SHORT REPORT

Olfactory function distinguishes vascular parkinsonism from Parkinson's disease

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Objective: To compare olfactory function in vascular parkinsonism and Parkinson's disease diagnosed according to published clinical diagnostic criteria.

Methods: The University of Pennsylvania smell identification test (UPSIT) was carried out in 14 patients with vascular parkinsonism, 18 with Parkinson's disease, and 27 normal controls matched for age, sex, and smoking status.

Results: UPSIT scores in vascular parkinsonism (mean 26.1, 95% confidence interval, 23.1 to 29.0) were significantly better than in Parkinson's disease (mean 17.1 (14.5 to 19.7)) ($p<0.0001$), and did not differ from the healthy controls (mean 27.6 (25.8 to 29.4)) ($p=0.32$).

Conclusions: Testing olfactory function may be helpful in differentiating vascular parkinsonism from Parkinson's disease.

It is now well established that patients with Parkinson's disease have markedly impaired olfactory function.[1][2] This clinical feature corresponds to neuropathological findings of Lewy bodies in the anterior olfactory nucleus, showing involvement of the olfactory system in the neurodegenerative process in Parkinson's disease.[2] Olfactory dysfunction occurs early in the course of the disease[3][4] and is independent of "on" or "off" state, treatment,[1] or age at onset.[2]

Olfactory function has been investigated in other neurodegenerative conditions associated with parkinsonism. It was found to be impaired in dementia with Lewy bodies,[5] mildly impaired in multiple system atrophy,[6] and normal in progressive supranuclear palsy,[6] corticobasal degeneration,[6] and parkin-positive parkinsonism.[7]

Vascular parkinsonism has been defined neuropathologically as parkinsonism occurring in cerebrovascular disease, after exclusion of Lewy body disease and other neurodegenerative conditions associated with parkinsonism.[8][9] However, vascular parkinsonism remains difficult to distinguish clinically from Parkinson's disease, because basal ganglia infarcts can occur without parkinsonism,[10][11] and vascular pathology commonly occurs in Lewy-body Parkinson's disease.[12] There is evidence from magnetic resonance imaging (MRI) studies suggesting that two different types of vascular lesion may cause vascular parkinsonism: widespread and bilateral ischaemic lesions have been linked to gradual onset parkinsonism, while basal ganglia infarcts have been reported to be associated with acute onset contralateral parkinsonism.[13][14] This differentiation was confirmed in a recent clinicopathological correlation study.[9]

Our aim in this study was to assess olfactory function in patients with vascular parkinsonism compared with those with Parkinson's disease and normal controls. To increase the accuracy of the clinical diagnosis of vascular parkinsonism, we required the patients to fulfil published clinical diagnostic criteria[14] and additional stricter clinical and MRI criteria.[9][13]

METHODS

Olfactory function was tested using the University of Pennsylvania smell identification test (UPSIT, Sensonics, Haddon Heights, New Jersey, USA). This test kit consists of 40 odours, which are microencapsulated in paper strips and released by scratching with a pencil. Patients are required to make a forced choice from four possible answers for each item, even if no odour is perceived. The maximum score is 40; normal values decrease with age and are lower in men.[15]

Eligible patients had to fulfil published clinical diagnostic criteria,[14] which include scores for vascular risk factors and for the temporal relation of stroke and onset of parkinsonism. Additionally, the localisation of MRI lesions in relation to the clinical picture,[9] rather than their absolute number, was taken into account. Relevant cognitive impairment (defined as a score of $\leqslant 24$ on the mini-mental state examination) was an exclusion criterion. L-dopa response was determined, based on the participants' subjective assessment and the case notes, but was not used as an exclusion criterion for vascular parkinsonism.

Consecutive patients attending the movement disorders clinics at the National Hospital for Neurology and Neurosurgery and the Middlesex Hospital, London, who fulfilled the outlined criteria were asked to participate.

Patients with vascular parkinsonism were matched for age, sex, and smoking status with normal controls, who were spouses and carers of patients, and with patients with Parkinson's disease from the same clinics. Parkinson's disease was diagnosed according to the Queen Square Brain Bank criteria.[16] In Parkinson's disease patients, vascular lesions on MRI precluded participation, the only exception being minimal evidence of small vessel disease in areas other than the basal ganglia, interpreted as normal for age by an independent radiologist. Subjects were excluded if there was a history of nasal or sinus surgery, severe head trauma, obstructive pulmonary disease, or allergies causing nasal congestion.

For statistical analysis, group means were compared using the unpaired t test. The Kolmogorov–Smirnov test for difference from a normal distribution was non-significant, and inspection of histograms revealed no substantial outliers.

