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Diagnosis and treatment of hallucinations in elderly palliative care patients with Parkinson’s disease

[Running title: Hallucinations in Parkinson's disease]

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Abstract

Parkinson's disease is the most common neurodegenerative disease. Until recently, the treatment was focused on dopamine deficiency and enabling patient activity. Much less attention was paid to the cognitive impairment and non-motor symptoms of the disease. Dementia, hallucinations and delusions are the most common cognitive disorder influencing a patient's quality of life. Hallucinations are probably the most common and bothersome non-motoric symptom. This paper discusses the diagnosis and treatment of hallucinations with atypical antipsychotics and possible alternatives. We also suggest a sensible approach for patients with hallucinations and delusions.

Key words: Parkinson's disease, non-motoric symptoms, hallucination, quetiapine, clozapine

Introduction

Parkinson's disease (PD) is a neurodegenerative disease affecting, among other **the substantia nigra** of the midbrain. In virtually all cases of Parkinson's disease, Lewy bodies are found on autopsy, and it is believed that they are characteristic of the neurodegenerative processes in this disease [1]. Lewy bodies are composed of structurally altered neurofilaments wherever there is excessive loss of neurons. They are usually connected to the development of dementia, but it is still uncertain how they connect to the development of hallucinations [2]. Neurodegeneration of the substantia nigra and decrease of dopamine levels in the brain are pathognomonic for characteristic symptoms of PD like resting tremor and reduced mobility. Patients experience increased muscle tension of plastic-type (lead-pipe rigidity), vegetative disorders or posture disorders. Non-motor symptoms, such as drooling, increased sweating or constipation, may appear many years before motor symptoms [3]. Patients with PD may also develop cognitive disorders such as depression, dementia, hallucinations and delusions [4]. These symptoms contribute significantly to the loss of quality of life (QOL) [5].

Hallucinations may be part of the phenomenon of psychosis, which will not be discussed here in all detail. Visual hallucinations are most common and are present in 23 to 38% of the patients, and auditory in up to 20% [4, 6]. With the understanding that very few patients report auditory hallucinations unaccompanied by visual hallucinations [7]. Tactile/somatic and olfactory hallucinations are much less common [8]. Minor phenomena (MH), typical for Parkinson's disease, such as a sense of presence and visual illusions, affect 17 to 72% of the patients, and delusions affect about 5% [6]. Cognitive impairment is more common among patients experiencing hallucinations (64%, 50%, and 25% among patients with visual, auditory, and non- hallucinating PD patients, respectively) [7]. This paper will focus on recognizing and treating hallucinations in PD, because they are the most troublesome in the end stage PD.

Pathophysiology

The exact mechanisms leading to hallucinations and psychosis are not well understood. For a long time, dopamine precursors or agonists, administered to alleviate motor symptoms, were thought to be the culprit of hallucinations in PD [6]. The reason for this was the clinical observation that hallucinations are rare in patients untreated with dopaminergic

agonists [9], and dopamine replacement therapy has been shown to increase the risk of developing hallucinations following prolonged use [10, 11]. But the dopaminergic effects alone do not explain the whole phenomenon of hallucinations. As demonstrated with post-mortem human brain histology, degeneration includes the loss of dopaminergic and cholinergic neurons [12, 13]. And precisely, loss of cholinergic neurons correlates strongly with cognitive decline and hallucinations [14]. Dopaminergic replacement therapy may stimulate the cholinergic system by inhibiting acetylcholinesterase [15] and be the reason for the exacerbation of hallucinations. For this reason, modern strategies in treating PD patients with hallucinations include dopaminergic replacement and anticholinergic treatment. Treatment of hallucinations with rivastigmine, an anticholinergic agent used in treating dementia, is moderately successful in PD patients [16].

