Journal of the Neurological Sciences 398 (2019) 101–106

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Review Article

Impulse control disorders in Parkinson's disease: A systematic review on risk factors and pathophysiology

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ARTICLE INFO

Keywords:
Binge eating
Gambling
Hypersexuality
Neurodegenerative disorders

ABSTRACT

Aim: Purpose of this review is to evaluate the potential risk factors that may predispose to the development of Impulse control disorders (ICDs) in Parkinson's Disease (PD) patients, including the effects of dopaminergic therapy.

Methods: This descriptive review was conducted to identificate risk factors that could cause impulsive control disorders in PD. Studies were found on PubMed (2010–2018), Web Of Science (January 2010–July 2018) and Cochrane (2010–2018) databases.

Results: The data suggest that intrinsic and extrinsic factors may be involved in the development of behavioral complications. To date, the link between PD and the development of ICDs is not very clear, but studies highlight the existence of a predisposition to ICDs in the presence of risk factors.

Conclusions: A better assessment of the behavioral disorders of PD may be useful in the rehabilitative intervention for increasing the quality of life.

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease. PD prevalence increases with age, resulting in 1–2% of the population over 60 and in 3–5% over 85, with a median age of onset at the age of 68 for men, and 70 for women. Nonetheless, in 5% of cases there is an early onset (i.e. before 50) [1,2].

In PD, dopamine deficiency in the basal ganglia leads to classical parkinsonian motor symptoms, such as bradykinesia, tremor, rigidity and later postural instability. This disease can also be associated with a wide spectrum of non-motor symptoms, due to nigral degeneration (apathy, dysphoria, cognitive impairment) and extra-nigral degeneration (hyposmia, sleep disorders, autonomic dysfunctions, cognitive deficits, psychosis, depression, anxiety and apathy) [3].

> 60% of patients with PD have one or more psychiatric symptoms, which may precede the onset of motor symptoms, even by years. These symptoms, such as depression and anxiety disorders, are independent of therapy, whereas others, such as psychosis and impulse control disorders (ICDs), are triggered by dopaminergic therapy [4]. Early recognition and monitoring of cognitive and behavioral difficulties in PD are important to promote patient management and adequate rehabilitative strategies. PD is best managed by a combination of medication with regular physiotherapy and cognitive treatment [5–7]. The gold standard for this disorder is Levodopa, which continues to be the most effective treatment for PD. Moreover, the use of Levodopa allows an improvement in the motor level, but can highlight psychiatric disorders, including ICDs [8]. ICDs greatly affect the quality of life and can lead to legal, criminal and familiar problems. However, there are just a few studies in the literature concerning these disabling symptoms, which negatively affect patient's management.

For this reason, the purpose of this review is to evaluate the potential risk factors that may predispose to the development of ICDs in PD patients, including the effects of dopaminergic therapy.

2. Methods

2.1. Search strategy

This review was conducted to identificate risk factors that could cause impulsive control disorders in PD. Studies published between

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https://doi.org/10.1016/j.jns.2019.01.034
Received 29 September 2018; Received in revised form 29 December 2018; Accepted 21 January 2019
Available online 22 January 2019
0022-510X/

January 2000 and July 2018 were found (by searching) on PubMed, Web Of Science and Cochrane databases. The search combined the following terms: ("parkinson's disease"[MeSH Terms] OR ("parkinson"[All Fields] AND "disease"[All Fields]) OR "parkinson's disease"[All Fields] OR ("parkinson's"[All Fields] AND "disease"[All Fields]) OR "parkinson's disease"[All Fields]) AND ("impulsive behavior"[MeSH Terms] OR ("impulsive"[All Fields] AND "behavior"[All Fields]) OR "impulsive behavior"[All Fields] OR "impulsive"[All Fields]) AND ("risk factors"[MeSH Terms] OR ("risk"[All Fields] AND "factors"[All Fields]) OR "risk factors"[All Fields] OR ("risk"[All Fields] AND "factor"[All Fields]) OR "risk factor"[All Fields]). The search terms were identified as title and abstract. Only English texts were selected. After removing duplicates, all articles were evaluated according to title, abstract, and text.

