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Hyposmia impending neurodegeneration in rapid eye movement sleep behavior disorder

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Abstract---Background- Approximately 50% to 80% of people with isolated rapid eye movement (REM) sleep behavior disorder (RBD) will likely be diagnosed with an overt synucleinopathy within their lifetimes. Objective- To determine if hyposmia in isolated REM sleep behavior disorder (IRBD) predicts short-term conversion. Methods- Olfaction was tested using the University of Pennsylvania Smell Identification Test (UPSIT-40) in 100 consecutive patients with polysomnography-confirmed IRBD and in 100 matched controls. Patients were followed up for two years. The study was approved by the institutional ethics committee, and participants provided written informed consent. Results- The study was a male preponderance comprising 76% in cases and 70% in controls, and they were comparable to females and were not significant.($p>0.05$). UPSIT-40 score was lower (poorer smell identification) in patients than in controls (20.3 ± 6.4 vs. 28.4 ± 4.9), and it was statistically significant ($p<0.05$). 60% of patients had hyposmia and showed 14.2 ± 2.8 scores. No differences occurred in age ($p = 0.11$), gender ($p = 0.38$) and follow-up duration ($p = 0.65$) between hyposmics and normosmics. Conclusion- In future neuroprotective trials, individuals at entry could be enriched for hyposmia, whereas serial evaluation of smell would not be useful to monitor the efficacy of a therapeutic intervention.

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Keywords---REM sleep behavior disorder, UPSIT-40, hyposmia, synucleinopathy, Parkinson's disease, dementia.

Introduction

Approximately 50% to 80% of people with isolated rapid eye movement (REM) sleep behavior disorder (RBD) will likely be diagnosed with an overt synucleinopathy. Normal sleep has two distinct phases: non-rapid eye movement (NREM) and rapid eye movement (REM) sleep. NREM sleep has three different stages. REM sleep is characterized by rapid eye movements, rhythmic breathing, a spike in blood pressure, and atonic muscles (paralysis). However, the brain is highly active, and its electrical activity is similar to during wakefulness. REM sleep is usually associated with dreaming. REM sleep makes up 20% to 25% of the sleep period.[1,2,3]. Past studies indicate that isolated REM sleep behavior disorder (IRBD) is an early manifestation of the synucleinopathies like Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA) [4]. The risk for diagnosing a clinical-defined synucleinopathy is about 35% at five years and 90% at 14 years from IRBD diagnosis [5,6]. Moreover, IRBD patients often show prodromal markers of PD such as hyposmia [6,7], and biopsies of peripheral tissues identify alpha-synuclein aggregates. Thus, IRBD constitutes a suitable population to be enrolled in neuroprotective trials to halt the neurodegenerative process [7].

The person may be awakened or wake spontaneously during the attack and vividly recall the dream that corresponds to the physical activity. The exact cause of RBD is unknown, but it may happen along with degenerative neurological conditions such as Parkinson's disease, multisystem atrophy (also known as Shy-Drager syndrome), and diffuse Lewy body dementia. In 55% of people, the cause is unknown, and in 45%, it’s linked with alcohol or sedative-hypnotic withdrawal, tricyclic antidepressant (such as imipramine), or serotonin reuptake inhibitor use (such as fluoxetine, sertraline, or paroxetine) or other types of antidepressants (mirtazapine).[7]. Olfactory loss is a reported sign of early neurodegenerative process which has been noted to have an association with dementia, Parkinson’s disease, etc. The link between RBD and the neurodegenerative process is evaluated by its relationship with olfactory involvement in this research. The rationale behind the study was investigated in a large IRBD cohort with short-term follow-up on the frequency of olfactory loss, which was done by an assessment of olfaction by smell tests which is easy, non-invasive, inexpensive, and rapid.

Materials and Methods

Olfaction was evaluated in 100 consecutive IRBD patients at the Department of Neurology in a tertiary care center between Jan 2021 to March 2022 during routine visits and other research projects. IRBD diagnosis required a history of dream-enacting behaviors, audiovisual-polysomnographic demonstration of increased electromyographic activity linked to abnormal behaviors in REM sleep, and absence of motor and cognitive impairment [1]. For comparisons, 100

healthy/screened did not have signs of RBD controls who were friends or non-blood relatives of the patients who underwent olfactory testing.

