Olfactory Hallucinations in Parkinson's Disease

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Abstract. Parkinson's disease is a neurodegenerative disorder characterized by some motor and non-motor symptoms, becoming one of the most common diseases among old people. Olfactory hallucinations are odor sensations with no present stimulus in the environment. More and more studies have begun to pay attention to the prevalence rate of olfactory hallucinations in Parkinson's disease. Nevertheless, there are still many limitations in existing studies. This research aims to explore the relationship between olfactory hallucinations and Parkinson's disease, find effective treatment of olfactory hallucinations in Parkinson's disease, analyze existing studies' conclusions and shortcomings, and provide suggestions for future studies.

Keywords: olfactory hallucinations, Parkinson's disease, neurodegenerative disorder, odor, treatment.

1. Introduction

1.1. Definitions

Olfactory hallucinations refer to an odor sensation without a present stimulus, which means disturbances of perception where a person can experience a smell although there is no source of the odor in the environment [1]. Olfactory hallucination is one type of qualitative olfactory dysfunction [2]. Olfactory hallucinations are also termed Phantosmia. Phantosmia is a term originated in the Ancient Greek words, the only difference between the two is the duration.

Phantosmia may occur in idiopathic olfactory dysfunction, tumors, or neuropsychiatric conditions [3]. Some specific odorants may lead to parosmia and affect one's eating habits, nutrition, weight, mental health, and many other aspects of daily life. Olfactory hallucinations have some association with depression, anxiety, and other mental illnesses at the same time. An individual who is chronically stressed might exhibit symptoms of olfactory hallucinations as well. Many existing studies have also experimentally demonstrated that neurodegenerative diseases also have the potential to be a factor in the occurrence of olfactory hallucinations in patients. Olfactory hallucinations are generally associated with quantitative olfactory loss, with no relationship to impaired odor identification [2]. In some existing research, the association between olfactory hallucinations and an early onset of psychosis in psychopathic susceptible individuals may be transient phenomena during healthy development. Those studies have shown that there are some more significant associations between stressful and traumatic events and psychotic experiences. Anxiety and stressful life events remained necessary predictors of olfactory hallucinations in the multivariate model.

Parkinson's disease is a neurodegenerative disorder characterized by some motor and non-motor symptoms, such as bradykinesia, rigidity, tremor, and postural instability, which is an increasingly prevalent disease [4]. This clinical syndrome was described by James Parkinson in an essay written by himself in 1817 and then referred to as 'Parkinson's disease'. Parkinson's disease is becoming a more and more significant source of mortality and disability during neurological conditions [1].

Various observations have shown that Parkinson's disease might not exist as an entity solely [5]. Every person has unique symptoms of Parkinson's disease of themselves. Individual manifestations of Parkinson's symptoms with the same toxic cause vary greatly. Some of the major molecular and cellular features are commonly associated with a variety of other interrelated events, including disruption of vesicle transport, loss of microtubule integrity, disruption of trophic factors, and so on [4]. The dysfunction caused by the particular vulnerability of axonal mitochondria can contribute to impaired axonal transport. Some existing research has suggested that distal axons of the striatum may be the initial site of neurodegeneration in Parkinson's disease. Parkinson's disease can usually be diagnosed when an individual's substantia nigra is dense and shows a loss of dopaminergic neurons. A feature characteristic of Parkinson's disease is that deficiencies of Complex I are associated with nerve cell apoptosis [6].

1.2. Background

Frequent occurrence of non-motor symptoms at the early stages of Parkinson's disease is normal, although it may be intense and disturbing for some patients [7]. Studies indicate that as the duration of the disease increases, non-motor symptoms will worsen and worsen. Reduce quality of life, and finally become a driver of the overall cost of care. Patients with Parkinson's disease present a wide range of non-motor symptoms that can lead to damage to several nervous systems, including cognitive impairment, autonomic nerve failure, smell and taste deficits, and sleep disturbances [1]. Lots of patients with Parkinson's disease also experience issues with attention, memory, and executive functions at the same time. Mood disorders such as anxiety, depression, and apathy may sometimes precede the onset of some motor symptoms. Olfactory functions, with estimates of prevalence rate up to approximately 65% to 90%, have become a common non-motor symptom in Parkinson's disease [8].