3. Impulse control disorders in PD: focus on epidemilogy

ICDs are a group of psychiatric disorders in the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) [9], and are characterized by a failure to resist an impulse, drive, or temptation to perform a dangerous behavior for oneself or for others; a growing sense of tension or activation before committing the act; a sense of pleasure, grafting or "release" at the time of committing the act [10].

As a result of our search, we found a few works on the incidence and prevalence of ICDs in patients affected by PD.

Driver-Dunckley et al. [11] performed a retrospective review of all PD patients attending the Muhammad Ali Parkinson Research Center from May 1999 to April 2000. Among the 1884 PD patients evaluated during this period, the authors identified seven men and two women with serious gambling behaviors (with an overall incidence of 0.05%). Subsequently, larger cross-sectional studies reported a prevalence of 1.7 to 7.0% for gambling, 2.0–4.0% for compulsive sexual behavior, and 0.4 to 3.0% for compulsive shopping [11,12].

Moreover, binge eating has been reported in patients with PD, although its prevalence has not been calculated [11,12]. In the DOMINION study [11], one or more ICDs have been identified in 13.6% of patients (5.0% gambling, hypersexuality 3.5%, compulsive shopping in 5,7%, and 4.3% binge eating), presenting 3.9% of participants 2 or more ICDs. Recent epidemiological studies suggest a prevalence of ICDs in parkinsonian patients (7.2%) seven times greater than controls (1%) [11–19]. The role of dopamine agonists (DAs) is predominant in triggering this condition and therefore dose reduction or suspension of such drugs should be considered as a therapeutic strategy [20].

Recent literature shows that PD patients have an increased risk of developing one or more of the main ICDs: binge eating disorder (BED) [21], pathological gambling (PG) [22], hypersexuality (HS) [23], compulsive shopping (CS) [24] and dopamine dysregulation syndrome (DDS) [25].

BED is characterized by eating compulsively with a perceived lack of control over one's eating; the amount of food is larger than most people would eat during the same period of time and under similar circumstances. This disorder has a significant impact on physical health or psychosocial functioning. The main effect of BED is excessive weight gain, which can lead to self-loathing. A severity specific scale has been proposed for BED, including mild (1–3 binge-eating episodes per week), moderate (4–7), severe (8–13) and extreme ($\geq$14) pathological behavior [26]. In a detailed revision of the literature, Lim et al. [21] underline the apparent contrast between uncontrolled food intake and the classic weight loss of patients with PD, highlighting the mechanisms for weight loss (i.e. dyskinesia or dysphagia).

PG is currently categorized as a habit and impulse disorder. It is a chronic and progressive condition, defined as persistent and recurrent maladaptive gambling behavior. There is an association between the development of PG and premorbid alcohol abuse, anxiety, and depression [27,28]. Gallagher et al. [29] showed that slot machine gambling is the most common form of PG in PD patients, probably for some features like repetition of gestures and lower cortical activation.

CS is a disorder characterized by an irresistible urge to purchase more than you need or can afford and can lead to contraction of debts with continuous delay of payment [30].

The repetitive loss of control over spending and the following negative emotional state resemble craving in substance use disorders [31].

DDS (also known as dopamine replacement therapy) is a recently described neuropsychiatric syndrome that manifests itself (3.4%) during PD treated with dopaminergic drugs [32]. This condition is specific for the unregulated self-administration and dependence on dopaminergic drugs. Patients increase drugs dose spontaneously and progressively and this is often associated to behavioral and mood disorders, such as hallucinations, manic states, aggression, psychomotor agitation and delusions [10,25].