Methodology

In patients and controls, odor identification was evaluated by the 40-item University of Pennsylvania Smell Identification Test™ (UPSIT-40)[8]. UPSIT-40 is a scratch-and-sniff test that takes 15 min to administer where 40 microencapsulated odors are identified in a forced-choice format. The identification score is the number of correct answers and ranges from 0 to 40 points. Higher scores entail better olfactory identification. As several odors used in UPSIT-40 are unfamiliar to individuals and normative data are unavailable, smell deficit was defined when the patient's score was less than two standard deviations of the controls' mean value. After the smell test, patients were followed-up every 3–12 months at the Neurology OPD. The study was approved by the institutional ethics committee, and participants provided written informed consent.

Statistical Analysis

Analysis of data was done by using SPSS software ver. 22. Data were statistically described in terms of mean (±SD), frequencies (number of cases), and percentages when appropriate. The association between study groups and variables were tested using inferential statistics, t-test for continuous-normally distributed variables, and a chi-square test for categorical variables. A comparison of quantitative variables between the study groups was made using the Student t-test for independent samples if normally distributed. For comparing categorical data, a Chi-square test was performed. A probability value (p value) less than 0.05 was considered statistically significant.

Results

Table 1
Baseline comparison between Cases and Control

Variables	Cases	Controls	p-value
Males	76	70	0.79
Females	24	30	
Age (years)	67.5±5.8	66.9±5.7	0.32

As per table 1, the study was male preponderance comprising 76% in cases and 70% in controls, and they were comparable to females, and it was not significant.($p>0.05$). The mean age for cases was 67.5±5.8 and for controls 66.9±5.7, which was also comparable.

Table 2
UPSIT-40 among Cases and Controls

Variables	Cases	Controls	p-value
UPSIT-40	20.3±6.4	28.4±4.9	0.01*

Hyposmics	60	42	0.65
Normosmics	40	58	

As per table 2 UPSIT-40 score was lower (poorer smell identification) in patients than in controls (20.3 ± 6.4 vs. 28.4 ± 4.9) and it was statistically significant ($p<0.05$). 60% of patients had hyposmia and showed 14.2 ± 2.8 scores. No differences occurred in age ($p = 0.11$), gender ($p = 0.38$) and follow-up duration ($p = 0.65$) between hyposmics and normosmics.

Table 3
Development of Synucleinopathy and its association

Variables	Cases		p-value
	Yes	No	
Synucleinopathy	32	68	0.01*
	Synucleinopathy (N=32)		
	Yes	No	
Olfactory loss	15	17	0.01*
Hyposmia	21	11	0.01*
Annual conversion rate	5.9%		

As per table 3 at the end of study 32(32%) patients converted to a clinical-defined which was significant; Baseline UPSIT-40 score was similar between patients who developed synucleinopathy. The olfactory loss occurred in 15 of 32 (55.6%) patients who developed synucleinopathy. Smell deficit did not distinguish between patients. Patients with hyposmia had a higher risk of developing a clinical-defined synucleinopathy than patients with normosmia which was statistically significant ($p<0.05$). The annual conversion rate was 5.9% in hyposmics.

Discussion

The present study in a large cohort of IRBD patients with a follow-up of up to 2 years showed that olfactory impairment identifies patients at short-term risk but cannot predict the evolution of each condition separately. We also found that in IRBD, the olfactory function does not worsen over time. These observations may be useful in delineating and selecting candidates for neuroprotective trials in IRBD. As the prodromal period in IRBD can last up to 15 years, for the design of neuroprotective trials, it is important to identify prodromal markers of short-term conversion and be able to monitor the neurodegenerative process over time [2–4]. In these trials, the combination of prodromal markers is a strategy that may serve to enrich the sample and reduce its size [4]. The addition of olfactory loss highly predictive markers of the synucleinopathies would help to better select IRBD patients at close risk for phenoconversion [9].

The findings of this research did not establish a relationship between IRBD and serial olfactory loss. The serial olfactory evaluation was not significant and found stable over time, probably reflecting a floor effect. According to our observations,

serial olfactory testing is not useful to monitor disease progression in IRBD, because olfactory loss was stable with time, probably reflecting a floor effect. This is in agreement with the finding that the mean UPSIT-40 score in our IRBD cohort (20.2 points) is similar to the score of an advanced PD cohort (21.8 points) evaluated at our institution [10]. Some studies showed that the olfactory bulb and the anterior olfactory nucleus are impaired before damage to the substantia nigra and the cortex [11]. This is in line with the observations that (1) reduced smell is frequently reported by patients and that (2) individuals with idiopathic hyposmia have an increased risk and may show synuclein pathology in the brains at autopsy [12,13]. Smell deficit is also common in prodromal and manifests in contrast; olfaction is usually intact [14]. This study could not establish a relationship between the early development of Parkinsonism and cognitive involvement in individuals with IRBD. The literature says mild cognitive impairment is a predictor of the neurodegenerative process. This study shows that olfactory loss could not predict if Parkinsonism or cognitive impairment will first develop in an IRBD individual. To the best of our knowledge, mild cognitive impairment is the only known marker that predicts [3].

