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Prevalence of Impaired Odor Identification in Parkinson Disease with Imaging Evidence of Nigrostriatal Denervation

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Abstract

There is wide variability in reported prevalence rates of abnormal smell in Parkinson disease (PD). This study assessed the prevalence of abnormal smell, using the University of Pennsylvania Smell Identification Test (UPSIT), in 183 patients with PD with confirmed PET imaging evidence of nigrostriatal denervation. Impaired olfaction in this sample was nearly universal (97.8%). Wide-ranging prior olfactory impairment estimates may reflect not only uncertainty regarding diagnostic classification, but also the use of inaccurate normative data and differences in olfactory tests used.

Keywords

Parkinson disease; PET; olfaction; dopamine; aging

Introduction

Impaired odor identification is common and often severe in Parkinson disease (PD). However, there is inconsistency in the literature regarding the prevalence of hyposmia, with estimates ranging from slightly below 50% to roughly 97% (Haehner et al. 2009; Lee et al. 2015). Factors affecting hyposmia frequency estimates in PD may include the type of olfactory test, normative data to which patients were compared, age distribution and duration of disease (Haehner et al. 2009). For example, the recent study by Lee et al. showing a low hyposmia rate included PD patients with disease duration of 3 years or less (Lee et al. 2015) Another factor that may explain the significantly lower hyposmia rate in the Lee et al. study is the use of normative cut-off values that are in part derived from unscreened elderly subjects. An additional factor is the uncertainty of a PD diagnosis in patients with clinical symptoms without confirmed nigrostriatal denervation.

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The University of Pennsylvania Smell Identification Test (UPSIT) is a well-validated assessment instrument of olfactory identification function that uses age-independent cutoff values to define abnormal smell (Doty et al. 1984). The use of formal olfactory testing is necessary, as patients often do not recognize their olfactory impairment (Muller et al. 2002). The goal of this study was to test the hypothesis that abnormal smell is a frequent symptom in PD patients with confirmed positron emission tomography (PET) imaging evidence of nigrostriatal dopaminergic denervation and using a well-validated, sensitive odor identification test.

Methods

This cross-sectional study involved 183 patients with PD (139 males/44 females; mean age 67.0±8.3, range 50–86 years), mean duration of motor disease (6.4±4.3, range 0.5–22 years), and mean Hoehn and Yahr stage (2.5±0.6, range 1–5). All subjects met the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria for PD (Hughes et al. 1992) and additional evidence of nigrostriatal dopaminergic denervation on [^{11}C]dihydrotetrabenazine vesicular monoamine type 2 (VMAT2) PET as previously described (Bohnen et al. 2010). The patient population was predominantly non-demented with only 4 PD patients meeting criteria for (mild) dementia following neuropsychological testing (Shah et al. 2016). None of the subjects had MR imaging evidence of obstructed nasal airways or other significant sinunasal disorders.

Subjects on dopaminergic drugs were imaged the morning after withholding dopaminergic drugs overnight. Patients underwent olfactory testing using the 40-odor UPSIT (Sensonics, Inc. Haddon Heights, NJ, USA), which has age-independent cut-off values to distinguish normal smell (thresholds of >34 for females and >33 for males) from abnormal smell (Doty et al. 1984).

The study was approved by the Institutional Review Board of the University of Michigan for studies involving human subjects and was in compliance with the 1964 Helsinki declaration and its later amendments. Written informed consent was obtained from all subjects.

Results

The mean UPSIT score was 16.0±8.1 (range 0–36). There were a total of 3 out of 139 males with UPSIT scores above the gender cut-off value of 33, resulting in a anosmia/hyposmia rate of 97.8% in males with PD. There was a single woman (out of 44) with an UPSIT score above the gender cut-off of 34, which resulted in a rate of 97.7% for abnormal smell in women with PD. The combined gender impaired olfaction rate in this sample was 97.8%. The distribution of functional anosmia (UPSIT score of 10 or less), hyposmia and normosmia were 24.6%, 73.2% and 2.2%, respectively.

The four subjects classified as normosmic had scores ranging from 34 to 36. There were no subjects with the maximum score (40) on this test. The age of the normosmic patients were 54 (female), 63, 63 and 67, which was below or at the average of the study population (67 years). The duration of their motor disease were 2, 2.5, 4 and 5 years, respectively and were below the average duration in this population (6.4 years). Retrospective review of the

clinical characteristics of these subjects did not yield atypical features. Furthermore, inspection of the flow delivery images of the dynamic PET images did not show flow abnormalities to indicate the presence of atypical parkinsonism.

A *post hoc* analysis limited the subjects to a disease duration of 3 years or less, showed that only a single subject (female) out of 56 subjects (40 males, 16 females) had a score in the normosmic range yielding a hyposmia rate of 98.2% in this sub-group of early PD.

