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PSYCHOTIC SYMPTOMS IN PARKINSON’S DISEASE: ETIOLOGY, PREVALENCE AND TREATMENT

PSIHOTIČNI SIMPTOMI U PARKINSONOVOJ BOLESTI – ETIOLOGIJA, PREVALENCIJA I TERAPIJA

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Summary

Introduction. Parkinson’s disease is the second most common neurodegenerative disease with as many as 50 – 70% of patients experiencing psychotic symptoms during the course of the illness. Our aim was to provide an evidence-based review on the etiology, prevalence and management of psychotic symptoms in Parkinson’s disease. Material and Methods. We used references from the “Medline” database published from 1999 to 2019. Results. The most common psychotic symptoms in Parkinson’s disease are visual hallucinations, which occur in 25 - 30% of patients, acoustic hallucinations in about 20%, and delusions in around 5% of these patients. The etiology of psychotic symptoms is not fully clarified, but researchers suggest a complex interrelationship of factors associated with the disease itself and the factors associated with antiparkinsonian medications. After exclusion of other etiologic causes of psychotic symptoms, it is necessary to revise the type and dose of antiparkinsonian drugs. Although pimavanserin has recently been approved by the United States Food and Drug Administration, the current treatment of choice for psychotic symptoms in Parkinson’s disease is still quetiapine. Only patients who do not tolerate or do not respond to quetiapine are treated with clozapine, which has been proven more effective, but with significant side effects. Conclusion. Timely diagnosis and adequate treatment of psychotic symptoms in Parkinson’s disease are essential, because they dramatically affect the quality of life of patients and their families. Therefore, it is necessary to establish more effective tools for screening and treatment of psychotic symptoms in Parkinson’s disease.

Key words: Parkinson Disease; Psychotic Disorders; Hallucinations; Antiparkinson Agents; Drug-Related Side Effects and Adverse Reactions; Risk Factors; Quality of Life

Sažetak

Uvod. Poznato je da u Parkinsonovoj bolesti, drugoj po učestalosti u grupi neurodegenerativnih bolesti, čak 50–70% pacijenata doživljava psihotične simptome. Cilj akutnog istraživanja je da obezbedi pregled podataka iz literature koji se odnose na etiologiju, prevalenciju i tretman psihotičnih simptoma u Parkinsonovoj bolesti. Materijal i metode. Identifikovali smo referencije koristeći bazu podataka Medline za period od 1999. do 2019. godine. Rezultati. Najčešći psihotični simptomi u Parkinsonovoj bolesti jesu optičke halucinacije koje se javljaju kod 25–30% pacijenata, akustičke halucinacije koje se javljaju kod oko 20% pacijenata i sumarnosti koje se javljaju kod oko 5% pacijenata. Etioškog psihotičnih simptoma nije u potpunosti razjašnjen, ali istraživači ukazuju na kompleksan međusobni odnos faktora povezanih sa samom bolestju i faktora povezanih sa antiparkinsonišćim lekovima. Na kon isključivanja drugih etioških faktora, kod pojave psihotičnih simptoma u Parkinsonovoj bolesti, potrebno je revidirati doze i vrstu ordiniranih antiparkinsonika. Iako je atipični antipsihotik pimavanserin nedavno odobren za lečenje psihotičnih simptoma u Parkinsonovoj bolesti od američke Uprave za hranu i lekove, akutni tretman izbora za ovu indikaciju je i dalje antipsihotik klozapin. Samo kod pacijenata kod kojih postoji problem sa efikasnošću ili tolerabilnošću kvetiapina uvodi se klozapin, koji je dokazano efikasniji, ali koji ima i značajne neželjene efekte. Zaključak. Pravovremena dijagnoza i adekvatan tretman psihotičnih simptoma u Parkinsonovoj bolesti su neophodni jer drastično nepovoljno utiču na kvalitet života pacijenata i njihovih porodica. Zbog toga je neophodno uspostaviti efikasnije algoritme za skrivanje i lečenje psihotičnih simptoma u Parkinsonovoj bolesti.

