortical and cortical Lewy bodies conjoined with Lewy neurites composed of deposits of fibril accumulations made of alpha-synuclein. Clinical presentation of PD is represented by asymmetric Parkinsonism which is a term used to represent motor complications including rigidity, tremor, Bradykinesia and late postural instability. Parkinsonism frequently coincides with other neurodegenerative disorders with the most commonly known as atypical parkinsonism or atypical parkinsonian syndromes (APS).

Initially, APS is often misdiagnosed as PD due to similar clinical presentation with considerable symptom overlap. APS resembling PD also demonstrates loss of dopaminergic neurons in the substantia nigra spreading to regions of the striatum, putamen and caudate nucleus. APS includes dementia with Lewy bodies (DLB), progressive supranuclear palsy (PSP), multiple system atrophy (MSA), corticobasal degeneration (CBD), vascular parkinsonism and drug-induced parkinsonism (DIP). PD, DLB and MSA can be further differentiated into synucleinopathies with abnormal deposition of the protein alpha-synuclein identical to pathological manifestations in PD. PSP and CBD are considered to be tauopathies with abnormal depositions of tau proteins. In addition, APS can be further differentiated into degenerative and nondegenerative disorders. Degenerative disorders include MSA, PSP, CBD and DLB whereas nondegenerative disorders include vascular parkinsonism and DIP. APS has rapid and poor prognosis and in most cases, a duration of less than 10 years results in death.

Pharmacological therapies, ablative and surgical procedures have been specifically designed to reduce the progression of symptoms relevant in PD. These treatment plans function by increasing dopamine levels in the affected areas of the brain. The primary treatment for PD is the use of pharmacological agents essentially levodopa, dopamine receptor agonists (DRA) and monoamine oxidase B inhibitors (MAOB-I). Additional treatment for PD includes deep brain stimulation (DBS), pallidotomy and thalamotomy. The most proficient and commonly
prescribed medication today for PD is Levodopa. Levodopa is used to control motor symptoms but increased and prolonged use causes abnormal involuntary movements known as dyskinesias. Clinical research incorporating DRA and MAOB-I has proven a synergistic relationship for therapy with levodopa showing a significant reduction of motor fluctuations and dyskinesias. Levodopa is commonly prescribed if PD is suspected, but it typically does not respond to symptoms of APS. Additionally, DBS may also be an effective treatment for PD but may not be as an effective treatment for APS. The present therapies are focused on alleviation of symptomology primarily because the etiology of the disease remains unknown.

As of today, there are no treatments for APS but future efforts have been taken to better understand the prognosis and differential diagnosis of APS from PD. Several imaging studies have been applicable in distinguishing the differences between PD and APS. These associated imaging techniques have allowed researchers to identify dopamine transporters. Nonetheless, prospective clinical research including cerebrospinal fluid (CSF) biomarkers coalescence with other biological investigations may be of promise allowing for new possibilities. The objective of this review is to evaluate the different approaches in differentiating PD from APS and identify different types of treatment options for patients with PD.

**Etiology and Symptoms**

The clinical manifestations of PD mainly consists of motor symptoms but may also be characterized by nonmotor symptoms. The cardinal Parkinsonism symptoms include resting tremors, rigidity, postural instability, dyskinesia and bradykinesia. Resting tremors can occur intermittently and unilaterally typically in the foot or hand in approximately 70% of patients with PD. Rigidity refers to stiffness in the neck, limbs and trunk thereby may affect movements associated with walking. Postural instability refers to the loss of balance and proprioception whereas dyskinesias is impairment of voluntary muscle jerking or involuntary spasms. Postural instability usually does not occur until late into the disease of PD, which can help with a differential diagnosis between APS and PD. Bradykinesia is known as slow movements and can be further detrimental to PD and APS patients.

