Drug induced Parkinson's: A comprehensive review of the issues and measures required to tackle the same

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Abstract. Drug-inducedParkinsonism(DIP) closelyresemblesParkinson'sdisease(PD)inmotorsymptoms butiscausedbyspecificmedicationsdisruptingdopaminereceptorsandneurotransmitterbalance. PD involves a complex interplay of genetic, environmental, and biochemical factors resulting in the gradual degeneration of dopaminergic neurons. Environmental toxins and genetic mutations, such as LRRK2 and SNCA, contribute to the risk of developing PD. DIP primarily occurs due to the obstruction of dopamine receptors by certain drugs, notably antipsychotics and antiemetics, affecting dopamine transmission and causing Parkinsonian symptoms. Toxin-induced Parkinsonism(TIP)arisesfromexposuretosubstanceslikemanganese,herbicides,pesticides,and specific drugs, disrupting dopaminergic pathways and altering neurotransmission. This study examines various cases of DIP, emphasizing the significance of timely identification and intervention. A thorough understanding and proactive management of DIP are crucial for alleviatingsymptomsandimprovingpatientoutcomes.Healthcareprofessionalsneedtodiligently monitor patients using medications associated with DIP, adjust treatment plans, and educate patientsaboutpotentialsideeffects. Further researchisimperativetounravelthepathophysiology of DIP, considering genetic, environmental, and drug-related factors, to enhance clinical practices and optimize patient care. Addressing DIP requires a multifaceted approach, including early recognition, thoughtful management, and patient-centred care.

1 Introduction

Parkinson's disease (PD) is a complicated neurodegenerative condition marked by the gradual degeneration of dopaminergic neurons in the substantia nigra area of the brain. The underlying mechanisms of PD are multifaceted, encompassing a blend of genetic, environmental, and biochemical factors. This complex interaction ultimately results in the distinctive motor and non-motor symptoms linked to the disorder [1].The exact cause of PD's pathophysiology is still under investigation, but it is widely acknowledged that both genetic and environmental factors have significant roles to play. Some genetic mutations, such as those found in the LRRK2 and SNCA genes, have been detected in certain PD cases, indicating a genetic influence. Moreover, exposure to toxins such as pesticides and metals has been associated with an elevated PD risk. These environmental elements can potentially trigger oxidative stress and inflammation, thereby contributing to the advancement of the disease [2].A significant pathological aspect of PD involves the creation of Lewy bodies, which are abnormal protein clusters primarily made up of alpha-synuclein. These Lewy bodies are believed to interfere with regular cell functions and initiate harm to neurons (Wakabayashi et al. 2013). Alpha-synuclein is typically found in neurons, but in PD, it undergoes misfolding and clustering, resulting in its harmful buildup. The precise mechanisms that cause this misfolding are currently the subject of rigorous research [3].With the accumulation of alpha-synuclein aggregates, various cellular functions in dopaminergic neurons become impaired. A prominent issue is mitochondrial dysfunction, which results in reduced energy production and heightened oxidative stress. Mitochondria play a crucial role in supplying energy to neurons, and when they malfunction, it can lead to adecline in cell health. Consequently, this oxidative stress causes harm to cellular components such as proteins, lipids, and DNA, intensifying the degeneration of neurons [4].

Inflammation is a vital component of PD's pathophysiology. Microglia, which are the immune cells in the brain, become activated when they encounter alpha-synuclein aggregates and injured neurons. Although microglia activation is a normal

response aimed at eliminating harmful substances, in PD, this mechanism becomes disrupted. Hyperactive microglia release pro-inflammatory cytokines and free radicals, which contribute to neuroinflammation and further damage to neurons [5].

The gradual decline of dopaminergic neurons in the substantia nigra is a defining feature of PD and leads to a significant reduction in dopamine production within the brain. Dopamine is a neurotransmitter essential for motor control and various other functions. As dopamine levels decrease, the basal ganglia, a brain region responsible for coordinating movement, becomes impaired in its functioning. This disruption in the motor circuitry gives rise to the distinctive motor symptoms seen in PD, including bradykinesia (slow movement), rigidity, resting tremors, and postural instability [6].