RESULTS

Table 1 shows the demographic and clinical details, imaging results, vascular risk factors,[15] and UPSIT scores for the 14 patients with vascular parkinsonism. Mean age was 74.1 years in the vascular parkinsonism group, 72.6 years (range 63 to 85) in the 27 control subjects, and 70.6 years (64 to 85) in the 18 patients with Parkinson's disease. Mean disease duration was 6.6 years for the vascular parkinsonism group and 9.1 years (range 2 to 17) for the Parkinson's disease group. Mean age and disease duration did not differ significantly among the groups.

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Abbreviation: UPSIT, University of Pennsylvania smell identification test

Table 1 Demographic data, clinical features, and magnetic resonance imaging findings in the patients with vascular parkinsonism

No	Sex	Age (years)	Duration (years)	Onset	Clinical features	MRI	Vascular risk factors	L-dopa response	MMSE	UPSIT
1	M	66	7	Acute	Hemiparkinsonism following stroke, later shuffling gait	Acute MRI: haemorrhagic infarct contralateral LN; later: DWML, PWML	Stroke	Equivocal	30	23
2	M	67	3	Acute	Hemiparkinsonism following stroke	Lesion contralateral SN	Hypertension, smoking, hyperlipidaemia, stroke	Not tried	30	32
3	M	71	5	Insidious	Shuffling gait, lower body parkinsonism	DWML, PWML	Hypertension, CHD, MI, hyperlipidaemia	Not tried (declined)	28	31
4	M	75	6	Insidious	Predominantly lower body parkinsonism	DWML, PWML	Hypertension, mitral valve prolapse, CHD	Good	27	24
5	M	76	9	Insidious	Shuffling gait, later bradykinesia including upper limbs, blepharospasm	DWML, PWML	Hypertension	Poor	29	23
6	M	82	4	Acute	Shuffling gait, predominantly lower body parkinsonism following stroke	Bilateral GP lesions, DWML, PWML	Stroke	Poor	27	18
7	M	88	28	Acute	Hemiparkinsonism with tremor, slowly progressive tremor dominant parkinsonism	Bilateral GP lesions, DWML, PWML	Hypertension, two strokes	Absent	29	25
8	M	82	5	Insidious	Asymmetric tremor dominant parkinsonism	Bilateral PWML, bilateral midbrain lesions	Hypertension, diabetes, CHD, HF	Good	27	33
9	F	65	3	Insidious	Shuffling gait, start hesitation. Mild central hemiparesis resulting from stroke	Bilateral lesions inferior BG, DWML, PWML	Hypertension, stroke	Not tried	28	32
10	F	67	3	Acute	Asymmetric parkinsonism with tremor, later predominantly lower body parkinsonism	Lesion contralateral GP, DWML, PWML	Hypertension, family history of stroke	Moderate	30	29
11	F	68	4	Acute	Hemiparesis resulting from stroke, later shuffling gait, bradykinesia	Lesion contralateral LN, DWML, PWML	Hypertension, stroke	Equivocal	30	19
12	F	75	9	Insidious	Shuffling gait, later asymmetrical parkinsonism with rest tremor	DWML, PWML	Hypertension, hyperlipidaemia, stroke	Equivocal (poor tolerability on low doses)	27	21
13	F	76	4	Insidious	Tremor, gait ignition failure	DWML, PWML	CHD, AF	Moderate	29	25
14	F	79	3	Acute	Hemiparkinsonism <1 month after stroke, later shuffling gait	Lesion contralateral LN, DWML, PWML	Hypertension, stroke, hyperuricaemia, CHD, family history of stroke	Moderate	28	30

AF, atrial fibrillation; BG, basal ganglia; CHD, coronary heart disease; DWML, deep subcortical white matter lesions (bilaterally); GP, globus pallidus; HF, heart failure; LN, lentiform nucleus; MI, myocardial infarction; MMSE, mini-mental state examination; MRI, magnetic resonance imaging; PWML, periventricular white matter lesions (bilaterally); SN, substantia nigra; UPSIT, University of Pennsylvania smell identification test.
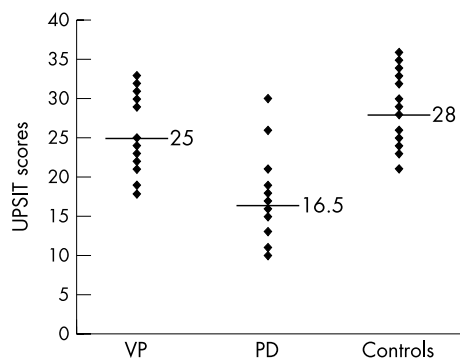
Figure 1 Scatterplot showing UPSIT scores in vascular parkinsonism (VP), Parkinson's disease (PD), and normal controls. Horizontal lines indicate median values. UPSIT, University of Pennsylvania smell identification test.