Ključne reči: Parkinsonova bolest; psihotični poremećaji; halucinacije; antiparkinsonici; nuspojave i neželjene reakcije izazvane lekovima; faktori rizika; kvalitet života

Introduction

Parkinson’s disease (PD) is a common neurodegenerative disease diagnosed based on motor impairment. It usually occurs in people older than 65 years, but it is estimated that 5% of patients are diagnosed before the age of 40 years [1, 2]. PD predominantly affects subcortical brain structures and the cerebral cortex is affected during disease progression. The histopathological substrate of this disorder is hypofunction of dopaminergic neurons in substantia nigra, but serotonergic and noradrenergic nerve pathways are also affected [3].

In addition to the primary motor symptoms, there are non-motor symptoms that have been recognized as a possible complication of long-term treatment, but often remain unrecognized and untreated [4, 5]. Psychiatric symptoms of PD, such as psychosis, mood...
In addition to visual and auditory, there are so-called hallucinations in PD are without emotional content [25]. Unlike hallucinations in schizophrenia, hallucinations occurring in dark or dim light in the evening. They are often recurrent and stereotype, occurring in one-quarter to one-third of all patients with PD. Auditory hallucinations occur in approximately 20%, while delusions occur in 5% of patients [23, 24]. Visual hallucinations in PD are usually complex, well-established and most often imply human beings or animals. They are often recurrent and stereotype, occurring in dark or dim light in the evening. Unlike hallucinations in schizophrenia, hallucinations in PD are without emotional content [25]. In addition to visual and auditory, there are so-called “minor” hallucinations where the patient feels someone’s presence or sees somebody passing through his peripheral visual field. There is also “selective diplopia” as a specific type of hallucination [26]. Isolated delusions rarely exist in PD, however, it is estimated that 10% of patients experience delusions in addition to hallucinations [27]. One of the most common delusions is partner’s infidelity. Additionally, literature describes “Capgras syndrome” - experiencing that acquaintances are replaced by similar persons, “Fragola syndrome” - experiencing that acquaintances are disguised as strangers and “reduplicative paramnesia” when patients have the impression of duplicated place or location [28].

The etiology of psychotic symptoms in PD is not fully clarified, but researchers suggest a complex interaction of factors associated with the disease itself and factors associated with antiparkinsonian drugs [14]. It has been proven that all classes of antiparkinsonian drugs (dopamine receptor agonists, N-methyl D-aspartate (NMDA) receptor antagonists, levodopa, monoamine oxidase B inhibitors of catechol-O-methyltransferase and antimuscarinic drugs) may induce psychotic symptoms [15]. There is a classification of antiparkinsonian drugs in terms of their potency to cause psychotic symptoms and some controlled studies support these claims. Levodopa and dopamine agonists, two drugs of first choice for the treatment of motor symptoms of PD are also associated with the appearance of psychotic symptoms. Controlled studies show that psychotic symptoms are more likely to occur during the use of dopamine agonists than during the use of levodopa [29, 30]. Levodopa, as the drug which has the lowest potency to induce psychotic symptoms, should be used in patients with PD and suffering from psychosis [31, 32]. Dopaminergic drugs lead to excessive stimulation or hypersensitivity of mesolimbic D2 and D3 receptors and may induce psychosis. Serotonergic and dopaminergic system imbalance is also associated with the onset of psychosis in PD [33]. In addition to the effects of dose and duration of the drug treatment, there is a strong interaction between antiparkinsonian medications themselves and comorbid vulnerability for the development of psychotic symptoms such as cognitive deficits and visual disturbances. Risk factors for the development of psychotic symptoms in PD include primary deficits of processing visual information (reduced visual acuity deficit in recognizing colors and contrast, optic nerve damage and functional abnormalities of the brain). There are additional factors, such as sleep disturbances, structural brain abnormalities and genetic factors that may contribute to the occurrence of psychotic symptoms in PD [14]. It is necessary to rule out other possible causes of psychotic symptoms in PD, including infection, intoxication, endocrine disorders, acute metabolic imbalance and certain medications, before starting the treatment [34, 35].