Apart from motor symptoms, PD also involves various non-motor symptoms. The decline in neurons that produce dopamine can influence other neurotransmitter systems, resulting in changes in mood, cognitive function, and autonomic function. To illustrate, deficiencies in the noradrenergic and serotonergic systems can play a role in causing depression and anxiety in individuals with PD [7].

2 Types of Parkinsons disease

2.1 Idiopathic Parkinson's disease

Parkinson's disease, also known as idiopathic Parkinson's disease, is a perplexing neurological disorder that poses significant challenges for medical science. It is marked by a range of motor and non-motor symptoms, significantly affecting the lives of patients and their families [8]. This intricate condition, which primarily disturbs movement and originates from the gradual breakdown of dopaminergic neurons in the substantia nigra of the brain, has been a focal point of extensive research. Scientists are dedicated to unraveling its fundamental mechanisms, factors contributing to its onset, and potential approaches for treatment. The exact origin of idiopathic Parkinson's disease remains mysterious, although a complex interplay of genetic, environmental, and biochemical elements is thought to play a part [9]. The primary identifiable feature is the decline of dopaminergic neurons in the substantia nigra, resulting in decreased dopamine, a crucial neurotransmitter for coordinated movement. Additionally, the buildup of irregular protein clusters within neurons, including alpha-synuclein, also contributes to the deterioration of nerve cells. Genetics also have an impact, as particular mutations and genetic variances are connected to an elevated risk of developing Parkinson's.Nonetheless, most instances are considered sporadic, implying a multifaceted origin involving both genetic predisposition and environmental triggers [10].

2.2 Drug-induced parkinsonism

Drug-induced Parkinsonism (DIP) is characterized by the emergence of motor symptoms resembling those of Parkinson's disease due to specific medications. The underlying mechanisms and pathophysiology of DIP involve the disturbance of the delicate equilibrium of neurotransmitters, particularly dopamine, in the neural networks responsible for motor control within the brain. Dopamine plays a pivotal role in ensuring coordinated and fluid movement, and any disruption in its availability or proper transmission can lead to motor manifestations akin to those seen in Parkinson’s disease [11]. The central mechanism contributing to DIP involves the obstruction or antagonism of dopamine receptors by particular medications. This interference impedes the transmission of dopamine signals, inducing a deficiency of functional dopamine and consequently triggering motor symptoms [12]. The specific dopamine receptor types impacted determine both the nature and intensity of the resulting symptoms. DIP often stems from medications that target dopamine receptors, primarily antipsychotic drugs. First-generation antipsychotics like haloperidol and chlorpromazine, which are commonly employed in managing psychiatric disorders, are recognized culprits in inducing DIP. These drugs exert their therapeutic effects by antagonizing dopamine D2 receptors, culminating in reduced dopamine transmission and the appearance of symptoms reminiscent of Parkinson's disease [13]. Moreover, specific medications utilized to address gastrointestinal issues, such as anti-nausea medications like metoclopramide, can prompt DIP by influencing dopamine receptors in both the gut and the brain. These medications can disrupt the harmonious movement of the digestive system and subsequently impact the brain's dopaminergic system. Additionally, calcium channel blockers, frequently prescribed for conditions such as hypertension, can contribute to DIP. These medications can alter the flow of calcium ions, pivotal for neurotransmitter release, including dopamine. This disturbance in calcium signalling consequently affects dopamine transmission and contributes to motor impairments. Typically, discontinuing the medication responsible for DIP leads to the reversal of symptoms. However, the duration of recovery can vary, and certain individuals might experience lingering manifestations even after ceasing the medication [14].

