Impulse Control Disorders in patients with Parkinson's Disease

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Abstract

In patients with Parkinson's disease with higher prevalence than in current population there appear pathological behaviours characterized by compulsion, repetitiveness and impulsivity, which are connected with material profit or pleasurable experience. They are, in particular, pathological gambling, hypersexuality, compulsive shopping and compulsive eating (in the literature they are collectively referred to as impulse control disorders). Pathological preoccupation with repeated mechanical activities (so-called punding) and excessive compulsive intake of dopaminergic medication (so-called dopamine dysregulation syndrome or also syndrome of hedonistic homeostatic dysregulation) are of similar nature. The paper treats briefly the risk factors and prevalence of these pathological behaviours. In current clinical practice, these psychiatric complications frequently escape doctors' attention, they are underdiagnosed. Although no generally valid recommendations for their therapy are currently available, they can be influenced medically. Of advantage can be modified dopaminergic medication (usually dose reduction of dopaminergic agonists); multidisciplinary approach to the problem is appropriate.

The pathological behaviours given above can frequently lead to considerable material losses and markedly aggravate patients' handicap in the social sphere; it can be expected that in the future they can become a problem also from the ethical and legal points of view.

Key words: Parkinson's disease; impulse control disorders; pathological gambling; hypersexuality; punding; dopamine dysregulation syndrome; dopaminergic agonists.

Introduction

The quality of life of patients with Parkinson's disease (PD) can considerably be affected by some non-motor symptoms from the psychic region. In addition to the relatively frequent depression or impairment of cognitive functions, it concerns pathological impulsive excessive and/or repetitive behaviour – pathological gambling, hypersexuality, compulsive shopping or compulsive eating; they are collectively referred to as impulse control disorders (ICD). They also include other types of behaviour such as pyromania and trichotillomania, which are probably of no profound significance in patients with PD. Figuratively speaking, ICD can be understood as sort of "behavioural addiction". Also, patients may come to pathologically occupy themselves with repetitive mechanical activities (punding) or excessive compulsive overuse of dopaminergic medication, so-called dopamine dysregulation syndrome (DDS). The above pathological behaviours can markedly aggravate patients' handicap in the social sphere and cause considerable material losses (1, 2).

Diagnostics, prevalence, risk factors

Pathological behaviours that are referred to as ICD exhibit a number of common symptoms: They are associated with strong compulsion, and any effort aimed at controlling them brings an unpleasant feeling of internal stress. These behaviours are associated with a desire to be rewarded – be it a material gain or some pleasant experience. This is explained by the interference of damaged system of dopaminergic transmission (due to the pathological process itself or the dopaminergic therapy used) with the brain reward system (see below). The behaviours appear repeatedly (frequently or even stereotypically) or in waves (excessively).

Diagnostic criteria of individual ICD are embodied in the Diagnostic and Statistical Manual of Mental Disorders – fourth edition (DSM IV) and in the International Classification of Diseases and Related Health Problems. The diagnostics is based on anamnestic data, which are verified using goal-directed questionnaires. A number of such questionnaires are currently available; some authors modify

them or prepare new ones to be used in their studies. The Minnesota Impulse Disorders Interview (MIDI) is commonly used for ICD screening. There is also another successful screening questionnaire, namely the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP) (3). Data on ICD prevalence given in available studies frequently differ, which is due to the application of different diagnostic tests. In view of the great cultural diversity it can be expected that data on ICD prevalence in the populations of individual countries will differ considerably (the opinion on what is normal, for example, in the area of gambling or sexuality is not uniform in different countries). Generally it holds that the tests used are usually based on subjective evaluation and their results are thus influenced by the patient's motivation for truthful answers. Patients often do not regard ICD as a serious problem and thus they mention them to their doctor only rarely while doctors during a current medical examination seldom inquire about potential pathological behaviours. ICD thus often remain unnoticed and are therefore underdiagnosed in patients with PD and their actual prevalence is probably higher than reported (2, 4).

PATHOLOGICAL GAMBLING

Pathological gambling (PG) in patients with PD was described for the first time in 2000 (Molina *et al.*) (5). The first to appear were casuistries or descriptions of smaller groups of patients (6, 7); today, extensive studies exist that focus on the prevalence of the PG risk factors (8-11).