Although it sounds plausible that dopaminergic medication can be responsible for hallucinations, a thorough analysis of 245 hallucinating patients with PD suggested that factors like disease severity, dementia, depression and worse visual acuity may be more important determinants of hallucinations [9]. There is also an indication that abnormality of the visual system may be related to visual hallucinations in PD, like in other diseases like Alzheimer's' or macular degeneration [4, 17, 18]. Interestingly, in the study by Holroyd et al. [4] covering about a hundred patients with PD and hallucinations, there was no indication that the hallucinations were drug-induced.

However, recent studies by Zarkali et al. [19] showed with the advent of functional magnetic resonance imaging (fMRI) that hallucinations are related to the regional neurotransmitter density and gene expression for serotoninergic, GABA-ergic, noradrenergic and cholinergic, but not dopaminergic receptors. Another study suggests that increased serotonin neurotransmission involving 5-HT2A receptors also may play a role in visual hallucinations [20]. A specific 5-HT3 receptor antagonist, ondansetron, is considered for treating hallucinations in PD ahead of controlled trials [21].

Diagnostic workup

Hallucinations are one of the most common psychotic symptoms in PD, mainly visual hallucinations. There are no widely accepted, validated rating scales for hallucinations, and there is a clear need to develop better ones. In the diagnosis of hallucinations, the interview conducted by the physician with both the patient and his/her caregivers is of paramount

importance. Wada-Isoe et al. [22] performed a comprehensive study on 41 PD patients, among whom 13/41 (31.4%) experienced hallucinations. In addition to a thorough history and a physical examination, analysis of medication used, a neurological examination, an assessment of cognitive functioning using the Mini-Mental State Examination (MMSE), computed tomography (CT) or magnetic resonance imaging (MRI), single photon emission tomography (SPECT) of the head, electroencephalography (EEG), myocardial scintigraphy using metaiodobenzylguanidine-123I (MIBG) and routine laboratory tests were performed. Based on these data, they composed a Tottori University Hallucination Rating Scale (TUHARS) with a Cronbach's alpha of 0.88, suitable for assessments of hallucinations. Visual hallucinations were the most common, but half of the patients also experienced auditory hallucinations. Patients who have dementia and experience hallucinations scored much higher than patients without dementia.

Studies performed on patients from the Department of Neurology at the University Hospital of Tottori are essential because they help determine the presence of different symptoms in PD and rule out other causes that may cause hallucinations, such as brain tumors, mental illnesses or hallucinations caused by the use of narcotic drugs or other medications.

Treatment

Treatment of well-structured hallucinations in PD is not easy and complex. According to Kuzuhara [23] and NICE guidelines for treating PD [24], treating hallucinations and other symptoms of psychosis should be stepwise. In the 1st step, drugs with a psychotomimetic potential should be eliminated; these drugs are antidepressants [25], spasmolytics [26] and H2 receptor antagonists [27–29]. Diagnostic workup should be undertaken to exclude metabolic encephalopathies, infections and subdural hematoma. In 2nd step, other medications with anticholinergic effects as well as amantadine and selegiline as, well as bromocriptine, pergoline, talipexole should be reduced or discontinued. The dopaminergic drugs should be slowly reduced.

In the 3rd step, when previous actions prove ineffective atypical antipsychotics should be added to the medication. If ineffective, rivastigmine [16] or ondansetron [21] can be added. A promising treatment option for well-established hallucinations is the introduction of

atypical antipsychotics, such as clozapine or quetiapine, which do not cause a pronounced worsening of parkinsonism [30].

Several randomized controlled trials of clozapine (a D1, D2 and 5-HT2 receptor antagonist) have shown efficacy in alleviating psychotic symptoms in patients with PD, with little or no deterioration in their motor function. However, complete blood counts should be monitored with clozapine, as it may cause life-threatening agranulocytosis [31]. However, studies on quetiapine, an antagonist of D1, D2, 5-HT2, H1 and α-adrenergic receptors, revealed contradictory results [32]. Several randomized controlled trials showed that quetiapine did not impair motor function but did not significantly improve hallucinations in the patients studied [33–37]. A randomized, open-label, double-blinded study compared the efficacy and safety of clozapine and quetiapine in 40 patients in two parallel groups of 20 patients. In both treatment groups, hallucinations were relieved, and no worsening of movement disorders was observed, except for mild severity in 3 patients treated with quetiapine [38]. Clozapine is seen as slightly superior to quetiapine when monitoring for blood count is possible, but both drugs were never compared head-to-head. Nevertheless, this superiority is based on the therapist's preferences [39] and the failure of quetiapine to control hallucinations in some studies.