2.3 Toxin-induced Parkinson’s disease

The intricate interaction between environmental toxins and the intricate neural networks controlling movement is revealed by the pathophysiology and mechanisms of toxin-induced Parkinson's disease (TIP) [15]. TIP emerges when various toxins disturb the finely tuned neurotransmitter systems, particularly the essential dopaminergic pathways responsible for motor control. These toxins can influence various stages of neurotransmission, causing disruptions in the production, release, reuptake, and binding of critical neurotransmitters like dopamine. Such disturbances lead to an altered dopamine equilibrium, reminiscent of the neurotransmitter imbalances observed in idiopathic Parkinson's disease [16]. Common toxins linked to TIP, including substances like manganese, herbicides, pesticides, industrial chemicals, carbon monoxide, and specific medications, elicit their negative effects through a range of mechanisms. For instance, manganese accumulates within the basal ganglia, impairing dopamine function and initiating motor symptoms [17]. Herbicides and pesticides like paraquat and rotenone impede cellular energy production and induce oxidative stress, causing harm to dopaminergic neurons. Industrial chemicals like organochlorines and solvents disrupt dopamine signaling and activate neuroinflammation [18]. Carbon monoxide, frequently resulting from incomplete combustion, reduces oxygen supply and inflicts brain damage, contributing to parkinsonian manifestations. Some medications, notably antipsychotic drugs such as haloperidol, can upset dopamine equilibrium as an adverse effect, leading to motor impairments. These mechanisms collectively highlight the intricate connection between environmental toxins and the disturbance of dopaminergic neurotransmission and neural pathways. Grasping these mechanisms is pivotal for devising focused interventions and preventive measures to alleviate the effects of toxin-induced parkinsonism and enhance patient well-being [19].

2.4 Hydrocephalus

Hydrocephalus-associated parkinsonism reveals a distinct interaction between fluid dynamics and motor dysfunction within the brain. This condition emerges from hydrocephalus, a state marked by an anomalous accumulation of cerebrospinal fluid (CSF) in the brain's ventricles [20]. The mechanisms at the core of hydrocephalus-related parkinsonism revolve around the modified pressure dynamics triggered by excessive CSF accumulation. The amassed CSF applies pressure to neighboring brain structures, disturbing the delicate equilibrium of neural circuits responsible for motor regulation [21]. This pressure can hinder the operation of pivotal regions like the basal ganglia and substantia nigra, essential for orchestrating movement. Furthermore, the compression of white matter pathways that interconnect various brain areas can disrupt the seamless communication vital for coordinated motion [22]. These mechanical interruptions can give rise to motor symptoms akin to those observed in Parkinson's disease, such as tremors, rigidity, and bradykinesia. The pathophysiology of hydrocephalus-related parkinsonism underscores the significance of recognizing how modified fluid dynamics can adversely influence neural circuitry, leading to motor impairments. Precise diagnosis and timely intervention for the root hydrocephalus, often involving surgical procedures to reinstate CSF flow, hold critical importance in alleviating both the hydrocephalus itself and the accompanying parkinsonian manifestations [23].

2.5 Vascular parkinsonism

Vascular parkinsonism differs from idiopathic Parkinson's disease, even though they exhibit similar motor symptoms. Unlike Parkinson's disease, which primarily originates from the deterioration of dopaminergic neurons, VP is linked to cerebrovascular ailments [24]. This vascular dysfunction impacts the brains blood vessels, resulting in diminished blood circulation, inadequate oxygen supply, and subsequent harm to regions of the brain responsible for motor function [25]. The precise mechanisms connecting vascular issues to parkinsonism are intricate and varied. Small vessel disease, often affecting the deep white matter and basal ganglia, plays a significant role [26]. The buildup of white matter lesions and lacunar infarcts disrupts neural circuits essential for coordinating movement, thereby contributing to VP's motor symptoms. Additionally, impaired blood flow deprives brain cells of vital oxygen and nutrients, intensifying neuronal dysfunction [27].

2.6 Parkinson’s disease dementia

PDD emerges as a complication of Parkinson's disease, marked by the buildup of abnormal protein clusters, primarily alpha-synuclein, in brain regions crucial for both movement and cognitive function [28]. This misfolded protein disrupts neural activity, triggers inflammation, and results in the deterioration of dopaminergic neurons in the substantia nigra,responsible for motor symptoms, as well as other regions governing cognitive functions [29]. A distinctive hallmark of PDD is the creation of Lewy bodies, aberrant protein clumps within nerve cells. These Lewy bodies contain alpha-

synuclein aggregates and are present in brain regions linked to memory, attention, and executive function [30]. The dispersion of Lewy bodies throughout the brain contributes to the emergence of both motor and cognitive symptoms in PDD. PDD is characterized by structural brain changes, including gray and white matter atrophy. These alterations impact the connectivity among different brain areas, intensifying cognitive impairment [31]. The accumulation of alpha-synuclein also disrupts cellular processes, leading to oxidative stress, malfunctioning mitochondria, and impaired cellular energy production, all of which contribute to neuronal harm and death. PDD's advancement is gradual, with cognitive decline often trailing behind the appearance of Parkinson's motor symptoms. With time, the extensive neurodegeneration and accumulation of protein clusters result in deteriorating cognitive impairments encompassing memory loss, attention deficits, language challenges, and behavioral shifts. Grasping the intricate mechanisms and pathophysiology of PDD is pivotal for crafting precise interventions aimed at alleviating its impact [32].

