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Rhinorrhea: A common non-dopaminergic feature of Parkinson disease

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Abstract

We compared the frequency of rhinorrhea between 34 Parkinson disease (PD) subjects and 15 normal controls (NC), and explored relationships between rhinorrhea and clinical functions, and degree of nigrostriatal dopaminergic denervation using ¹¹C-dihydrotetrabenazine (DTBZ) brain positron emission tomography (PET) imaging. 68% (23/34) of PD subjects reported rhinorrhea of any cause compared to 27% (4/15) of NC ($\chi^2=7.07$, $p=0.008$). Rhinorrhea frequency remained higher in the PD group after excluding possible rhinitic etiologies: 35% (12/34) PD versus 7% (1/15) of NC ($\chi^2=4.38$, $p=0.04$). There were no differences in demographics, nigrostriatal dopaminergic denervation, and clinical motor or non-motor variables between PD subjects with and without rhinorrhea, except that more PD subjects with rhinorrhea complained of lightheadedness (52% vs. 9%, $\chi^2=5.85$, $p=0.02$). Rhinorrhea is a common non-dopaminergic feature of PD, unrelated to olfactory or motor deficits. Further investigations are needed to determine if rhinorrhea correlates with sympathetic denervation or other autonomic symptoms in PD.

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Keywords

Parkinson disease; rhinorrhea; PET; olfaction; dopamine transporter

INTRODUCTION

Rhinorrhea, defined in previous studies involving patients with Parkinson disease (PD) as the presence of a runny nose unrelated to allergies, respiratory infections or sinus problems, has been reported to occur more frequently among PD patients than healthy controls.^{1,2} The two existing studies on rhinorrhea in PD have originated from only one center,^{1,2} and it remains unclear if rhinorrhea is common to all PD patients or restricted to a specific geographic region.

Friedman and colleagues have hypothesized that rhinorrhea in PD may be due to sympathetic denervation of the nasal mucosa,^{1,2} but they did not investigate other autonomic signs or symptoms. The association of rhinorrhea with olfaction, motor function, and nigrostriatal dopaminergic denervation on PET imaging has also not been explored. One study reported an association between rhinorrhea and hyposmia, but olfaction was assessed by self-report only.¹

In this study, we compare the frequency of rhinorrhea between PD subjects and normal controls (NC) and investigate the relationship between rhinorrhea and clinical (olfaction, motor and autonomic) features, and the degree of nigrostriatal dopaminergic denervation in PD. We hypothesized that (1) rhinorrhea would be more prevalent in PD than in NC, (2) rhinorrhea would be unrelated to olfaction, motor function, or nigrostriatal dopaminergic denervation in PD patients, and (3) rhinorrhea would be related to other autonomic problems in PD.

METHODS

Subjects and patient consents

Thirty-four men between 50–85 years of age meeting UK PD Society Brain Bank criteria for PD³ were enrolled in this study. These subjects were originally recruited for a study on falls in PD. For that study, they had to be ambulatory, non-demented (defined as MMSE ≥ 25), willing to undergo brain PET imaging, and could not be taking cholinesterase inhibitors or pure anti-cholinergic drugs. All were recruited prospectively from the Neurology and Geriatric, Research, Education, Clinical Center (GRECC) clinics at the Veterans Affairs (VA) Hospital. The diagnosis of PD was confirmed by nigrostriatal dopaminergic denervation on [¹¹C]dihydrotetrabenazine (DBTZ) vesicular monoamine transporter type 2 (VMAT2) brain PET imaging. The mean Unified PD Rating Scale (UPDRS) motor score was 27.6 ± 7.3 (range 15–45) and mean disease duration was 6.2 ± 3.1 years (range 0.5–12). All PD subjects were on dopaminergic treatment, but none on apomorphine.

Fifteen male NC were recruited from existing databases/advertisements. They had no known neurological or psychiatric illness, or family history of significant neurological or psychiatric illness in first-degree relatives. All had MMSE ≥ 25 . None were taking centrally-acting medications.