Nonmotor clinical manifestations of PD includes sensory dysfunction, dementia, mood and
affect disorders including depression, anxiety, apathy, fatigue, psychosis, sleep disturbances, autonomic dysfunction and cognitive impairment. Autonomic dysfunctions include sexual dysfunction, sialorrhea (excessive saliva or drooling), gastrointestinal dysfunction, sweating, and orthostatic hypotension. The symptoms of PD may manifest differently in different patients, usually increase in severity over time and occur gradually. Symptoms may be extremely detrimental to a patients’ quality of life as some symptoms may reduce the ability for one to care for oneself.

The etiology and pathophysiology of APS is typically unknown. The clinical signs and presentation for APS include gait disorders for instance freezing of gait (FOG), abnormal tandem walk, balance impairments, lack of resting tremor, dysautonomia, frequent and early falls and symmetric motor signs. Other Parkinsonism symptoms that are present in PD may be also present in APS such as rigidity, akinesia and postural instability. MSA symptoms include autonomic failure, cerebellar/pyramidal deficits, unstable blood pressure causing falling upon standing (orthostatic hypertension), erectile dysfunction and urinary incontinence. DLB symptoms include cognitive impairment, hallucinations and vivid dreams. PSP main symptoms include early onset of falls with postural instability and slow vertical saccades (slow vertical eye movement) followed by supranuclear gaze palsy (limitations with downward and upward gaze). CBD symptoms include alien limb phenomenon (limbs having a “mind of their own”), aphasia, sensory deficits, apraxia (inability to carry out learned purposeful movements) and asymmetric parkinsonism. Vascular Parkinsonism symptoms include difficulty in gait, lower body Parkinsonism’s (the waist down is affected) which are mostly caused by multiple small strokes. DIP is mainly caused by use of antipsychotic medications, commonly known as neuroleptics, including but not limited to promazine, haloperidol, perphenazine, fluphenazine, pimozide, chlorpromazine but can additionally be induced by calcium channel blockers, GI motility and anticonvulsant medications. Considering these syndromes are closely related to PD, some symptoms may occur earlier often ruling out PD and giving a diagnosis of APS.

**Diagnosis**

**Neurological and Physical Examination**

The primary technique in diagnosing PD is through a thorough neurological and physical examination and further referral to a movement specialist. When two of the four
Parkinsonism classical symptoms are present, there can be accurate diagnoses of PD\(^1\). In distinguishing between PD and APS, the primary focus of diagnosis is the clinical symptoms. For instance, if symptoms like postural instability, frequent falling, and orthostatic hypertension or if dementia symptoms exist in the primordial disease stages this could be indicative that PD is not the related disorder because these symptoms typically arise in the more progressive stages of PD\(^3\). If resting tremor is present, usually a diagnosis of PD is sufficient because resting tremor typically does not occur in APS\(^15\). In addition, neurological examination of ataxia using tandem gait test can demonstrate gait abnormalities in APS, which could be part of obtaining a differential diagnosis between APS and PD. A study conducted by Morales-Briceno et al. 2014, researchers evaluated ataxia using a tandem gait test to demonstrate gait abnormalities in 32 patients with APS and 54 subjects with PD. The tandem gait test required patients to walk in a straight line, touching heel-toe to heel-toe. Study results demonstrated 90.6% of APS subjects presented with abnormal tandem gait and 33.3% of PD subjects presented with abnormal gait. The principal focus of this research was to rule out PD.

**Rating Scales**

The Unified Parkinson’s Disease Rating Scale (UPDRS) is a scale developed to diagnose patients and rate the severity of PD\(^1\). This rating scale allows physicians to closely monitor drug effectiveness on the reduction of PD symptoms and follow the longitudinal course of PD\(^2\). There are four parts of the UPDRS scale: Part I (non-motor involvement-mental activity, behavior and mood), Part II (activities of daily life), Part III (motor symptoms) and Part IV (difficulty with therapy)\(^3\),\(^3\),\(^5\). The UK PD Society (UK PDS) Brain Bank diagnostic criteria is a test used to rule out other conditions than PD and involves three steps which are 1. Evaluation of possible symptoms of PD 2. Considering other factors that would rule out PD 3. Other supportive evidence to support a diagnosis of PD\(^6\). UK PDS criterion is met, when bradykinesia is associated with one of the symptoms of rigidity, 4-6 Hz resting tremor or postural instability\(^17\).

