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Review

IMPULSIVITY IN PATIENTS WITH PARKINSON'S DISEASE

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Summary

In recent years focus has been increasingly placed on impulse control disorders (ICDs) in patients with Parkinson's disease (PD). ICDs include pathological attraction to gambling, compulsive shopping, compulsive eating and compulsive sexual behaviour and are associated mostly with the intake of dopamine agonists. Another impulsive and compulsive behaviour in PD is the dopamine dysregulation syndrome, which is associated with compulsive intake of L-dopa, and short-acting dopamine agonists. Diagnostics and prevention of this group of disorders is essential, considering the difficulties related to their treatment and their negative impact on the patients themselves as well as on their relatives.
Key words: dopamine, impulsivity, Parkinson's disease

Introduction

In recent years attention is paid increasingly on various neuropsychiatric manifestations of Parkinson's disease (PD) such as depression, anxiety, cognitive affection, psychosis, and impulse control disorders (ICDs). ICDs are associated with deeper functional affection, lower quality of life of patients and significant distress for their relatives, hence their identification, monitoring and treatment in the clinical practice is crucial.

Definition and Classification

Key characteristic of ICDs is impulsive behaviour, which can be defined as the failure to resist an impulse, drive, or temptation to perform an act that is harmful to the person or others [1, 2]. The group of ICDs in patients with PD under treatment with dopaminergic drugs includes unhealthy addiction to gambling, compulsive sexual behaviour, compulsive shopping and compulsive eating disorders [3, 4]. Similar disorders observed in patients with PD include: 1) dopamine dysregulation syndrome associated with excessive intake of dopaminergic drugs, L-dopa and short-action dopamine agonists in particular; 2) carrying out repetitive, aimless acts such as aimlessly moving, rearranging or collecting objects; 3) carrying out repetitive aimless acts of higher order such as

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excessive aimless wandering, internet browsing or reading; and 4) compulsive hoarding [5-7]. Taking into consideration the similarity between ICDs (in terms of risk factors, clinical picture, cognitive changes, neurobiological substrate and therapeutic approach) and the addiction to psychoactive substances, in the latest edition of the Diagnostic and Statistical Manual of Mental Diseases published by the American Psychiatric Association, pathologic addiction to gambling has been moved from the category of ICDs to a new category: "Substance-related and addictive disorders" [1]. This disorder is characterised by over-involvement with gambling, spending large amounts of money, anxiety or irritability when the activity has to be ceased, lying to others on gambling-related matters and unsuccessful attempts to control the condition. Hypersexuality is characterised by over-involvement with sexual thoughts, need for sex, desire for sex, need for frequent genital stimulation, use of sex telephone lines and watching porn websites. Compulsive shopping may be described as repetitive, impulsive and excessive buying of unnecessary items, resulting in financial issues [8]. Compulsive overeating is characterized by uncontrolled consumption of particularly large quantities of food exceeding the need to quench hunger. The dopamine dysregulation syndrome is described as a condition in which patients take dopaminergic drugs in doses exceeding the need to control motor symptoms with all resulting negative consequences [5]. In hobbyism, which may lead to highly debilitating stereotyped behaviour, patients usually engage in collecting different objects, cleaning, repairing or writing [6]. Compulsive hoarding means that patients are unable to discard items of little or insignificant material value and therefore often leads to excessive accumulation of unnecessary objects [9].

Prevalence of ICDs in PD

The largest study focused on the prevalence of ICDs and their relation to the intake of dopaminergic medications by patients with PD has shown that 13.6% of patients with PD meet the diagnostic criteria for such a disorder, with problem gambling or pathological addiction to gambling in 5%, compulsive sexual behaviour in 3.5%, compulsive shopping disorder 5.7%, and binge eating in 4.3% [10]. ICDs are more common in men, in patients with early onset of PD or patients with personal or family history of addiction to psychoactive substances, bipolar affective disorders or problem gambling [7]. Furthermore, ICDs occur more frequently in patients treated with dopamine agonists than in patients treated with L-dopa alone. ICDs were observed in 14% of patients treated with a dopamine agonists only, in 17.7% of patients treated with both dopamine agonist and L-dopa, and in 7.2% of patients on L-dopa treatment only [10]. Another interesting result from the same study is the absence of statistically significant difference in ICD frequency between patients treated with two of the most commonly used dopamine agonists: pramipexole and ropinirole. The authors further established a correlation between L-dopa dosage and frequency of ICDs, whereas such correlation was not present in dopamine agonists.