All participants were non-smokers with no history of trauma or concurrent respiratory infection that could interfere with olfaction. None had clinically significant abnormalities (*i.e.* large vessel strokes, excessive white matter changes, or tumors) on brain MRI. Participants gave informed written consent, and the protocol was approved by the

Institutional Review Boards of the University of Michigan and the Ann Arbor VA (ClinicalTrials.gov identifier: NCT00736671).

Clinical testing procedures

Participants were asked if they had a runny nose, allergies, sinus problems, or frequent colds/respiratory infections. Participants had *rhinorrhea* if they answered yes to the question “Do you have a runny nose?” A stricter definition, *non-rhinitic rhinorrhea*, was considered if participants had a runny nose but no allergies, sinus problems, or frequent colds/respiratory infections. This stricter definition was used in previous studies.^{1,2}

Participants were asked (using a yes/no format) if they experienced subjective lightheadedness or passed out during the past year, had a problem with “dusky hands”, or experienced bladder problems, erectile dysfunction or constipation. They were also asked about the presence of diabetes or prostate problems to rule out possible confounding factors. Orthostatic blood pressures were measured. Medications reported to cause rhinorrhea,⁴ including anti-hypertensives, α -antagonists, aspirin and other non-steroidal anti-inflammatory agents, were recorded. Olfaction was assessed using the 40-item University of Pennsylvania Smell Identification Test (UPSIT; Sensonics, Inc. Haddon Heights, NJ)⁵. Motor severity was assessed using the UPDRS motor subsection. PD subjects were tested and imaged in the morning after withholding dopaminergic medications overnight.

Imaging techniques and data analysis

DTBZ PET image acquisition and analysis has been described previously.⁶ The binding potential relative to the non-displaceable uptake (BP_{ND}) was estimated as before,⁶ except that for this analysis, the whole neocortex was used as a reference region instead of the occipital cortex for more robust assessment. Group comparisons were performed using standard t-tests or χ^2 analyses as appropriate. Data were analyzed using SAS, version 9.1 (SAS Institute Inc., Cary, NC).

RESULTS

Rhinorrhea frequency in PD and NC

Rhinorrhea of any cause occurred more frequently in PD compared with NC (68% PD vs. 27% of NC; $\chi^2=7.07$, $p=0.008$, see Table 1). Non-rhinitic rhinorrhea was five times more prevalent in PD than NC (35% vs. 7%; $\chi^2=4.38$, $p=0.04$). Mean UPSIT scores and VMAT2 BP_{ND} activity throughout the striatum were significantly lower in the PD group (Table 1). There was no difference in age or rhinorrhea medications between the patients and controls, but NC had a slightly higher MMSE score ($t=2.10$, $p=0.04$).

PD subjects with and without rhinorrhea

There were no differences in most clinical variables, including baseline demographics, motor function, autonomic symptoms, olfactory performance, and striatal VMAT2 binding using DTBZ PET between PD subjects with and without rhinorrhea (Table 2). There were also no differences in the frequency of diabetes or prostate problems between the 2 groups.

The rhinorrhea group had slightly lower MMSE scores ($t=2.11$, $P=0.04$) and complained more about lightheadedness (52% vs. 9%; $\chi^2=5.85$, $p=0.02$) compared to the non-rhinorrhea PD group. There was also a trend towards a prior history of passing out ($p=0.09$) and lower sitting systolic blood pressures ($p=0.09$) in PD subjects with rhinorrhea. When using a stricter definition of rhinorrhea, there were no significant differences in any baseline demographic, motor, olfactory, autonomic or PET variables, including MMSE, subjective lightheadedness, passing out, and sitting systolic blood pressures.

DISCUSSION

Our results are consistent with the findings of Friedman and others^{1,2} that a runny nose not due to allergies, sinus problems or colds occurs more frequently in PD than non-PD subjects. We further extend these findings and demonstrate that both rhinorrhea due to any cause and non-rhinitic rhinorrhea are unrelated to severity of nigrostriatal dopaminergic activity, or olfactory and motor dysfunction in PD.

The prevalence of non-rhinitic rhinorrhea in our PD subjects (35%) was lower than previously reported (~50%).^{1,2} This could be due to our smaller sample size or the fact that our PD population was comprised of only men. Non-rhinitic rhinorrhea tends to occur more commonly in women with PD, with one study reporting a frequency of 68% in women and 33% in men,¹ a figure more consistent with our findings.