**Neuroimaging**

DaTSCAN with single photon emission computed tomography (SPECT) and positron-emission tomography (PET) using fluorine-18-labelled fluorodeoxyglucose (FDG)-PET neuroimages is the latest technique in discriminating between PD and APS\(^3\). SPECT scans visualize dopamine
transporter availability utilizing radioligands $^{123}$I-FP-CIT, $^{123}$I-Ioflupane DaTSCAN, or B-CIT or use PET scans to distinguish alterations in brain activity or metabolic and cerebral flow using F-FDG. Currently, the principal neuropathological alterations shown on neuroimaging are deposits of fibrillary aggregates in the substantia nigra that can be used as target areas for medications.

Neuroimaging via SPECT typically uses the radiopharmaceutical drug $^{123}$I-Ioflupane DaTSCAN. DaTSCAN gets intravenously injected into the patient in order to acquire SPECT images of the brain, particularly the degeneration of nigrostriatal regions and visualization of presynaptic dopamine transporters (DaT). Dopamine transporters function to recycle dopamine from the synaptic cleft located in the putamen and caudate nucleus. DaTSCAN’s main function is to differentiate PD from non-degenerative types of Parkinsonism (vascular Parkinsonism, DIP, essential tremor) because in these conditions, dopamine transporters are not affected and therefore can be distinguished between abnormal images of PD compared to normal images of non-degenerative form of Parkinsonism on the DaTSCAN. Comparably, DaTSCAN cannot be utilized to differentiate PD from atypical types of degenerative Parkinsonism with high accuracy because both disorders show a reduction in presynaptic dopamine receptors making it hard to differentiate between the two diseases. Although, to test the accuracy of differentiating PD from degenerative APS, a recent study conducted by Badoud et al (2016) showed differences in brain images opposing precedent research. In this study, PD patients and degenerative APS patients were evaluated using $^{123}$I-Ioflupane SPECT; 32 with PSP, 306 with PD, 30 with CBD and 24 with MSA were scanned on the same machine for over a period of 10 years. They investigated dopaminergic deficiency and to see whether $^{123}$I-Ioflupane SPECT showed recognizable patterns in specific areas of the brain while attempting to exclude non-degenerative forms of Parkinsonism. $^{123}$I-Ioflupane uptake in the region of the head of the caudate nucleus was significantly reduced in all APS vs PD (p<0.002) with MSA and PSP showing a lower uptake in the head of the caudate nucleus in comparison to PD (p<0.002). In addition, increase in uptake in the ipsilateral putamen in APS compared to PD (p<0.05) and CBS vs PD showed an elevated uptake in the putamen bilaterally. The results demonstrated that they were able to differentiate distinct pattern changes in particular areas of the brain in regards to degenerative forms of APS vs PD by $^{123}$I-Ioflupane as opposed to other studies and showed regions other than the nigrostriatal pathway were involved.

In addition, FDG-PET images are utilized to show abnormalities and provide differential
diagnoses of PD, MSA and PSP. In a study conducted by Tang and colleagues 2010, 167 patients with parkinsonian symptoms underwent FDG PET in attempt to differentiate PD from MSA and PSP. After FDG PET imaging over a longitudinal study of 2 years, movement specialists confirmed clinical diagnosis for MSA with 85% sensitivity and 96% specificity, idiopathic Parkinson’s disease with 84% sensitivity and 97% specificity and PSP patients demonstrating 88% sensitivity and 94% specificity. Even though some studies have shown proof of differentiation between PD and APS, neuroimaging still needs further investigation to prove accuracy.