Discussion

PD tends to be over-diagnosed when only using clinical symptoms and not confirming the presence of nigrostriatal denervation (Hughes et al. 1992). This study was unique in the use of PET scans to confirm the presence of nigrostriatal nerve terminal losses in all patients, whereas previous studies have only partially used dopamine transporter scans to improve the accuracy of the diagnosis of PD (Haehner et al. 2009; Berendse et al. 2011). Our findings show a high rate of impaired olfaction, 97.8%, in PD subjects based on age-independent normative cutoff values. However, none of the patients in the normosmic range had an UPSIT score >36. This figure is supported by previous literature, including Haehner et al. whose multicenter study found only 3.3% of PD patients presented with normosmia when compared to “Sniffin’ sticks” age-independent normative data (Haehner et al. 2009). The comparable normosmia rates between our and the Haehner et al. studies suggest that both the UPSIT and the olfactory assessment used by Haehner et al. (i.e. “Sniffin’ Sticks”) have similar reliability for diagnosis of impaired olfaction in PD when using age-independent cut-off criteria.

A recent study by Lee et al. however, found a prevalence of only 46.1% of abnormal smell in PD despite PET imaging confirmation of nigrostriatal denervation in the patients (Lee et al. 2015). A plausible explanation for this significant discrepancy in prevalence is that Lee et al. used an abbreviated odor identification test of only 12 odors. The use of an abbreviated olfactory test is expected to lower its sensitivity in identifying hyposmia. Another reason may be that the study by Lee *et al*. included subjects with disease duration of 3 years or less only. However, our *post hoc* analysis showed a rate of 98.2% of abnormal smell in this early PD sub-group. Another factor that may explain the significantly lower olfactory impairment rate in the Lee et al. study is the use of arbitrary cut-off values that were in part derived from unscreened elderly subjects, whereas this study used an age-independent and well-validated cutoff value to distinguish normal from abnormal smell (Doty et al. 1984). It should be noted that current age-stratified normative data are generally derived from older subjects unscreened for prodromal neurodegenerative diseases. This may represent a significant confounding factor as the prevalence of incidental prodromal Alzheimer and Lewy body neurodegenerative pathology in cognitively normal elderly has been reported as high as 44% and 20%, respectively. Such presence of prodromal neurodegenerative pathology, frequently found in otherwise normal elderly subjects, may negatively affect olfaction (Adler et al. 2010; Jansen et al. 2015). Consequently, inclusion of non-screened elderly subjects with prodromal neurodegeneration in normative databases may artificially lower age-dependent hyposmia cutoffs.

The use of normative data derived from age-matched elderly in PD olfactory diagnostic studies also explains lower olfactory scores to distinguish PD from non-PD control subjects. For example, we previously used an area under receiver operating curve to find the best discrimination between PD and age-matched normal control subjects yielding an UPSIT cut-off score of 29 (Bohnen et al. 2008). This lower value indicates the (expected) presence of hyposmia in a subset of non-PD control subjects. As olfactory testing in elderly subjects may be abnormal in those with prodromal neurodegenerations, in particular Alzheimer disease (Jansen et al. 2015), its diagnostic performance will be limited because of this non-specificity. Our data show that olfactory diagnostic testing may be very useful for screening purposes to detect PD because of high sensitivity but will require a multi-tiered approach with combination with other diagnostic tests to increase its diagnostic specificity.

The term functional anosmia refers to a significantly reduced or absent ability to smell, although some smell sensations can be present. These do however not give patients a normal ability to smell, which would be meaningful in daily life. Hyposmia refers to a reduced ability to smell (Hummel et al. 2011). The majority of our patients (73.2%) had evidence of hyposmia. Therefore, odor impairment should always be measured with formal testing as it cannot be reliably assessed based on patients' history alone (Muller et al. 2002).

Atypical parkinsonism is generally not associated with impaired olfactory function (Wenning et al. 1995). Therefore, a limitation of our study was the cross-sectional design without longitudinal assessment to determine whether some of the 4 normosmic patients may ultimately prove to have atypical parkinsonism and not Lewy body parkinsonism. However, inspection of the flow delivery images of the dynamic PET images did not show abnormalities to indicate the presence of atypical parkinsonism.

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Abbreviations

PET	positron emission tomography
PD	Parkinson disease
UPSIT	University of Pennsylvania Smell Identification Test
VMAT2	vesicular monoamine transporter type 2

References

Adler CH, Connor DJ, Hentz JG, Sabbagh MN, Caviness JN, Shill HA, Noble B, Beach TG. Incidental Lewy body disease: clinical comparison to a control cohort. Mov Disord. 2010; 25(5):642–646. [PubMed: 20175211]

Berendse HW, Roos DS, Raijmakers P, Doty RL. Motor and non-motor correlates of olfactory dysfunction in Parkinson's disease. J Neurol Sci. 2011; 310(1–2):21–24. doi:S0022-510X(11)00332-7 [pii]10.1016/j.jns.2011.06.020. [PubMed: 21705022]