Previous studies on rhinorrhea in PD have reported an association with olfactory impairment, but the presence of olfactory impairment was ascertained by self-report only.¹ We objectively tested odor identification using the UPSIT in this study and found no significant differences between PD patients with and without rhinorrhea, regardless of the rhinorrhea definition used. This is consistent with the observation that PD patients are hyposmic in general⁷ and suggests that rhinorrhea is unrelated to olfaction.

While nigrostriatal pathology correlates with specific motor symptoms in PD, it is now recognized that non-motor comorbidities extend beyond the loss of dopaminergic nigral neurons.⁸ We found no gross differences in striatal VMAT2 binding using DTBZ PET between PD subjects with and without rhinorrhea, but our sample size was small. These findings suggest that rhinorrhea can be added to the growing list of non-dopaminergic features in PD and are also consistent with the possibility that rhinorrhea may be due to sympathetic denervation.^{1,2} Sympathetic denervation in the heart has been reported in PD,⁹ but it is unclear if sympathetic dysfunction also occurs in the nasal mucosa. If it does, it may leave unopposed parasympathetic stimulation, which increases nasal secretions.² We did not perform cardiac noradrenergic PET imaging in this study, but investigated other autonomic symptoms. The percentage of PD subjects with constipation, bladder problems, erectile dysfunction or dusky hands did not differ between the rhinorrhea and non-rhinorrhea groups, regardless of the rhinorrhea definition used. However, patients with rhinorrhea of any cause had more subjective lightheadedness and a trend toward more frequent passing out and lower systolic blood pressures when sitting. These findings were no longer significant after excluding those with a rhinitic cause of rhinorrhea, but we may have had too small a sample size to detect such a difference. Further investigations are clearly needed to see if rhinorrhea correlates with cardiac and/or cerebral sympathetic denervation or other autonomic symptoms in PD.

A limitation of the study is that we did not study women as our patients were recruited from a VA population. Another limitation is that the presence of rhinorrhea was established by questionnaire only. Anatomic causes of rhinorrhea such as nasal polyps, which are common in men and the elderly,¹⁰ cannot be completely excluded. It is possible that rhinorrhea was caused by medications in some subjects, but group comparisons showed no differences in the proportion of participants taking medications with the potential to induce rhinorrhea.

In summary, rhinorrhea is a common, non-dopaminergic feature in PD that is unrelated to the severity of olfactory or motor deficits. The relationship between rhinorrhea, sympathetic denervation, and autonomic dysfunction needs to be further explored using validated questionnaires.

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References

1. Friedman JH, Amick MM. Rhinorrhea is increased in Parkinson's disease. *Mov Disord*. 2008; 23(3):452–454. [PubMed: 18074378]
2. Friedman JH, Amick MM, Chou KL. Rhinorrhea and olfaction in Parkinson disease. *Neurology*. 2008; 70(6):487–489. [PubMed: 18250295]
3. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *J Neurol Neurosurg Psychiatry*. 1992; 55(3):181–184. [PubMed: 1564476]
4. van Rijswijk JB, Blom HM, Fokkens WJ. Idiopathic rhinitis, the ongoing quest. *Allergy*. 2005; 60(12):1471–1481. [PubMed: 16266377]
5. Doty RL, Shaman P, Dann M. Development of the University of Pennsylvania Smell Identification Test: a standardized microencapsulated test of olfactory function. *Physiol Behav*. 1984; 32(3):489–502. [PubMed: 6463130]
6. Bohnen NI, Muller ML, Koeppe RA, et al. History of falls in Parkinson disease is associated with reduced cholinergic activity. *Neurology*. 2009; 73(20):1670–1676. [PubMed: 19917989]
7. Haehner A, Boesveldt S, Berendse HW, et al. Prevalence of smell loss in Parkinson's disease--a multicenter study. *Parkinsonism Relat Disord*. 2009; 15(7):490–494. [PubMed: 19138875]
8. Braak H, Ghebremedhin E, Rub U, Bratzke H, Del Tredici K. Stages in the development of Parkinson's disease-related pathology. *Cell Tissue Res*. 2004; 318(1):121–134. [PubMed: 15338272]
9. Fujishiro H, Frigerio R, Burnett M, et al. Cardiac sympathetic denervation correlates with clinical and pathologic stages of Parkinson's disease. *Mov Disord*. 2008; 23(8):1085–1092. [PubMed: 18442129]
10. Larsen K, Tos M. The estimated incidence of symptomatic nasal polyps. *Acta Otolaryngol*. 2002; 122(2):179–182. [PubMed: 11936910]