An alternative to atypical antipsychotics is believed to be cholinesterase inhibitors. They are widely used to treat dementia In PD disease [40]. A large placebo-controlled, double-blind trial involving 188 hallucinating and 348 not hallucinating PD patients revealed the efficacy of rivastigmine. Hallucinating patients had more benefits from the treatment [10]. Finally, pimavanserin, a new antipsychotic not yet widely available outside USA but the only FDA-approved for this purpose, has been proposed as an alternative, supposedly being additionally effective against delusions in PD and has been recently registered for this purpose [41–43]. An unsurpassed and comprehensive review of the atypical antipsychotics in psychosis and hallucinations in PD was published by Zahodne et al. [44].

Much less is known about treating minor hallucinations (MH), or passage hallucinations. MH often precede the onset of well-structured visual hallucinations and are associated with other non-motor symptoms such as REM sleep behavior disorder and depression. Some clinicians have the tendency not to treat these phenomena. However, they respond to low doses of clozapine [45, 46]. Other authors suggest treating patients with MH using rivastigmine or a wait-and-see policy [47].

Non-pharmacological approach to hallucinations

Patients with PD experiencing psychotic episodes very often suffer from depression. Their apathetic and psychotic symptoms make it even more difficult for them and their caregivers to function in everyday life. These patients need appropriate psychological support [48]. Such patients could be helped by cognitive-behavioral therapy (CBT). However, experience with this therapy is limited to auditory hallucinations in other diseases [49, 50]. Occupational therapy or music therapy was tried in PD, and found beneficial for the quality of life, but specific effects on hallucinations are unclear [51].

Patients in the advanced stage of PD often have problems with communication; there are falls and fatigue that make it challenging to maintain everyday activities, their relationships with others deteriorate, and they are dependent on another person. Such situations can lead to social isolation of patients [48]. Caregivers, usually the family, must accept the new reality. Patients get used to their current situation to some extent, and staying at home with their families and visiting children and grandchildren fulfil them with happiness. Often the problem is a visit to the doctor due to the inability to move independently and the need for better listening on the part of the medical staff. It happens that caregivers are left alone and need to be made aware of the availability of professional health care. They learn about the treatment of the patient from their own experience [52]. When caring for someone with hallucinations, one should show empathy and understanding, build a relationship based on trust. If the patient experiences hallucinations, he should not be convinced otherwise because it can give rise to conflicts, intensify stress and worsen his condition. Instead, one can suggest that “we are not seeing anything, but we understand that it is disturbing for him”. The patient, during hallucinations, may have difficulty concentrating, so it is necessary to speak clearly, in simple and short sentences. The patient cannot be ignored or laughed at for his/her behavior, but he/she should always be listened to, not judged. It is also essential to find ways to manage stress [48].

Conclusions

Hallucinations and delusions are symptoms that occur regularly in PD and can severely impact the patient's quality of life and those around him. These symptoms tend to be more severe toward the end of life and with higher doses of anti-Parkinsonic drugs. Diagnosis consists of collecting a detailed medical history from the patient and his caregiver and

excluding other causes of hallucinations. After discontinuing drugs that may provoke hallucinations and slowly decreasing the dose of dopaminergic drugs, clozapine is used for treatment, which is the drug of first choice, and quetiapine when there are contraindications to therapy with clozapine. In case of no improvement, rivastigmine or ondansetron, although still its efficacy is less evidence-based than clozapine, may be used as an alternative. In addition to pharmacological treatment, patients and their families should undergo psychotherapy, thanks to which the symptoms of mental illness can be alleviated and their quality of life improved.

Article information and declarations

Author contributions

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Conflict of interest

The authors declare no conflict of interest.

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