2. Objectives & Aims

Olfactory hallucinations are gradually becoming one of the most common non-motor symptoms caused by Parkinson's disease. And the prevalence rate of olfactory hallucinations in Parkinson's disease will become higher and higher in the future. Within this context, as olfactory hallucinations are a complex and often overlooked symptom of Parkinson's disease, they not only relate to the pathology and treatment of Parkinson's disease but may also provide reference and inspiration for research on other neurodegenerative diseases such as Alzheimer's disease. Therefore, it is particularly urgent and necessary to raise awareness of olfactory hallucinations among all sectors of society. This not only helps us to have a more comprehensive understanding of the various symptoms of Parkinson's disease, but lays the foundation for early diagnosis, timely prevention, and the subsequent treatment strategies of related mental disorders at the same time.

The original purpose of this research was to deeply analyze and reveal the intricate causal relationship between olfactory hallucinations and Parkinson's disease. On the one hand, this exploration is not only limited to understanding the direct connection between the two but also desires to explore the underlying physiological mechanisms and pathological processes. On the other hand, this research also focused on effective treatment for olfactory hallucinations in Parkinson's disease as well. Furthermore, as a unique phenomenon in the field of neurodegenerative diseases, olfactory hallucinations may reflect broader patterns and patterns of neurological decline during their existence and evolution. Therefore, the direction of this research was also extended to explore the relationship between neurodegenerative diseases as a whole. This study attempts to construct a more comprehensive and systematic cognitive framework to improve understanding and response to such a wide range of diseases.

3. Method

This research conducted a thorough search for relevant literature on platforms such as Google Scholar, PubMed, and ResearchRabbit, using specific keywords including "olfactory hallucinations," "Parkinson's disease," "neurodegenerative diseases," and "non-motor symptoms." The search aimed to gather a comprehensive overview of existing research and studies related to these topics. Through careful screening and analysis of the content, this study has drawn important results, conclusions, and discussions. The analysis involved evaluating the methodologies, findings, and implications of the selected literature, allowing for a deeper understanding of the subject matter. Through this process, this research has contributed to the existing studies and provides valuable insights into the relationship between olfactory hallucinations, Parkinson's disease, neurodegenerative diseases, and non-motor symptoms.

4. Results

4.1. Results of experiment

In particular, in the Parkinson's disease group, olfactory hallucinations were reported by about 15-18% of patients. The feelings of olfactory hallucinations are qualitatively heterogeneous. About 18% of patients reported a perception of unpleasant odors such as rotten eggs, garbage, or other noxious odors, while the remaining about 82% of patients reported smelling pleasant odors such as fruits and flowers [1, 9].

Regarding the determinant of gender on olfactory hallucinations in Parkinson's disease, women showed a high frequency of olfactory hallucinations in Parkinson's disease. A female prevalence was about 65-75% of patients, this is the result of the lowering of estrogen levels during menopause and longer life expectancy [6].

Several studies have shown the concurrent presence of other types of hallucinations alongside phantosmia as well. Among Parkinson's disease patients with olfactory hallucinations, 2.8% of patients also presented gustatory hallucinations [9]. Visual hallucinations and auditory hallucinations were reported by 17.7% and 4.3%. Among healthy controls, 44% of patients showed normosmia, 54% of patients presented hyposmia, and 2% were affected by functional anosmia. Among Parkinson's disease patients, 4% of patients showed normosmia, 52% of patients presented hyposmia, and 44% of patients were affected by functional anosmia.

Only a few experiments in existing research have investigated the impact of olfactory hallucinations on the quality of patients' daily lives. Studies indicated that olfactory hallucinations can interfere with daily activities variably [1]. For example, some patients exhibited compulsive behavior linked to phantosmia, others suffered from sleep disturbances due to olfactory misperception.

4.2. Association with neurodegenerative disorders

Characteristic protein aggregation is a key pathological marker of a variety of neurodegenerative diseases and is often used in diagnosis and disease classification [10]. Parkinson's disease and Alzheimer's disease are the two most common neurodegenerative diseases. Compared with other neurodegenerative disorders, Parkinson's disease and Alzheimer's disease are the two most prevalent and well-recognized disabilities among patients over 60 years old. These neurological conditions often manifest in later life, significantly impacting the quality of life for those afflicted [6]. The underlying etiology of these disorders is complex and multifaceted, with two primary theories gaining traction: an augmentation of free radicals within the body and a compromised defense system against these harmful molecules, specifically a reduction in the availability or effectiveness of antioxidants. A common feature of neurodegenerative diseases is oxidative stress. Oxidative stress is caused by unregulated production of reactive oxygen species. Molecules involved in the aging progress will oxidatively degrade when reactive oxygen species are overproduced. Overproduction of reactive oxygen species can also generate several disorders such as cancer, cardiovascular diseases, and so on [6]. In addition, by enhancing the production of reactive oxygen species, the redox balance of the cell might be shifted towards an

oxidative state. Enhanced production of reactive oxygen species may lead to dysfunction and even death. In other words, it was observed that high oxygen consumption, low levels of antioxidants, and reduced regenerative capacity contributed to the susceptibility of brain tissue to oxidative damage. Moreover, reactive oxygen species produced through neurodegeneration can destroy lipid membranes and cellular proteins, eventually forming oxidative stress [6].