PG is defined as persistent and recurrent unfavourable behaviour with respect to a game of chance, often characterized by obsession and preoccupation with the game, increasing amounts of invested money, repeated unsuccessful attempts to limit or give up gambling, irritation and restlessness accompanying the attempts to limit gambling, resorting to gambling as a means of avoiding problems, efforts to win back the money lost, lying to one's nearest because of gambling, acting illegally in order to procure money for gambling, neglecting and losing family relations, education or career, relying on others as regards financial means (according to DSM IV).

To assess PG, the South Oaks Gambling Screen questionnaire is used worldwide.

Johnson *et al*. give two questions as a screening tool:

1. Did you ever feel the need to win more and more money?

2. Did you, because of gambling, have to lie to people who are important for you?

Positive answers to the two questions probably indicate PG but it is necessary to take into account false negative results (12).

Lifelong PG prevalence in PD patients is given between 2.3-9.3% in systematic studies (1). In a prospective study covering 297 PD patients monitored at a Toronto clinic, a lifelong PG prevalence of 3.4% was established. In a group of patients who used medicines from the group of dopaminergic agonists the lifelong prevalence was higher -7.2%. For comparison, lifelong prevalence among the common Ontario population is 1% (8). PG risk factors among the common population are in particular: male sex, alcohol abuse, tendency to impulsive behaviour, disorders of cognitive functions or tendency to sensation- and novelty-seeking. In PD patients, the following risk factors were established: being on dopaminergic agonists (subsequent analysis proved a higher risk in a therapy combined with L-DOPA while for monotherapy with dopaminergic agonist no higher risk was proved; also, there are not enough data to enable comparing the PG risk when taking various types of medicine from this group, and no unambiguous correlation was established between the risk and the total dose of dopaminergic agonist) (11); earlier age at PD onset, higher tendency to novelty-seeking, personal or family history anamnesis of alcohol abuse, medication-induced mania or hypomania, reduced tendency to planning and increased tendency to impulsive behaviour. PG is less significantly associated with factors such as left-hemisphere PD onset or young age. Correlation with the disease duration, length of L-DOPA or dopaminergic agonist medication, and agonist dosage has not been proved unequivocally (as mentioned above) (2, 9, 10).

HYPERSEXUALITY

Hypersexuality is characterized by excessive preoccupation with thoughts turned to region of sexuality, inappropriately or excessively requesting sex from spouse or partner, promiscuity, compulsive masturbation, searching for pornography or resorting to sex phone services; sometimes it can be associated with paraphilia (transvestite fetishism, paedophilia, zoophilia, sadomasochism); sexual behaviour causes stress and interferes with patient's everyday activities (1, 4).

According to an international cross-sectional study using MIDI, hypersexuality prevalence in PD patients is 3.5% (13). The following are regarded

as risk factors: male sex, earlier disease onset, dopamine agonist therapy, and depression (1, 14). On the other hand, some reports refer the improvement of the sexual erectile dysfuntions during the treatment with dopamine agonists (15-18).

COMPULSIVE SHOPPING, COMPULSIVE EATING

Compulsive shopping amounts to excessive irresistible intrusive compulsion to buy often absurd and unnecessary things, spending money beyond what the patient can afford; shopping frequently takes up a lot of time, it can cause stress, interfere with patient's everyday activities and bring about financial problems. Diagnostic criteria after McElroy are available. Diagnostics leans on MIDI, and in some international studies Lejoyeux's Compulsive Shopping Questionnaire is used (4). In an extensive cross-sectional study, Weintraub *et al*. established a prevalence of 5.7% (13).

Comparatively few data are available on compulsive eating in PD patients; Niremberg and Waters described seven cases of PD patients whose compulsive overeating was caused by taking dopaminergic agonists. However, data on overall prevalence in PD patients are not available (1).

Several of the ICD given above can often occur in patients simultaneously, the same as punding (described below) or dopamine dysregulation syndrome. ICD prevalence in patients under treatment is usually given around 14%; it is strikingly higher in patients treated with dopamine agonists -17.1% (1, 13, 14, 19, 20). Every third patient with ICD exhibits more than one type of ICD (1, 20, 21).

PUNDING

Punding is pathological preoccupation with repetitive, excessive, purposeless mechanical activities: they may be simple activities such as rearranging things on table, taking things into pieces and putting them together, but also more complex activities such as hobbyism (excessive preoccupation with hobbies, e.g. gardening) or excessive use of the Internet (4). Evans *et al*. give in their study a punding prevalence of 14% in PD patients (22). The risk factors given here are younger age at disease onset, concomitant using of dopaminergic agonists, higher impulsivity, and lower quality of life in connection with PD (1).