The first step in the treatment of psychotic symptoms is dose reduction or withdrawal of benzodiazepines and tricyclic antidepressants. The next step
is to reduce the dose of antiparkinsonian drugs with respect to their potency for inducing psychotic symptoms. This sequence implies anticholinergics first, then amantadine, dopaminergic agonists, monoamine oxidase-B (MAO-B), catechol O-methyltransferase (COMT) and eventually levodopa. However, these interventions may lead to motor symptoms worsening, so the main aim is to achieve an optimal balance between motor and psychotic symptoms of PD [2]. The treatment of psychotic symptoms in PD is challenging, because the treatment of motor symptoms leads to exacerbation of psychotic symptoms, and the treatment of psychotic symptoms leads to worsening of motor symptoms [35].

When it is necessary the introduce antipsychotics, professionals should avoid classical antipsychotics such as haloperidol due to increased risk of extrapyramidal side-effects causing worsening of motor symptoms [18]. It is important to point out that extrapyramidal syndrome induced by conventional antipsychotics withdraws after 4 to 16 weeks after the discontinuation of antipsychotic therapy [36]. That is the main reason for introduction of atypical antipsychotics from the beginning.

The course of psychosis in PD is not sufficiently explored and there is no empirical evidence about the duration of psychosis treatment. One study showed that psychotic relapses occurred in 83% of fully recovered patients after a gradual withdrawal of antipsychotic drugs [36].

According to literature and clinical experience, the current treatment of choice for psychotic symptoms in PD is still quetiapine - 25 to 300 mg per day, with an average maintenance dose of 75 mg. It is known that quetiapine is well tolerated, safe and effective. However, quetiapine has not shown efficacy better than placebo in two placebo-controlled trials [37, 38]. While clozapine has proven the most effective, its introduction is recommended only for patients who do not tolerate or do not respond to quetiapine, due to considerable side effects [35]. Three adequately designed, placebo-controlled trials in which low dose clozapine was used in PD showed a reduction of psychotic symptoms, without motor-symptoms worsening [31, 38, 39]. There is some evidence justifying the introduction of olanzapine and risperidone as well, but more pronounced extrapyramidal side effects can be expected, in comparison with quetiapine. Another study showed that both olanzapine and clozapine significantly reduced psychotic symptoms and did not lead to worsening of motor symptoms [40]. However, two placebo-controlled trials did not identify differences in efficiency between olanzapine and placebo. In addition, olanzapine is associated with a significant worsening of motor symptoms [41, 42]. One interesting study showed risperidone as more effective in reducing psychotic symptoms than clozapine, without motor side effects [43]. Recent meta-analysis of trials on treatment of psychotic symptoms in PD concluded that only clozapine can be fully recommended [44]. We have to point out that pimavanserin, 5-hydroxytryptamine receptor serotonin 2A inverse agonist was recently approved by the United States Food and Drug Administration for the treatment of PD psychosis and may prove to be a more targeted therapy without the downsides of atypical antipsychotics [45, 46].

**Conclusion**

New definitions and medications have raised the research interest and led to expansion of the literature concerning psychosis in patients with Parkinson’s disease, with the main interests being the etiology and treatment. Timely diagnosis and adequate treatment of psychotic symptoms is essential, because these symptoms dramatically affect the quality of life of the patients and their families. It is known that patients often do not report psychotic symptoms spontaneously to their clinicians. Therefore, it is necessary to establish more effective instruments for screening and treatment strategies for psychotic symptoms in Parkinson’s disease, taking into account the importance of this phenomenon.

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