3 Drug induced Parkinson's: Medical failure, treatment issues and other adverse events associated reasons

3.1 CaseReport:Trazodone-InducedParkinsonism

In this reported case, a 78-year-old Caucasian male with a medical history of atrial fibrillation, major depressive disorder, and a prescription for trazodone to manage insomnia, experienced symptoms consistent with parkinsonism, such as tremors, impaired writing ability, gait issues, and rigidity, emerging after a month of trazodone usage. These symptoms showed rapid resolution within a week after discontinuation of trazodone, strongly indicating trazodone as the probable causative agent. The presence of amiodarone in the patient's medication history was also considered, as it might have impeded trazodone metabolism, potentially elevating trazodone levels in the blood. The patient demonstrated recovery and resolution of parkinsonian symptoms after discontinuation of trazodone [33].

3.2 Case Report: Paliperidone Long-Acting Injection (LAI)-Induced Parkinsonism

In this reported case, a 68-year-old white male with a history of bipolar disorder experienced a decline in cognitive and functional status after receiving a paliperidone long-acting injection (LAI).This led to a diagnosis of drug-induced parkinsonism attributed to paliperidone LAI. However, specific recovery details and subsequent treatment were not provided in the report. Unfortunately, the patient passed away approximately 5 months after the administration of paliperidone LAI. This case emphasizes the importance for practitioners to exercise caution when prescribing paliperidone LAI, particularly in individuals with pre-existing psychiatric conditions [34].

3.3 Case report: Valbenazine

In this documented case, the patient showed improvement in symptoms related to tardive dyskinesia and parkinsonism using a treatment plan involving valbenazine at varying doses (80mg and 120mg on alternate days), highlighting the efficacy of valbenazine in managing these conditions, even when a DaT scan yielded normal results [35].

3.4 Case Report: Drug-Induced Parkinsonism Manifesting as Freezing of Gait after Traumatic Brain Injury

In this reported case, a 35-year-old male with a prior traumatic brain injury demonstrated drug- induced parkinsonism, specifically presenting as freezing of gait. Notable improvement was observed after discontinuing the suspected medications and undergoing comprehensive rehabilitation, highlighting the unusual link between traumatic brain injury and freezing of gait in drug-induced parkinsonism [36].

3.5 Case report: Escitalopram-induced Parkinsonism

In this reported case, a 29-year-old male, prescribed escitalopram for impulse control, developed symptoms of drug-induced Parkinsonism after two weeks of starting the medication. The patient's symptoms fully resolved within four weeks of starting biperiden, and at a follow-up of 1.5 years, there were no further complaints, demonstrating a complete recovery from escitalopram-induced Parkinsonism [37].

3.6 Case Report: Tramadol-Induced Parkinsonism

In this reported case, a 75-year-old woman, prescribed tramadol for post-operative pain following breast cancer surgery, developed tramadol-induced parkinsonism, which resolved within a week of starting levodopa/carbidopa, highlighting the risk of this adverse drug reaction with long-term tramadol use in older patients [38].

3.7 Case Report: Benzodiazepine-Induced Dysphagia in a Parkinson's Disease

PatientIn this reported case, a 53-year-old man with Parkinson's disease experienced dysphagia for over 3 months, which was attributed to the long-term use of benzodiazepines; however, discontinuation of these medications resulted in improved dysphagia and enhanced pharyngeal bolus passage, highlighting the potential for recovery after discontinuing benzodiazepines and the role of these drugs in inducing dysphagia [39].

3.8 Case Report: Likely Drug-Induced Parkinsonism (DIP) and Medication Management

In this reported case, a 54-year-old female patient with suspected Parkinson's disease or drug- induced Parkinsonism (DIP) was advised by a pharmacist to discontinue bupropion, a potential causative drug for DIP; however, the patient chose to continue bupropion due to concerns about depression severity, and recovery outcomes or symptom resolution were not specified in the case, emphasizing the importance of patient preferences in treatment decisions [40].