**Clinical Management**

**Levodopa and Carbidopa/Levodopa**

One way to distinguish between PD and APS is the effect and responsiveness of the pharmaceutical drug Levodopa because Levodopa seems to have a poor prognosis and short lived response in patients with APS in comparison to PD. Levodopa is well known as exogenous dopamine that functions by crossing the blood-brain barrier and reconstructing dopamine in dopaminergic and serotonergic neurons via the enzyme dopa decarboxylase. Levodopa may be simultaneously combined with a peripheral decarboxylase inhibitor called carbidopa to alleviate adverse symptoms such as nausea and vomiting. The mechanism of action of carbidopa works by blocking conversion of levodopa to dopamine in the peripheral circulation and liver thereby reducing nausea and vomiting and increasing absorption of levodopa in the brain. In addition, Acute Levodopa Challenge (ALC) is a pharmacological test to determine dopaminergic responsiveness through chronic administration of levodopa to differentiate between PD and APS.

In a cohort study conducted by Vasta et al. 2017, an acute levodopa challenge with 34 PD patients never receiving treatment of levodopa (drug naïve patients) and 29 APS patients diagnosed with MSA, PSP and CBD were examined to study the frequency of side effects of levodopa over 4 years. A single dose of levodopa/carbidopa 250/25mg was administered in all patients and they were pre-treated with domperidone 20 mg TID for 3 days to minimize peripheral dopaminergic side effects. UPDRS III and Hoehn Yahr (HY) were recorded before drug intake and every hour after until motor symptoms returned to baseline. Patients with atypical Parkinsonism showed higher scores of HY scale and UPDRS III in comparison with PD patients showing higher amplitude of motor response (p 0.02). During ALC a five-fold increase
of developing adverse effects like dizziness, nausea, vomiting, empty head, confusion, asthenia and headache were more prevalent in patients with APS in comparison to PD patients (62.1% vs 23.5% p 0.002). MSA showed the highest side effects at 90%, CBD at 71.4%, PSP at 33.3%.

During the initial stages of PD, response to immediate release levodopa is generally adequate but as the disease progresses the therapeutic window of levodopa narrows with a decreasing response to the drug and wearing off effects may occur causing motor fluctuations and levodopa induced dyskinesias (LID)1, 7, 20, 31. Motor fluctuations are characterized by “ON” when a patient has a decrease in stiffness and tremors, increase in motor control such as balancing and walking which correlates to peak effectiveness of levodopa. Comparably, “OFF” effects, are reemergence of motor symptoms and caused by reduced plasma concentrations of levodopa2. The underlying risk factors for LID consist of the dose of levodopa, the duration of the illness and age at first presentation of PD; although, this doesn’t necessary mean patients with PD will develop LID19. Increase risk of LID motor complications occur in 50-90% of patients taking levodopa for five to ten years or more39.

**Dopamine Receptor Agonists**

An alternative to levodopa for the treatment of PD is non-ergoline dopamine receptor agonist (DRA)18. Current research has also correlated potential treatment of DRA in APS patients12. DRA are used to bind dopamine receptors for activation of dopamine to produce a biological response. Dopamine receptors can be individualized into two classifications, which are D1-like receptors: D1 and D5 and D2-like receptors in which all non-ergoline DRA bind: D2, D3 and D429. D1 and D2 dopaminergic receptors are the main clinical receptors for movement and thus these medications act on the dopaminergic receptors to reduce tremors41.