Finally, HS is a compulsive behavior due to sexual thoughts and desire for sexual practice. It may be different from the sexual activities previously practiced, with abuse of pornography on the Internet or risky and promiscuous sexual behaviors. HS can interfere with important goals, activities and obligations in ordinary life. Sexual activity can also become a response to stressful life events, without weighing the risk for physical or emotional harm to oneself or others [33]. HS shares several features with substance abuse disorders. In fact, the patients can present pursuit of short-term reward (orgasm) and, like in an addiction, may develop tolerance to increasing levels of sexual stimulation [33]. BE, PG, CS, HS and DDS related to DAs often have devastating consequences that may overshadow even the symptoms of PD [34,35]. The relationship between ICD and PD is not very clear, although it seems that there is a predisposition to the development of behavioral addiction, besides specific risk factors [36,37].

4. Risk factors of ICD in PD

The development of ICDs may be due to several risk factors (see Table 1). The association between dopaminergic treatment, in particular DAs at higher dosages, and ICDs, has raised many doubts [38–43]. Giladi et al. [44] demonstrated that the development of addiction-like behaviors is dependent on both the type of dopaminergic treatment and the dose and duration of treatment. Pezzella et al. screened 202 PD patients for DDS, demonstrating a significant correlation between DDS and both history of mood disorders and previous use of dopamine replacement therapies, especially DAs, either as monotherapy or in combination [45]. Voon et al. [46] proposed that ICDs may be associated with multiple psychiatric and cognitive impairments, such as affective and anxiety symptoms, elevated obsessionality, novelty-seeking, and impulsivity.

Potenza et al. showed that major depression in middle-aged men is frequently co-morbid with PG and over-lapping genetic factors that contribute substantially to their co-occurrence [47,48].

Some authors pointed out that younger patients are likely to be more sensitive to DAs, and dopamine turnover in younger-onset patients undergoes a greater alteration probably leading to a striking imbalance between dopamine synthesis, storage, and release. Further, PD younger-onset is associated with slower progression of motor symptoms, longer disease duration with preserved cognition, but also with earlier appearance of motor fluctuations, dyskinesia and psychiatric symptoms [49]. Moreover, greater impulsive choice, faster reaction time, impulsive decision and executive dysfunction could be determining factors in the development of ICDs in PD patients [36]. With regard to gender, Joutsa et al. concluded that ICDs are not only more frequent in men but also six times more difficult to manage compared to women after a 15-months follow-up [50].

Furthermore, in the general population, risk factors for ICDs are: male gender, co-morbid mood, alcohol or substance use disorders [51,52], higher novelty seeking or impulsivity traits [53,54].

PD patients with ICDs are often young, male, sleepless, and have psychiatric co-morbidity [55]. In PD, additional factors independently

Table 1
Shows the main studies concerning the most common risk factors related to the development of ICD in PD patients.

Risk factor	Study	Patients	Major findings
Dopaminergic treatment	Giladi N. et al. [44]	193 PD/190 CG	The study shows that a longer duration of treatment with DA can promote the development of ICDs.
	Pezzella FR. et al. [45]	202 PD	The authors demonstrate a significant correlation between ICDs and previous use of DA, both in monotherapy and in combination therapy.
	Gallagher D.A. et al. [29]	177 PD	The authors found that a large proportion of patients with PG were taking a dose of DA greater than the maximum authorized dose.
	Ondo W.G. et al. [64]	300 PD	Authors found that increased reward-seeking behavior or impulsivity is common in patients taking DA for PD.
	Weintraub D. et al. [18,36]	3090 PD	Dopamine agonist treatment in PD is associated with a higher probability of ICD.
	Voon V. et al. [59]	297 PD	PG was associated with dopamine agonists but not with agonist subtype or dose.
Cognitive and psychiatric impairments (as impulsivity, novelty-seeking, anxiety, depression)	Voon V. et al. [46]	282 PD with ICDs/ 282 PD without ICDs	ICDs are associated with multiple psychiatric and cognitive impairments.
	Potenza M.N. et al. [47]	7869	The correlation between PG and Major Depression in middle-age appears to be largely influenced by overlapping genetic factors.
	Romer Thomsen K. et al. [48]	20 PD with PG/20 CG	The authors found a correlation between depression levels and PG.
	[57]	607 PD	The authors showed that risk factors for ICD include male sex, young or younger age at the onset of PD, a pre-PD history of ICD symptoms, history of substance use or bipolar disorder, and a personality profile characterized by impulsivity.
	Grucza R.A. et al. [63]	60 PD	BED are associated with psychiatric co-morbidity.
Gender	Joutsa J. et al. [50]	290 PD	The gender is associated with the ICDs.
	Giladi N. et al. [44]	193 PD/190 CG	The study shows that the male gender can be considered among the risk factors for the development of ICDs.
Younger-onset	Sossi V. et al. [49]	27 PD	Patients with younger onset have more motor and cognitive complications.
	Voon V. et al. [59]	297 PD	PG was associated with earlier PD onset and with DA, but not with agonist subtype or doses
	Giladi N. et al. [44]	193 PD/190 CG	The study found that younger age of PD motor symptom onset might be considered as a risk factor for the development of ICDs.
Current cigarette smoking	Weintraub D. et al. [18,36]	3090 PD	Smoking cigarettes can be associated with the development of ICDs.