4.3. Treatment

During this period of clinical uncertainty, the use of olfactory testing may help distinguish from common differential diagnoses including other neurodegenerative disorders, secondary causes of Parkinsonism, and other tremor disorders [11].

Generally, there are two most common pharmacological interventions, one is to adjust antiparkinsonian therapy by gradually reducing the daily dose of levodopa equivalent and the other is to introduce atypical neuroleptics [1]. The results reported in these studies were usually positive, accompanied by the disappearance or improvement of those hallucinations.

Deferiprone therapy would not make an adverse difference in cognitive function and mood, with reduced iron levels in specific regions of the brain [6]. Biomarkers of reactive oxygen species have the potential to be utilized as diagnostic instruments or therapeutic targets. Antioxidant therapy, which may involve the use of resveratrol or other nutritional compounds, combined with moderate physical exercise, could have a positive impact on the clinical damage caused by oxidative stress.

Moreover, it is important to check for glutathione deficiencies in the brains of people with Parkinson's disease, which can be mitigated by dietary supplementation with N-acetylcysteine. N-acetylcysteine is a substance with antioxidant and anti-inflammatory properties [12]. Antioxidants and fruits, such as vitamins C and E, can reduce the adverse effects of free radicals [6]. The lipid-soluble characteristics of vitamin E enable it to interact with cell membranes, trap reactive oxygen species, and disrupt the mechanisms involved in the production of free radicals. Therefore, by preventing oxidative stress in cells and inhibiting apoptosis the administration of vitamin E can provide neuroprotective effects [13]. As it is all known, in the human body, vitamin C is the most valuable antioxidant agent and has a neuroprotective effect protecting body health from neurodegenerative disorders. It is worth mentioning that vitamin C plays an considerable role in the protection of the brain under ischemic conditions [14].

It is worth mentioning that patients have the potential to feel embarrassed about their experiences. These feelings may hinder them from discussing or seeking support for their symptoms [15]. So the first step is supposed to raise awareness among clinicians and proactive case-finding. A multicomponent intervention targeting risk factors and care processes called the Hospital Elder Life Program (HELP) has been shown to outperform pharmacological strategies.

Evidence Table With Instruction					
ID	Setting	Method	Variables	Results	Conclusion
Solla et al., 2021	141 PD patients and 132 healthy controls; no difference in gender or age; no history of other disease	Sniffin' Sticks test: OT, OD, OI	gender, feelings, and other types of hallucinations	feelings range from pleasant smells to unpleasant smells, female patients, occurrence with other types of hallucinations	female, simultaneous with VHs and AHs, with no relation to olfactory impairment

Table 1. Evidence 7	Table with Instruction
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Ercoli et al., 2024	203 PD patients with OHs from 29 studies	UPSIT, Sniffin' Sticks test	gender, features, influence on quality of daily life, treatment used to manage phantosmia	OHs can variably affect daily activities, the two most common treatment	frequency, gender distribution, features, hallucinations coexist with OHs, impact on life, treatment
Teleanu et al., 2022	patients with different types of neurodegenerative diseases	Reactive Oxygen Species (ROS); oxidative stress (OS)	neuroprotection and antioxidants, OS, neuroinflammation, mitochondrial dysfunction	associations between OHs in PD and NDDs, treatment to OHs in PD	OS in NDDs

Table 1.	(continued).
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5. Conclusion

Female gender is a clinical variable that predicts the presence of olfactory hallucinations in Parkinson's disease patients. This phenomenon reinforces the putative core role of gender differences in the development of non-motor symptoms in Parkinson's disease patients, especially in olfactory symptoms [9]. The important subjective nature of olfactory hallucinations can be confirmed by a large amount of odor described by patients affected by olfactory hallucinations [1]. Patients experience these odors in a wide variety of ways, ranging from pleasant smells of flowers and fruits to foul aromas of garbage or burning. A significant increase in dopamine cells around the glomeruli in Parkinson's disease patients has the potential to lead to elevated dopamine levels in the olfactory glomeruli and the inhibition of olfactory transmission [16]. The frequency of olfactory hallucinations in conjunction with other types of hallucinations is quite high. This association suggests that the pathophysiological mechanisms underlying these phenomena might have overlapping parts.