DOPAMINE DYSREGULATION SYNDROME

The term dopamine dysregulation syndrome (also called hedonistic homeostatic dysregulation syndrome) is taken to mean compulsive use of dopaminergic medication beyond the measure necessary for adequately influencing motor symptoms, irrespective of medication-induced undesirable effects such as massive dyskinesias. Reduced medication leads to a relative hypodopaminergic state, which shows clinically by symptoms similar to the abstinence syndrome; in an effort to secure medication the patients can become aggressive towards their environment. The on phase may be associated with an urge to walk or travel (1, 4). DDS has been described in more than 4% of PD patients; the description for patients with DDS includes lower age at the onset of the disease, longer PD duration, higher intake of dopaminergic drug medication, greater experimental drug abuse in the past, higher depressivity and impulsivity, and higher alcohol intake in comparison with PD patients without DDS (23).

Pathophysiology

ICD are characterized by being motivated by pleasurable experience. Association can be seen here with the brain reward system, where dopaminergic neurotransmission plays an important role. It is known that the basic pathophysiological moment of Parkinson's disease is a reduced activity of dopaminergic neurons in the nigrostriatal pathway, i.e. also a disorder of dopaminergic neurotransmission. Dopaminergic medication adjusts this dopamine deficit in a nonphysiological way, which may interfere with the activity of dopaminergic neurons in various regions of the brain.

In drug addicts, long-term reduction of the number of dopamine inhibition D2 receptors in the striatum region was established; this may further affect activities in the region of frontal lobes connected within the functional circuits of basal ganglia. In cocaine addicts, reduced activity of dopaminergic neurons was established. All this can explain the reduced response of functional circuits involved in the brain reward system to physiological stimulation (24, 25).

It was further observed in drug addicts that increased tonic dopaminergic stimulation affects dopamine autoreceptors and results in decreased reward-related phasic dopamine. This state represents sort of dopamine deficit, which requires additional dopaminergic stimulation, for example behaviour associated with a pleasurable experience (26).

The time pattern of physiological release of dopamine from neurons from the ventral tegmental area to the nucleus accumbens is linked to the reward and its expectation. Phasic release of dopamine is associated with expecting a reward or with gaining a reward that was not expected. Phasic suppression

of dopamine release is associated with a situation when the reward is expected but does not materialize. The strength of the response depends on the magnitude of the reward. Tonic release of dopamine is associated with maximum reward uncertainty. A situation with much reward uncertainty, e.g. a game of chance, can in itself be stimulation and simultaneously a reward (27). Dopamine stimulation in PD therapy may interfere with the above time patterns of physiological dopamine secretion and thus affect the process of reward-based learning. For example, there may be a distorted feedback in the case when the reward did not materialize; in the given situation, the patient will continue expecting the reward (4).

The effect of dopamine on reward-and-punishment-based learning was proved experimentally. After administering dopamine to healthy people, the positive effect of reward was strengthened in the learning process but not the negative effect of punishment (28). PD patients with discontinued medication were observed to have reduced ability to learn on the basis of positive reward motivation whereas their ability to learn a behaviour leading to punishment avoidance was more pronounced. After administering dopaminergic medication, the situation changed – the positive effect of reward was enhanced and the ability to learn on the basis of negative experience was reduced (29).

ICD occur to a large extent in patients taking medicines from the group of dopaminergic agonists, which act postsynaptically by stimulating the dopamine receptors. By contrast, L-DOPA acts presynaptically – it is the precursor of dopamine, into which it is transformed in neurons; dopamine release thus comes closer to the physiological state (4).

In connection with ICD, considerable attention is devoted to the processes of decision making and reward-and-punishment-based learning. In the study of decision-making processes, the Iowa Gambling Task (IGT) test is used, which was introduced by A. Bechara in a study focused on impaired decision making in patients with damaged ventromedial prefrontal cortex; the test was created to prove the validity of the Somatic marker hypothesis, which explains decision making in situations when the result of choosing is not unambiguous at first glance. In the course of IGT, the person being examined is required to repeatedly choose from four decks of cards that yield prizes and penalties (which are not predictable at first glance); the task is to obtain maximum gain. Two of the packs bring big immediate prizes but sometimes also large losses; on balance, they are disadvantageous. The other two packs bring small immediate prizes but the losses are also small