Neuroanatomical Substrate and Mechanisms of Emergence of ICDs in PD

The ventral frontostriatal limbic circuit includes the orbitofrontal cortex, the ventromedial prefrontal cortex, the ventral striatum and the limbic connection with the amygdala, the anterior cingulate cortex, and the anterior insula [11, 12]. The ventral system is responsible for the so-called "automatic" behaviour [13]. The dorsal frontostriatal circuit that includes the dorsolateral prefrontal cortex, caudate nucleus and other structures associated with the circuit is responsible for the executive functions (i.e. working memory, planning, strategy elaboration and cognitive inhibition). It is well-known that when choosing delayed gratification, the dorsolateral prefrontal cortex modulates the activity of the ventromedial prefrontal cortex. The loss of balance between these two systems and the over-activation of the limbic structures lead to the impossibility for the individual to resist reward despite future negative consequences [11]. According to the limbic/executive theory, the decision-making process is a balance between "hot" and "cool" cognitive functions commonly called "emotion" and "cause" [12, 14].

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So far, there is no reliable data concerning the dosage and duration of intake of a specific medication leading to the onset of ICDs in PD patients. It has been established that upon starting treatment with dopaminergic medications PD patients report increase by more than 20% in the subjective feeling of impulsivity. These results show that dopaminergic medications cause a mild but sure increase in reward seeking behaviour [15]. Many studies have demonstrated that high dopamine levels result in behaviours oriented towards seeking quick rewards despite the higher risk. Dopamine neurons in the ventral tegmental area encode phase positive and negative consequences. Upon positive response, the activity of dopaminergic neurons increases. On the contrary, in the case of negative outcome, the activity of dopaminergic neurons decreases. These changes in the activity of dopaminergic neurons are signals used for training [16]. It has been found that in PD patients in an "off" phase there is no increase in dopaminergic neurons activity, which in turn is associated with loss of capacity to learn behaviours relating to positive consequences. To the difference of these, in PD patients in the "on" phase there is no decrease in dopaminergic neurons activity in case of behaviour with negative consequences [16]. Dopaminergic projections from the ventral tegmental area reach nucleus accumbens, which is considered a key structure in the rewarding process. L-dopa is known to inhibit the activity of nucleus accumbens in patients at early stages of PD.

The neurodegenerative process in PD does not equally affect the different dopaminergic pathways. Neurodegeneration starts from dorsal structures and affects ventral structures at a later stage. Initially, the nigrostriatal pathway is affected, resulting in clinical manifestation of motor symptoms of PD. Later on, the mesocortical pathway is also affected, leading to executive functions disorders. The mesolimbic pathway is the last to be affected by the degeneration process. Therefore, the dose of dopaminergic medications required to influence motor symptoms improves the function of the dorsal system but has an adverse effect on the ventral limbic system, which is responsible for rewarding processes [12, 17].

Additionally, dopamine agonists have higher D3:D2 and D3:D1 receptor ratios of activation, as compared to L-dopa [18]. D1 and D2 receptors are situated in the dorsal striatum and their activation is associated mainly with the effect on motor symptoms. In contrast, D3 receptors are located mainly in limbic cervical areas, including the ventral striatum, and their activation is most probably associated with psychiatric manifestations of anti-Parkinson's medications [19]. Many studies on pramipexole, which is a D2/D3 receptor agonist, associate the intake of the medication with the onset of ICDs. According to the limbic/executive theory, pramipexole stimulates the limbic circuit and leads to the onset of cognitive impulsivity. A single administration of low doses of pramipexole stimulates mostly presynaptic D2-receptors, which in turn results in decrease of dopaminergic transmission. On the contrary, chronic administration of high doses of pramipexole leads to a postsynaptic stimulation and increase of dopaminergic transmission [20].