In other words, there are two main conclusions drawn from this research. The first one is that the implications of the findings can be used for early detection of Parkinson's disease and related neurodegenerative disorders. This biomarker not only holds great potential as a valuable instrument for early detection and treatment but also aids in understanding the neuropathology of these diseases. The second one is when people start to show olfactory hallucinations, there might be an indicator that needs to be tested for the nerve to generate disease. Furthermore, it can also be used as an early marker for treatment success. By identifying these conclusions, studies may contribute to the advancement of early detection and treatment strategies for Parkinson's disease and related neurodegenerative disorders.

Education for patients, families, and caregivers is critical. Especially since the acute appearance of hallucinations may indicate a medical condition requiring treatment or a need to adjust the response to medication. Patients and their close contacts need to be fully aware that hallucinations are common symptoms of Parkinson's disease, it sometimes may be related to the disease itself [15].

6. Discussion

However, despite the potential importance and wide-ranging impact of olfactory hallucinations in Parkinson's disease, the limited availability of existing studies and the scarcity of high-quality and detailed available information greatly constrain the breadth and depth of research. Therefore, when exploring this topic, this research failed to conduct a comprehensive and in-depth analysis as expected, resulting in some key aspects still not being fully explored and elaborated. This not only reflects the

limitations of the current research environment but also points out the direction for further exploration in the future.

Moreover, there are still considerable limitations in existing studies. For example, many studies have only considered the role of Parkinson's disease in olfactory hallucinations and other hallucinations during experiments. Nevertheless, they have not taken into account whether patients have other mental illnesses or whether there are other mental illnesses involved in analyzing the role of Parkinson's disease in olfactory hallucinations. Some studies exploring the relationship between Parkinson's disease and olfactory hallucinations only considered the pathological mechanisms of Parkinson's disease, with very little analysis taking into account the various factors that cause hallucinations, such as high levels of mental stress, anxiety disorders, and so on. In other words, they did not control for variables in experiments.

There has been little attention to olfactory hallucinations in Parkinson's disease in existing studies. The increasing number of olfactory hallucinations detected in Parkinson's disease patients indicates that these symptoms have often been underestimated or even ignored in past experiments. Only a minority of patients mentioned the duration and severity of the hallucinations [17]. Patients are indeed unable to describe the severity of hallucinations accurately. Thus, this research suggests that rater-administered questionnaires can be used in future studies, such as dividing the severity of hallucinations into 1 to 10 levels, and each corresponding level can be analogized to what degree it is. In this way, patients can describe the severity of the hallucinations they are experiencing.

While there is evidence supporting the use of cognitive behavioral therapy in managing depression related to Parkinson's disease, the area of psychological therapies for Parkinson's disease psychosis remains largely unexplored. Most existing studies have primarily focused on exploring the prevalence rate of olfactory hallucinations in Parkinson's disease and the circumstances under which this prevalence rate is relatively high. However, there is a notable lack of research discussing the causal relationship between olfactory hallucinations and Parkinson's disease. Only a limited number of studies have provided effective treatments for Parkinson's disease patients experiencing olfactory hallucinations, leaving a significant gap in our understanding and management of this symptom. Furthermore, more investigations are needed to assess the true efficacy of all these therapeutic interventions. It is crucial to delve deeper into understanding the mechanisms behind these treatments and their impact on patients' lives. This is where the role of mitochondria and oxidative stress comes in. Gaining a better understanding of how these biological processes work in the context of aging and neurodegeneration can pave the way for developing new strategies. These strategies can not only improve the quality of life for older people but also address the broader challenges posed by neurodegenerative diseases [6]. Therefore, it is of vital importance for future studies to explore the causal relationship between olfactory hallucinations and Parkinson's disease. Understanding this relationship can lead to the development of more targeted and effective treatments for these symptoms, ultimately improving the lives of those affected by Parkinson's disease. In conclusion, this research suggests that future studies should pay more attention to these aspects, bridging the gap in our understanding and providing hope for better management and treatment of Parkinson's disease psychosis.

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