ICDs, Impulse Control Disorders; PD, Parkinson Disease; CG, Control Group; PG, Pathological Gambling; DA, dopamine agonist; BED, Binge Eating Disorder.

associated with ICDs are: personality traits of high novelty-seeking [56] or of impulsiveness [57]; depression [58]; male sex [59,60]; substance abuse [61]; younger age; younger age of PD onset [60]; concurrent L-dopa use [55]; longer duration of treatment with DAs [44]; being unmarried [62]; pre-PD history of ICDs [61]; current cigarette smoking; having more formal education; family history of substance abuse or of ICDs [36]; preserved executive functions; higher aggressiveness; irritability; disinhibition and eating disorders [63]. Age at onset and novelty-seeking personality traits are the two strongest predictors of DDS [64].

5. The pathophysiological mechanisms of ICDs

Some studies have shown that a biological and temperamental feature may predispose to the development of ICDs in PD. Two important dopaminergic circuits are the mesolimbic and mesocortical pathways (Fig. 1). The mesolimbic via is responsible for reward learning, while the mesocortical via is responsible for executive decision-making. The dysregulation of these circuits leads to the clinical manifestation of impulsive and compulsive behaviors. The mesocorticolimbic dopaminergic network links the key cortical and subcortical regions, especially the prefrontal cortex (PFC), ventral striatum, ventral tegmental area (VTA), and amygdale [65]. Also, the nucleus accumbens (NAc) plays a crucial role in learning reinforcement. The mesocortical pathway is important for executive functions, as the prefrontal cortex projects to the ventral striatum [66]. ICD behaviors emerge after exposure to certain rewards, which over time become compulsive in nature [67]. During the first instance of a reward, there is an “unexpected” activation of the ventral striatum, eliciting a strong emotional response, and an increase in ventral striatal dopamine [68]. After this action is repeated, the behavior starts to become a “habit”, and may be associated with craving [65]. At first time, this behavior probably localizes at the ventral striatum; later, behaviors are reinforced by the dorsal striatum [69].

A [11C]-raclopride study in cocaine-addicted subjects shows that patients have a greater release of dopamine from the dorsal, but not the ventral striatum. This finding has not been replicated in PD-associated reward behaviors, but deserves further study. The compulsion stems from the dorsal striatum, as this is useful in the maintenance of drug-seeking behaviors with little activity by the NAc [70]. This mechanism shows how an action can become a compulsive behavior as the shift from the ventral to dorsal striatum occurs [67]. The corticostriatal glutamatergic, nigrostriatal dopaminergic systems and striatal medium spiny projection neurons are critically involved in the control and integration of motor information [71]. Besides movement disorders, the dysfunction of these systems could lead to altered reward signalling with subsequent behavioral changes [72]. Regarding the neurotransmitter aspects, dopamine receptors are differentiated by their mechanisms of action:i) D1-type receptors (subtypes D1 and D5) modify gamma-aminobutyric acid (GABA) transmission directly to the globus pallidus interna and subsequently the substantia nigra pars reticulate; ii) Dopaminergic D2 type (subtypes D2, D3, D4) receptors modify substantia nigra pars reticulata activity in a different manner. D1-type and D2-type receptors are responsible respectively for the excitatory and the inhibitory signalling. In fact, the striatum projects to the inner segment of the pallidus through two main ways, with opposite end effects. The direct pathway (directly connecting the striatum and the internal segment of the pallidus) with final excitatory effect via D1-type receptors; the indirect pathway (connecting the striatum and inner segment of the pallidus passing through the outer segment of the pallidus and the subthalamic nucleus) with the final inhibitory effect, through D2-type receptors. These two receptor families have