Bohnen NI, Muller MLTM, Kotagal V, Koeppe RA, Kilbourn MA, Albin RL, Frey KA. Olfactory dysfunction, central cholinergic integrity and cognitive impairment in Parkinson disease. Brain. 2010; 133:1747–1754. [PubMed: 20413575]

Bohnen NI, Studenski SA, Constantine GM, Moore RY. Diagnostic performance of clinical motor and non-motor tests of Parkinson disease: a matched case-control study. Eur J Neurol. 2008; 15(7):685–691. doi:ENE2148 [pii]10.1111/j.1468-1331.2008.02148.x. [PubMed: 18435767]

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]

Haehner A, Boesveldt S, Berendse HW, Mackay-Sim A, Fleischmann J, Silburn PA, Johnston AN, Mellick GD, Herting B, Reichmann H, Hummel T. Prevalence of smell loss in Parkinson's disease--a multicenter study. Parkinsonism Relat Disord. 2009; 15(7):490–494. doi:S1353-8020(08)00349-0 [pii]10.1016/j.parkreldis.2008.12.005. [PubMed: 19138875]

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]

Hummel T, Landis BN, Huttenbrink KB. Smell and taste disorders. GMS current topics in otorhinolaryngology, head and neck surgery. 2011; 10:Doc04.

Jansen WJ, Ossenkoppele R, Knol DL, Tijms BM, Scheltens P, Verhey FR, Visser PJ, Amyloid Biomarker Study G. Aalten P, Aarsland D, Alcolea D, Alexander M, Almdahl IS, Arnold SE, Baldeiras I, Barthel H, van Berckel BN, Bibeau K, Blennow K, Brooks DJ, van Buchem MA, Camus V, Cavedo E, Chen K, Chetelat G, Cohen AD, Drzezga A, Engelborghs S, Fagan AM, Fladby T, Fleisher AS, van der Flier WM, Ford L, Forster S, Fortea J, Foskett N, Frederiksen KS, Freund-Levi Y, Frisoni GB, Froelich L, Gabryelewicz T, Gill KD, Gkatzima O, Gomez-Tortosa E, Gordon MF, Grimmer T, Hampel H, Hausner L, Hellwig S, Herukka SK, Hildebrandt H, Ishihara L, Ivanoiu A, Jagust WJ, Johannsen P, Kandimalla R, Kapaki E, Klimkowicz-Mrowiec A, Klunk WE, Kohler S, Koglin N, Kornhuber J, Kramberger MG, Van Laere K, Landau SM, Lee DY, de Leon M, Lisetti V, Lleo A, Madsen K, Maier W, Marcusson J, Mattsson N, de Mendonca A, Meulenbroek O, Meyer PT, Mintun MA, Mok V, Molinuevo JL, Mollergard HM, Morris JC, Mroczko B, Van der Mussele S, Na DL, Newberg A, Nordberg A, Nordlund A, Novak GP, Paraskevas GP, Parnetti L, Perera G, Peters O, Popp J, Prabhakar S, Rabinovici GD, Ramakers IH, Rami L, Resende de Oliveira C, Rinne JO, Rodrigue KM, Rodriguez-Rodriguez E, Roe CM, Rot U, Rowe CC, Ruther E, Sabri O, Sanchez-Juan P, Santana I, Sarazin M, Schroder J, Schutte C, Seo SW, Soetewey F, Soininen H, Spiru L, Struyfs H, Teunissen CE, Tsolaki M, Vandenberghe R, Verbeek MM, Villemagne VL, Vos SJ, van Waalwijk van Doorn LJ, Waldemar G, Wallin A, Wallin AK, Wiltfang J, Wolk DA, Zboch M, Zetterberg H. Prevalence of cerebral amyloid pathology in persons without dementia: a meta-analysis. JAMA. 2015; 313(19):1924–1938. [PubMed: 25988462]

Lee DH, Oh JS, Ham JH, Lee JJ, Lee I, Lee PH, Kim JS, Sohn YH. Is normosmic Parkinson disease a unique clinical phenotype? Neurology. 2015; 85(15):1270–1275. [PubMed: 26354986]

Muller A, Reichmann H, Livermore A, Hummel T. Olfactory function in idiopathic Parkinson's disease (IPD): results from cross-sectional studies in IPD patients and long-term follow-up of de-novo IPD patients. J Neural Transm. 2002; 109(5–6):805–811. [PubMed: 12111470]

Shah N, Frey KA, Muller MLTM, Petrou M, Kotagal V, Koeppe RA, Scott PJ, Albin RL, Bohnen NI. Striatal and Cortical beta-Amyloidopathy and Cognition in Parkinson's Disease. Mov Disord. 2016; 31(1):111–117. [PubMed: 26380951]

Wenning GK, Shephard B, Hawkes C, Petruckevitch A, Lees A, Quinn N. Olfactory function in atypical parkinsonian syndromes. Acta Neurol Scand. 1995; 91(4):247–250. [PubMed: 7625148]