3.9 Case Report: Citalopram-Induced Sudden-Onset Parkinsonian Syndrome

In this reported case, a 67-year-old woman developed a sudden-onset parkinsonian syndrome just 2 weeks after initiating citalopram, experiencing a complete recovery from these symptoms after discontinuation of the medication, highlighting the importance of recognizing and addressing adverse reactions associated with citalopram use [41].

3.10 Case Report: Tacrolimus-Induced Parkinsonism and Amantadine Therapy

In this reported case, a 62-year-old man experiencing significant neurologic impairments attributed to tacrolimus-induced parkinsonism following liver transplantation showed substantial recovery in symptoms and functional independence after initiating low-dose amantadine therapy, underscoring the potential efficacy of amantadine in managing this drug-induced parkinsonism [42].

3.11Case Report: Tacrolimus-Induced Parkinsonism after Liver Transplantation

In this reported case, a patient with chronic liver disease who underwent orthotopic liver transplant experienced signs of Parkinsonism post-transplant due to tacrolimus immunosuppressive treatment, and significant recovery was achieved by modifying the treatment regimen, shifting from tacrolimus to less toxic sirolimus, underscoring the importance of careful drug management to address neurotoxicity in post-organ transplant patients [43].

3.12Case Report: Fluphenazine-Induced Acute and Severe Parkinsonism

In this reported case, a 31-year-old healthy woman experienced a severe and rapid onset of Fluphenazine-induced parkinsonism due to a prescription error, leading to significant motor and sphincter disability, and although Fluphenazine was discontinued, the patient had an incomplete recovery with persistent motor symptoms, memory disturbances, and irreversible brain volume loss observed in MRI findings, highlighting the importance of accurate prescription and monitoring to prevent severe adverse effects associated with neuroleptics [44].

3.13 Case Report: POLG-Related Parkinsonism in an 80-Year-Old Male

In this reported case, an 80-year-old male presented with symptoms consistent with drug-induced Parkinsonism and tardive akathisia, linked to a non-pathogenic POLG mutation (E1143G), but the case did not provide specific information regarding the treatment and recovery of the patient, emphasizing the need for further research to comprehend the implications of the E1143G mutation[45].

3.14 Case Report: Cyclosporine-Induced Parkinsonism in a Bone Marrow Transplant

Patient In this reported case, a 51-year-old male who underwent allogeneic stem cell transplantation for acute lymphocytic leukemia developed reversible parkinsonian features attributed to Cyclosporine A (CyA) use for graft-versus-host disease prophylaxis; discontinuation of CyA and a brief course of low-dose levodopa/carbidopa therapy led to complete recovery, emphasizing the significance of recognizing and managing rare neurological side effects associated with immunosuppressive medications like CyA [46,47].

3.15 Case Report: Sertraline-Induced Parkinsonism in a Patient with Prodromal Dementia with Lewy Bodies (DLB)

In this reported case, a 75-year-old man with initial symptoms of anxiety, depression, and mild cognitive impairment developed parkinsonian symptoms after starting sertraline for depression, whichsignificantlyimprovedupondiscontinuationofthedrug,emphasizingtheneedforvigilance in monitoring medication effects in patients with prodromal dementia or cognitive impairments [48,49].

3.16 Case Report: Aripiprazole-Induced Parkinsonian Symptoms in a Patient with Paranoid Schizophrenia

In this reported case, a 37-year-old female patient with paranoid schizophrenia developed severe Parkinsonian symptoms after one month of aripiprazole treatment at 10mg per day, which were completely resolved within 5 days after reducing the aripiprazole dosage to 5mg per day,underlining the significance of vigilant monitoring and appropriate dosage adjustments to manage adverse effects effectively [50,51].

3.17 Case Report: Drug-Induced Parkinsonism with Prolonged Symptoms

In this reported case, two individuals with drug-induced parkinsonism experienced persistent symptoms lasting 22 and 27 months even after discontinuation of the causative agents, emphasizing the prolonged nature of this condition and its persistence beyond cessation of the offending drugs despite normal dopamine ioflupane iodine-123 (DaT) single-photon emission computed tomography (SPECT) scans at certain intervals post-drug discontinuation [52,53].