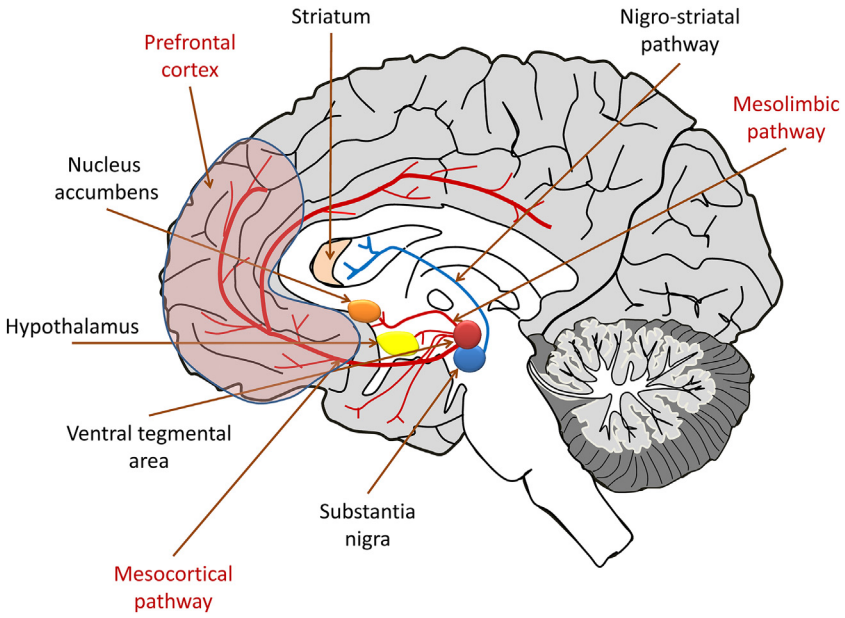

Fig. 1. The neural pathways involved in impulse control disorders.

contrasting roles with regard to reward-based decision making, where D1-type receptors localize to the direct pathway reward-based behaviors, whereas D2-type in the indirect pathway [73]. The direct pathway is associated with cue-based reward responses. When an unexpected reward occurs, D1-receptor-mediated phasic signalling results in a "positive" response, through an increased stimulation of striatal projections to the nucleus accumbens (NAc)/ventral striatum. On the other hand, it is thought that D2 receptors play an opposing role to the D1 receptors, signalling or negative behavior and eliciting suppression of the cortico-accumbens network [74]. In fact, in a PET study, carried out in PD patients with and without ICDs, showed that during a gambling task those with ICDs had reduced binding to D2 receptors in the ventral, but not the dorsal striatum, demonstrating that they might have difficulty in relating negative valence to actions. Impulsive choice correlates to reduced D2 receptor expression on the ventral striatum, whereas an unopposed stimulation of the direct pathway and D1 receptors and stimulation of the dorsal striatum, may bias reward-based choice [75]. Given that BED and PG share the same pathways, the progression of BED can cause an impairment in the dopamine signalling in the reward circuit [76]. The manifestation of BED is linked to changes of dopamine regulation in the ventral striatum and alterations associated to dopamine receptor biology. In a functional magnetic resonance imaging study comparing obese individuals with and without BED, those with BED had decreased ventral striatal activation in reward stimuli [77]. It can be connected to atrophy of the ventral striatum in BED individuals [78]. These findings are associated with reduced D2-receptor availability in obese BED patients [79]. Another neuroimaging study has shown that PG is related to the reduced activation of the mesolimbic reward system [80].