and from the viewpoint of long-term strategy these packs can be seen as advantageous (30). IGT results for PD patients were compared with a set of psychological tests, inclusive of an examination of cognitive functions. IGT was found to be suitable for the study of limbic functions in PD patients. No connection was found between the success rate in IGT and the length of disease or motor status and severity of the disease (Unified Parkinson's disease rating scale, Hoehn and Year scale). Thus it can be assumed that patients' impaired decision making does not develop simultaneously with motor symptoms or that its manifestation can be delayed by compensatory mechanisms (31). When detecting skin conductivity as a somatic marker of emotional state, PD patients generated in the course of IGT a smaller change as the reaction to reward or punishment in comparison with the control group; a smaller response was also observed in the course of anticipating a prize or a loss – in contrast to the control group no significant difference was evident in the patients when choosing between the advantageous and disadvantageous pack (2, 32). Positron emission tomography (PET) confirmed lower activity in the region of medial orbitofrontal cortex in the course of doing the IGT test with PD patients in comparison with healthy subjects. If we start from the model of functional loops of basalganglia, the finding testifies to the limbic loop being damaged but not the cognitive loop (33).

PD patients may differ by certain perceptiveness of and sensitivity to ICD development. Besides the above risk factors, genetic factors are taken into consideration – this concerns, in particular, the gene for dopamine transporter or the polymorphism of the gene for receptor D2 (34, 35).

Prevention and therapeutic measures

Currently there is not enough information to enable determining generally valid therapeutic or preventive measures in the area of ICD in PD patients.

It is important to diagnose ICD in time, i.e. it is necessary to ask the patients about ICD as part of regular check-ups and, in case of doubt, to have this information objectivized by the patient's family (with the patient's knowledge, of course). In patients exhibiting any risk factors (e.g. onset of disease at early age, alcoholic abuse anamnesis, tendency to seek novelties) it is opportune to avoid some therapeutic practices such as bolus doses of L-DOPA or intermittent injection administration of apomorphine (1). Interdisciplinary approach – cooperation with a psychologist and psychiatrist – is required in

the course of treatment. Regimen measures are often quite effective but they require cooperation with the patient's family. In the case of PG or compulsive shopping it is advisable to have finances controlled by another person and cash cards cancelled; access to the Internet should be limited and web sites with games of chance should be blocked (1, 2, 4). In the case of DDS there should be gradual reduction of medication. This, however, requires cooperation between the family, general practitioner and usually also psychiatrist. Frequently, it is necessary to make this change in medication during hospitalization (1), and, e.g. continuous apomorphine infusions instead of interminent injections of apomorphine (36), or amandatine sulphate infusions (37) could be given to the patients, if necessary.

Reducing the dosage or discontinuing the administration of dopaminergic agonists or substituting another drug from this group is frequently an effective therapeutic measure. Recently an effect of amantadine was described in a double blind crossover study in a group of 17 PD patients with PG; daily adminstration of 200 mg amantadine abolished or reduced PG in all treated patients (38). The case has been reported of a patient with punding, which was in remission after amantadine treatment (39). Individual cases have been described when in PD patients ICD were favourably affected by means of donepezil, small doses of risperidon, and medicines from the group of selective serotine reuptake inhibitors (SSRI) (23, 40, 41).

In a retrospective study, an adjustment of ICD is reported in patients after the beginning of deep brain stimulation (DBS) of subthalamic nucleus. This effect can be explained by the subsequent reduction of dopaminergic medication after the beginning of stimulation, by the specific effect on motor symptoms with stimulation targeted at a specific narrow region of the brain, and by changing the pulsatile stimulation to chronic stimulation. There are, however, also cases when ICD newly appeared in patients only after operation (2, 42). In the case of DBS indication, patients should be examined psychologically, exactly with a view to ICD; their pre-operative presence in patients is associated with the risk of subsequent tendency to self-inflicted injuries in the post-operative period. In the post-operative period, attention also needs to be devoted to the development of potential psychopathology (43).

Conclusion

ICD participate in impairing the quality of life of PD patients and greatly aggravate their handicap in the social sphere. Considerable attention is currently devoted to the study of ICD in PD patients. So far, not enough information is available to establish generally valid recommendations for their therapy. Nevertheless, they can be therapeutically affected. In PD patients it is imperative to take ICD into consideration and to recognize them in time. It frequently happens that for a long time they escape doctors' attention and therapeutic measures are taken only at a time when the patient has suffered considerable material losses and their social relations have been impaired. ICD prevention, diagnostics and treatment require multidisciplinary approach. In PD patients it is necessary to take ICD into consideration as a real problem not only from the medical but also ethical point of view and, for the future, be also aware of potential legal impacts.

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