3.18 Case Report: Escitalopram-Induced Parkinsonism

In this reported case, 29-year-old male experienced symptoms of Parkinsonism after initiating escitalopram for impulse control, and these symptoms completely resolved within 4 weeks of startingbiperiden,indicatingareversibleconditionandsustainedrecoveryatthe1.5-yearfollow- up without recurrence of Parkinsonism symptoms [54,55].

3.19 Case Report: Citalopram-Induced Parkinsonism

In this reported case, a 67-year-old woman developed sudden-onset parkinsonian symptoms two weeks after initiating citalopram, and a full recovery was achieved after discontinuation of the drug, highlighting the need for physicians to be vigilant about this potential adverse reaction and the importance of prompt discontinuation for significant recovery [56].

3.20 Case Report: Pregabalin-Induced Parkinsonism

Inthisreportedcase,a64-year-oldwomanwithdiabeticsensory-motorpolyneuropathydeveloped parkinsonian-like symptoms, including tremor, bradykinesia, and rigidity, three months after the introduction of pregabalin (PGB) to her treatment, and significant recovery was observed after PGB withdrawal, underscoring the need for caution and monitoring in PGB-treated patients and highlightingtheassociationbetweenPGBuseandparkinsoniansymptoms [57].

4 Conclusion

Drug-induced Parkinsonism (DIP) is a complex aspect of movement disorders, closely resembling Parkinson's disease (PD) in motor symptoms but differing in its cause—stemming from specific medications and their impact on dopamine receptors and neurotransmitter equilibrium. Addressing DIP is paramount due to its potential to significantly affect an individual's quality of life, often necessitating attentive management, potential adjustments to medication, and cessation to alleviate symptoms.The pathophysiology of Parkinson's disease, marked by the progressive degeneration of dopaminergic neurons, involves a complex interplay of genetic, environmental, and biochemical factors. In contrast, DIP results from the disruption of dopamine receptors, primarily due to certain medications like antipsychotics, antiemetics, and calcium channel blockers. These drugs interfere with dopamine transmission, leading to motor symptoms resembling Parkinson's disease. Recognizing and distinguishing idiopathic Parkinson's disease from DIP is crucial, as their management and prognosis can significantly vary. Environmental toxins, acknowledged as culprits in idiopathic Parkinson's disease, also contribute to toxin-induced Parkinsonism (TIP). Exposure to substances such as manganese, herbicides, pesticides, industrial chemicals, and specific medications can disrupt dopaminergic pathways, altering neurotransmission and inducing motor symptoms akin to Parkinson's disease. This highlights the intricate link between environmental factors and the disruption of neurotransmitter systems.Case reports shed light on various scenarios of drug-induced Parkinsonism, underscoring the importance of timely recognition and appropriate intervention. Understanding the potential culprits, monitoring their effects, and adjusting treatment regimens or discontinuing the offending drugs can lead to the resolution of symptoms. However, recovery may vary, emphasizing the need for personalized approaches to effectively manage DIP.Effectively addressing DIP requires a multidimensional approach. Healthcare professionals must remain vigilant regarding the potential for DIP, especially in patients using medications known to cause this condition. A solid grasp of the pharmacology and mechanisms of these medications is critical for predicting and managing adverse effects. Regular monitoring and communication with patients to assess emerging symptoms resembling Parkinsonism are vital, enabling early intervention and potential modification of the treatment plan.Further research is imperative to deepen our understanding of the pathophysiology and mechanisms underlying DIP. This involves investigating the roles of genetics, environmental factors, and specific drugs in inducing Parkinsonism. Additionally, developing strategies to mitigate DIP risk and enhance outcomes is essential. Patient education and awareness campaigns are pivotal to ensure individuals are well-informed about potential side effects, empowering them to actively engage in their healthcare decisions.In conclusion, drug-induced Parkinsonism is a significant phenomenon requiring ongoing research, awareness, and a proactive approach from healthcare providers. Timely identification, thoughtful management, and patient-centred care are critical in mitigating the impact of DIP and enhancing the overall well-being of affected individuals. A thorough understanding of the nuances' surrounding DIP is essential for promoting improved clinical practices and optimizing patient outcomes.

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