The advantages of DRA over levodopa is direct stimulation in the substantia nigra specifically on the degenerating neurons of postsynaptic neuron receptors, a decreased risk of instability of motor movements, longer half-life than levodopa, the diminished competition for transport systems such as the gastrointestinal tract (GIT) or crossing the blood-brain-barrier41. Compared to levodopa, DRA have a lower risk of dyskinesias and a greater ability to reduce motor fluctuations39. Consequently, over a few years of DRA monotherapy, DRA becomes inadequate by itself and if a higher dose is given a number of adverse effects occurs such as sudden-onset of sleep, edema, hallucinations, and impulse control disorders (ICDs)42. Some
DRA that require less frequent dosing than levodopa and have a longer half-life are Pramipexole, Ropinirole and Rotigotine18.

Rotigotine transdermal patch (RTG) has clinically demonstrated efficacious treatment in early and advanced PD with recent studies showing a potential treatment option for APS. RTG is applied to the skin and it effectively works by maintaining a stable plasma concentration over 24 hours16, 41. Rotigotine is a potent agonist that targets all dopamine receptors D1- D529, 41. A study conducted by Moretti et al., 2014, 51 PD patients with dementia, CBD, MSA, PSP, LBD and frontotemporal dementias were treated with RTG for 6 months-18months. Clinical evaluations were based off scores on rating scales Mini-mental state examination (MMSE), UPDRS III, adverse events and Neuropsychiatric Inventory (NPI). Results demonstrated alleviation of motor symptoms showing an overall significant reduction in UPDRS III (P<0.00005), a decline in MMSE (P<0.0004) and NPI (P<0.003) showing no indications of behavioral disturbances. Significant adverse events included vomiting, nausea, drowsiness, tachycardia, dystonia, and hypotension in which seven patients withdrew from the study. This study showed that RTG can be a possible treatment choice for patients with APS but is still under further investigation.

**Deep Brain Stimulation**

High frequency deep brain stimulation (DBS) is a neurosurgical option for PD patients in advanced stages where other medical therapies are insufficient or intolerable by patients 44. DBS is effective in improving betterment of life and movement functions in patients with PD over 24 months35. High frequency electrodes are surgically implanted either bilaterally or unilaterally and act as a neurostimulation system to deliver electrical current to the targeted areas to create a reversible disruption on the abnormal activities in these brain regions46. The primary focus and advantage of DBS is to reduce motor symptoms essentially tremor, limb rigidity, bradykinesia and akinesia3. Typically DBS is performed by stereotactic procedures relying on visualization of the STN and GPI on computed tomography (CT) or magnetic resonance imaging (MRI)46.

Numerous experiments demonstrate the perpetual outcome of DBS, how patients react to the treatment and compare the differences between GPI and STN DBS. In a long-term 36-month randomized study conducted by Weaver et al., 2012, responses of motor and nonmotor symptoms to DBS were recorded. The primary outcome was stimulation/off medication motor
function and the secondary outcome was quality of life and neurocognition. This study showed indications that motor function symptoms of PD by DBS showed improvements that remained stable over 3 years, improvements were similar and stable between GPi and STN stimulation indicating that target of DBS does not differ. Quality of life improved but diminished over time. Gradual declines in neurocognitive measures were recorded over time, which was one of the main limitations of DBS.

In regards to APS, limited studies are available on DBS. The most recent study conducted by Servello et al., 2014, three subjects with PSP were evaluated with DBS. Two underwent DBS of the peripedunculopontine nucleus (PPN) and one underwent DBS of the bilateral GPi and right PPN. Interestingly, low frequency of stimulation at 35Hz resulted in improved postural stability, continued with an increased frequency of 130 Hz, and showed no significant changes in clinical presentations. At the one-year follow-up in all patients that underwent DBS, reports of an increase in gait imbalance and decrease in falls was presented. The reported clinical improvements showed a mean decrease on PSP scale (PSPRS) of 26%. DBS of the GPi with PPN or PPN alone demonstrated reduction in falls and improvement in gait. PPN alone showed less of a clinical outcome than combined stimulation of GPi and PPN with a PSPRS decrease of (35.7%). These results indicate that DBS can be an alternative therapeutic advantage for patients with PSP but larger cohort and longitudinal experiments are imperative to investigate the adequacy of DBS on patients with PSP.