6. PD personality and dopaminergic deficit

ICDs could be related to a novelty seeking loss, which is related to specific biological and brain configurations. In particular, the symptoms are characterized by a compulsive reward-seeking behavior, and likely reflect dopamine effects on the mesolimbic and mesocortical networks [81], which receive dopaminergic inputs from the ventral tegmental area- (VTA-) associated networks. Second-generation non-ergot DAs are the most common risk factors for ICDs, and the preferential selectivity for D2-like receptors (D3 and D2 types), which are co-localized to the mesocorticolimbic system, may explain the unique side-effect profile for this class of medication [82]. Even before receiving dopamine therapy, PD patients may develop personality alterations, which may reflect changes to this mesocorticolimbic system. Descriptions such as "harm-avoidant," "introverted" and "meek" are often attributed to the PD-personality phenotype. These descriptions generate from cross-sectional studies and are difficult to experimentally replicate, but overall, PD patients are thought to display increased caution and be risk averse prior to diagnosis [83]. Termed as *Parkinson's disease personality*, these characteristics are certainly not predictive of a patient developing PD, as others have not replicated this personality as a risk factor or precursor for PD in larger longitudinal cohorts [84]. Notably, PD patients with impulsive and compulsive behaviors make immediate and uninformed decisions and compulsively pursue activities to receive reward. Another clinically troubling symptom that contrasts the PD-personality phenotype is DDS, characterized by a patient's compulsive desire to take and increase dopaminergic medication dosage to maintain their "high" (when in "on" state) or avoid the "lows" (when in "off" state) associated with the non-motor fluctuations commonly encountered with levodopa therapy [85]. The mesocorticolimbic network is the biological link between ICDs and DDS. In fact, the dysregulation of the reward pathways is responsible for these symptoms [86].

7. Future directions

The percentage of PD patients with ICDs is underrated and there is a need for their better management, which includes providing the patients and their caregivers with information useful aimed to grant them a better quality of life. The discussion and treatment of these problems in PD patients enters the framework of a holistic approach. From this review, it is evident that the main concerns of ICDs studies are related to the lack of standardized assessment and selection of the sample. In particular, the use of tools with unverified psychometric properties make the results obtained not comparable with others. Thus, standardized tests need to be used to evaluate the type and severity of the ICD and improve the assessment phase, and consequently the diagnosis. Moreover, not all the aforementioned studies used international criteria for PD diagnosis, with possible inclusion of patients affected by different parkinsonisms.

Furthermore, the link between the PD and the development of ICD has not been widely investigated in the literature. Thus, further prospective studies with larger samples are needed to detect those risk

factors responsible for producing behaviour changes in PD patients with ICD.

8. Conclusions

This review focuses on risk factors, pathophysiology and personality traits in patients with PD with ICD. To date, the link between PD and ICD development is not clear. The review suggests the presence of intrinsic and extrinsic factors that may be involved in the development of behavioral complications. Indeed, dysfunction of the mesocorticolimbic pathway and dopamine receptors may contribute to the development of impulsive behaviors in the presence of specific risk factors, drugs and premorbid personality. Further studies are needed to clarify the basic pathophysiology of the ICD in order to identify new, more effective and safer therapeutic targets.

Disclosure statement

The authors have no potential conflicts of interest to disclose. All of them are responsible for the content and writing of this paper.

Authors' contributions

All authors substantially participated in the acquisition of data and the revision of the manuscript. All authors determined the design, interpreted the data and drafted the manuscript. All authors read and gave-their final approval for the version submitted for publication.

Acknowledgments

We wish to thank Dr. Antonio Leo for figure drawing and Prof Agata Grosso for English editing.

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