Conclusion

Odour identification is the most frequently impaired domain. Evaluation of olfaction in IRBD is useful to identify individuals at high risk of phenoconversion but not helpful in monitoring the disease process or predicting the evolution.

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Conflict of Interest- None declared

References

1. Alcivar, M. S. G., Pérez, A. V., Gilert, B. I. C., & Gámez, M. R. (2017). Zeolite in wastewater decontamination as a local development solution. International Journal of Life Sciences, 1(3), 1–13. https://doi.org/10.21744/ijls.v1i3.52
2. Beach TG, Adler CH, Lue LF. Unified staging system for Lewy body disorders: correlation with nigrostratial degeneration, cognitive impairment and motor dysfunction. Acta Neuropathol.2009;117:613–634
3. Boeve, B. F., Silber, M. H., Saper, C. B., Ferman, T. J., Dickson, D. W., Parisi, J. E et al. Pathophysiology of REM sleep behaviour disorder and relevance to neurodegenerative disease. Brain. 2016; 130, 2770–2788.
4. Chaudhuri, K. R., Healy, D. G., and Schapira, A. H. National institute for clinical E. non-motor symptoms of Parkinson's disease: diagnosis and management. Lancet Neurol.2006; 5, 235–245.
5. Chen, W., Chen, S., Kang, W. Y., Li, B., Xu, Z. M., Xiao, Q., et al. Application of odor identification test in Parkinson's disease in China: a matched case-control study. J. Neurol. Sci.2013; 316, 47–50.
6. Doty RL, The Smell Identification Test (1995) TM administration manual, 3rd edn. Sensonics Inc., Philadephia
7. Fullard ME, Morley JF, Duda JE. Olfactory dysfunction as an early biomarker in Parkinson’s disease. Neurosci Bull. 2017;33:515–525.

8. Ibarretxe-Bilbao N, Junqué C, Martí MJ. Olfactory impairment in Parkinson's disease and white matter abnormalities in ventral olfactory areas: a voxel-based diffusion tensor imaging. Mov Disord.2010; 25:1888–1894
9. Iranzo A, Santamaria J, Tolosa E.Idiopathic rapid eye movement sleep behaviour disorder: diagnosis, management, and the need for neuroprotective interventions. Lancet Neurol.2017; 15:405–419
10. Iranzo A, Santamaría J, Valldeoriola F. Dopamine transporter imaging deficit predicts early transition to synucleinopathy in idiopathic rapid eye movement sleep behavior disorder. Ann Neurol.2017; 82:419–428
11. Iranzo A, Tolosa E, Gelpi E. Neurodegenerative disease status and post-mortem pathology in idiopathic rapid-eye-movement sleep behaviour disorder: an observational cohort study. Lancet Neurol. 2017; 12:443–453
12. Jecmenica-Lukic M, Poewe W, Tolosa E. Premotor signs and symptoms of multiple system atrophy. Lancet Neurol.2014; 11(4):361–368
13. Negara, I. K. S., Agung, A. A. G., Candiasa, I. M., & Dantes, K. R. (2022). Development of digital instruments for measuring the effect of open selection, job satisfaction, transformational leadership and work motivation on the performance of civil servants. International Journal of Health Sciences, 6(2), 661–681. https://doi.org/10.53730/ijhs.v6n2.7580
14. Postuma RB, Gagnon JF, Bertrand JA, Génier Marchand D, Montplaisir JY. Parkinson risk in idiopathic REM sleep behavior disorder: preparing for neuroprotective trials. Neurology. 2018;84:1104–1113.
15. Ross GW, Abbott RD, Petrovich H. Association of olfactory dysfunction with incidental Lewy bodies. Mov Disord. 2016;21:2062–2067.
16. Suryasa, I. W., Rodríguez-Gámez, M., & Koldoris, T. (2021). Health and treatment of diabetes mellitus. *International Journal of Health Sciences*, *5*(1), i-v. https://doi.org/10.53730/ijhs.v5n1.2864
17. Weil RS, Morris HR. REM sleep behaviour disorder: an early window for prevention in neurodegeneration? Brain.2019; 142:498–501