Innovative Preclinical and Future Trials

Cerebrospinal Fluid (CSF) Biomarkers

To progress diagnostic preciseness for the ambiguous diagnosis of PD from APS, CSF biomarkers may show promising potential. In a study conducted by Magalinou et al, 2015, nine of the following CSF biomarkers were studied: total and phosphorylated tau protein, B-amyloid 1-42 (Aβ42), neurofilament light chain (NFL), two inflammatory markers including monocyte chemoattractant protein (MCP)-1 and YKL-40, total α-synuclein and soluble amyloid precursor protein α and β (sAPPα and sAPPβ). A prospective longitudinal cohort study of two years included 160 patients with PD, CBS, MSA, frontotemporal dementia (FTD), PSP and Alzheimer’s Disease (AD) were compared to 30 healthy elderly participants who served as controls to the study. All markers with the exception of MCP-1 were significant with the most inequitable being sAPPα, NFL, and α-synuclein. The longitudinal group over the course of one
year showed an escalation in NFL levels in one patient with CBD and nine patients with PSP. The study resulted in the ability to differentiate patients with APS from PD, subclasses of APS from one another and APS from dementia disorders by comparing healthy controls with a sensitivity and specificity of 91%. Disease severity \( (p=0.002) \) along with duration \( (p<0.001) \) was significant. In this study, an 85-90% diagnostic accuracy was shown in differentiation between APS subgroups.

In a similar study conducted by Hall et al., 2012, they conducted a cross-sectional analysis examining the following five CSF biomarkers: NFL, Aβ1-42, α-synuclein, total tau and phosphorylated tau to differentiate between PD, DLB, PD with dementia, AD, PSP, MSA, and CBD versus normal healthy individuals serving as controls. 453 CSF samples were taken. NFL levels were increased considerably in APS, indicating a greater disease severity with rapid neuronal degeneration and greater parkinsonian symptoms as also seen in the previous study performed by Magalinou et al. However, comparably, in this present study disease duration did not correlate significantly \( (P>0.05) \). In addition, increases in NFL levels were present in all patients with APS in comparison with both PD patients and controls. The present study further supports the implications that APS can be recognizable from PD by certain biomarkers and particularly NFL alone can further help in this differentiation. The only limitation for this study was the small sample size of only one patient with PSP indicating that further longitudinal studies should be conducted to support these studies.

**Conclusion**

PD and APS are both progressive neurodegenerative diseases that can have overlapping symptoms and pathogenesis that can often be misdiagnosed predominately in the earlier stage of the disease. It’s crucial for clinicians to actively work to diagnose patients before the disease progresses and be aware of symptoms that occur both in PD and APS. Certain criteria may be followed such as attentiveness to when symptoms emerge, if Parkinsonism is present with other PD cardinal symptoms, is Parkinsonism symmetrical or asymmetrical, do Parkinsonism symptoms improve with dopaminergic medication and if diagnostic studies are supportive of PD or APS in helping rule out one or the other. Treatment for PD with levodopa and DRA has shown reduction in symptoms but has not been proven to cure all symptoms of PD. DBS of the Gpi and STN have also shown promising outcomes of reduction of
symptomology but has not been about to show substantial improvement. Currently, there are no approved treatments available for APS that provide substantial symptomatic relief.

Better techniques for differential diagnosis have been of interest, but are still yet to be established. Usually clinical diagnosis is made by physical and neurological examinations by movement specialist but other techniques involving neuroimaging using SPECT and PET scan have shown alterations in specific regions of the brain leading to future promises of differential diagnosis. CSF biomarkers can be of future interest to distinguish between PD and APS, but it needs further investigation. Due to complexities of APS, the vague diagnosis, lack of appropriate biomarkers and small sample sizes in clinical research, it is challenging to clearly differentiate PD from APS at this time.

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