Table 1

Baseline characteristics between Parkinson Disease (PD) and normal control (NC) subjects

	PD (n=34)	NC (n=15)	Statistic	P-value
Age (y)	68.3 ± 8.2	66.6 ± 11.7	t=-0.59	0.56
No.(%) with rhinorrhea (any cause)	23 (68)	4 (27)	$\chi^2=7.07$	0.008
No.(%) with non-rhinitic rhinorrhea	12 (35)	1 (7)	$\chi^2=4.38$	0.04
No. (%) on medications with potential to cause rhinorrhea	20 (59)	6 (40)	$\chi^2=1.48$	0.22
UPSIT scores	16.5 ± 8.3	32.2 ± 6.9	t=6.35	<0.0001
MMSE	29.0 ± 1.4	29.6 ± 0.6	t=2.10	0.04
VMAT2 BP _{ND} activity				
Caudate	1.02 ± 0.42	1.59 ± 0.24	t=5.96	<0.0001
Anterior putamen	0.90 ± 0.40	2.20 ± 0.33	t=11.03	<0.0001
Posterior putamen	0.63 ± 0.34	2.44 ± 0.35	t=16.68	<0.0001
Total striatum	0.92 ± 0.31	1.95 ± 0.26	t=11.09	<0.0001

Table 2Comparison of clinical variables and VMAT2 BP_{ND} activity in PD subjects with and without rhinorrhea

	Rhinorrhea + (n=23)	Rhinorrhea - (n=11)	t-statistic	P-value
Age (y)	68.8 ± 7.9	67.3 ± 9.2	-0.51	0.61
Disease duration (y)	6.2 ± 3.1	6.3 ± 3.2	0.15	0.89
No. (%) on medications with potential to cause rhinorrhea	15 (65)	5 (45)	$\chi^2=1.20$	0.27
MMSE	28.7 ± 1.5	29.5 ± 0.7	2.11	0.04
UPSIT score	17.5 ± 9.0	14.4 ± 6.3	-0.98	0.33
UPDRS motor	28.0 ± 8.0	26.6 ± 6.0	-0.53	0.60
No. (%) with lightheadedness	12 (52)	1 (9)	$\chi^2=5.85$	0.02
No. (%) who have passed out	5 (22)	0 (0)	$\chi^2=2.80$	0.09
SBP sitting (mm Hg)	120.0 ± 15.3	128.9 ± 11.5	1.70	0.09
DBP sitting (mm Hg)	74.7 ± 6.1	77.5 ± 9.6	1.04	0.31
Change in SBP with standing (mm Hg)	-2.9 ± 7.1	-4.3 ± 6.1	-0.56	0.58
Change in DBP with standing (mm Hg)	1.9 ± 3.9	0.5 ± 6.1	-0.80	0.43
No. (%) with bladder problems	15 (65)	7 (64)	$\chi^2=0.008$	0.93
No. (%) with constipation	12 (52)	3 (27)	$\chi^2=1.88$	0.17
No. (%) with dusky hands	2 (9)	0 (0)	$\chi^2=1.0$	0.31
No. (%) with impotence	15 (65)	5 (45)	$\chi^2=1.20$	0.27
VMAT2 BP _{ND} activity				
Caudate	1.02 ± 0.43	1.02 ± 0.41	0.02	0.99
Anterior putamen	0.93 ± 0.41	0.82 ± 0.38	-0.71	0.48
Posterior putamen	0.66 ± 0.37	0.59 ± 0.28	-0.51	0.61
Total striatum	0.92 ± 0.31	0.90 ± 0.34	-0.19	0.85

SBP=systolic blood pressure; DBP=diastolic blood pressure