Changes in the reward-related decision-making process occur as a result of the incapacity to control behaviours with favourable short-term outcome but associated with negative long-term consequences. Similar changes have been observed in patients addicted to psychoactive substances [21]. Literature unanimously confirms that the limbic system plays an essential role in these processes [12, 22], but the question whether the limbic system is overactivated or inhibited is still disputable. One of the current hypotheses explains the manifestation of psychoactive substances-related disorders and ICDs with inefficient activation of the mesolimbic pathway under the influence of natural rewards [12, 23], and the impulsivity as a mechanism used to counterbalance deficit in the rewarding system. According to that theory, natural rewards are recognised as positive, but the strength of their rewarding effect is insufficient. The decreased activation of structures in the rewarding circuit observed in PD patients after administration of pramipexole can be explained in a similar way. Contrary to it is the hypothesis of hypersensitivity to rewards, based on studies that have demonstrated that patients with high results from the self-assessment sensitivity to rewards also exhibit increased cognitive impulsivity [22], and that the mesolimbic dopaminergic transmission positively correlates with the self-assessment impulsivity and the sensitivity to

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rewards [24]. Furthermore, it is well known that D-amphetamine increases both the dopaminergic neurotransmission and the motivation for gambling in patients with pathologic gambling disorders, which involves understanding that dopaminergic neurotransmission and reward motivation are in close correlation [25].

Evaluation Instruments

ICDs often remain undiagnosed in PD patients, as they rarely report that kind of complaints. Before starting and during treatment with dopaminergic medications, detailed history should be taken not only from patients but also from their relatives, so that ICDs can be diagnosed promptly. The Questionnaire for Impulsive-Compulsive Disorders in Parkinson's disease – rating scale [26] has proved to have good psychometric capacities as a screening instrument. Another screening scale used to rate impulsive-compulsive behaviours in PD is the questionnaire for dopamine dysregulation syndrome [27]. The impulse control scale in PD was created to assess sub-syndrome and syndrome forms of impulsive compulsive disorders and has proved to be reliable and sensitive [28]. Widely used in clinical practice is Barratt's impulsiveness scale [29]. Personality traits such as "sensation-seeking", "novelty-seeking" and "reward dependence" are assessed using various self-evaluation questionnaires like Cloninger's Temperament and Character Inventory [30]. Motor impulsivity and response inhibition can be measured using Go/No-Go tasks or the Stroop Effect Test [31] and decision-making impulsivity can be assessed using Cambridge Gambling Task or the Iowa Gambling Task [32]. Another test used to assess risk taking behaviours in the process of decision making is the Balloon Analogue Risk Task, the results of which correlate with results obtained from self-assessment impulsivity rating scales. Tests like the Delay discounting task are used to study individual's preference for smaller but immediate rewards rather than for greater but delayed in time rewards [33].

Treatment

The treatment of ICDs in PD is often reduced to decreasing the dose of dopaminergic drugs, replacing the dopamine agonist or completely ceasing the administration of dopamine agonist [34, 35]. A study of the long-term clinical results in patients with PD and ICDs has found that in 80% of patients dopamine agonists have been discontinued or the dose has been reduced resulting in partial improvement or complete disappearance of ICDs. There is literature data on improved impulsive-compulsive symptoms in PD under the influence of quetiapine and clozapine [36, 37]. Some studies have found improvement of ICDs after deep brain stimulation or intrajejunal administration of L-dopa [38].

There are more and more indications that dopamine agonist treatment is associated with the onset of various ICDs in some PD patients. Impulse control disorders have adverse effects on patients, their relatives and society as a whole. Therefore, prevention and treatment of these conditions is complex and involves careful clinical evaluation and dosage of dopamine agonists, as well as thorough training of patients.

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