The mean UPSIT score in the vascular parkinsonism group was 26.1 (95% confidence interval (CI) 23.1 to 29.0), which was significantly different from the Parkinson's disease group, where mean UPSIT was 17.1 (14.5 to 19.7); 95% CI of the difference 5.2 to 12.7; p<0.0001). Mean UPSIT in the normal controls was 27.6 (25.6 to 29.4). Median values are shown in fig 1. The difference between Parkinson's disease and controls was significant (95% CI of difference, −13.5 to −7.6; p<0.0001), while the difference between vascular parkinsonism and controls was non-significant (p = 0.32). In this elderly age group, an UPSIT score of >22 had a sensitivity of 85.7% for detecting vascular parkinsonism and a specificity of 88.9% for distinguishing vascular parkinsonism from Parkinson's disease. As the subjects' age distribution spanned ages where considerable changes in olfactory function normally occur,[15] we analysed separate cut off points for two age groups (65–75 and 76–88 years). The cut off value showing the best balance between sensitivity and specificity was ⩽23 in the 65–75 group, with 100% sensitivity and a specificity of 85.7%. In the 76–88 group, an UPSIT score of ⩽22 yielded a sensitivity of 85.7% and a specificity of 80%.

DISCUSSION

Our results show that olfactory function in patients with a clinical diagnosis of vascular parkinsonism is substantially better than in patients with probable Parkinson's disease in whom relevant vascular lesions have been excluded. Olfactory function in vascular parkinsonism did not differ significantly from that in age matched normal controls. We conclude from our findings that testing patients' sense of smell may be a useful adjunct for differentiating between Parkinson's disease and suspected vascular parkinsonism.

The UPSIT can be done quickly and easily in an outpatient setting and can be self administered by patients. However, in view of possible cultural factors influencing results, normal values as published may not be universally applicable and may need to be established for each centre. It may therefore be of interest to investigate alternative testing methods in this patient population. Precise age matching is important in a group of patients where age has a considerable impact on olfactory performance.

The clinical presentation of cerebrovascular disease may be indistinguishable from Parkinson's disease. In a clinico-pathological study of 100 patients with a clinical diagnosis of Parkinson's disease, neuropathological examination confirmed this diagnosis in only 76%.[17] In three of the 24 misdiagnosed patients, cerebrovascular disease was the only abnormality. A recent clinicopathological study of vascular parkinsonism found that nine of 17 patients had been diagnosed as having Parkinson's disease during life,[9] also reflecting difficulties in differential diagnosis which exist in clinical practice.

The concept of vascular parkinsonism as a clinical entity was proposed in 1929.[8] Traditionally, ''lower body parkinsonism''[18] with predominant lower limb involvement and gait ignition failure was attributed to a vascular aetiology,[19] while features such as asymmetrical onset, tremor, upper limb involvement, and good L-dopa response were believed to represent Parkinson's disease. Recent clinical-radiological studies in suspected vascular parkinsonism have indicated that cerebrovascular disease can cause a variety of parkinsonian features[8 13 14] and a clinicopathological study showed a relation between the clinical presentation and the localisation and type of vascular lesions.[9]

Although most studies using psychophysical olfactory tests in Parkinson's disease showed little correlation with disease duration,[1] there is evidence from olfactory evoked responses suggesting some impact of progressing disability on olfactory function.[2 20] The early involvement of olfactory neurones in the neurodegenerative process in Parkinson's disease[21] explains the findings of early, including presymptomatic, smell deficits.[4] This suggests that olfactory testing may help in the differential diagnosis of Parkinson's disease and vascular parkinsonism when applied early.

A limitation of our study is the fact that the applied diagnostic criteria for vascular parkinsonism have not yet been validated prospectively. However, by requiring fulfilment of two sets of diagnostic criteria, we attempted to reduce the number of patients with alternative diagnoses. It is possible that excluding L-dopa responsive patients might have further increased the diagnostic accuracy for vascular parkinsonism. However, some degree of L-dopa responsiveness has been found in 23–71% of pathologically confirmed vascular parkinsonism cases,[13 22 23] and motor complications may occur.[23]

As would be expected, we found a small overlap in UPSIT scores between the groups: Four (28.6%) of the 14 patients with vascular parkinsonism and seven (25.9%) of the 27 controls had scores below published optimal cut off values for the respective age and sex groups in an American population.[24] This most probably reflects the fact that these reference values do not distinguish age groups above 71 and therefore do not fully represent the continuing olfactory loss in very elderly subjects, such as those involved in this study. Moreover, it has been suggested[2 6 25] that the UPSIT normative values may not be easily transferable from the USA to other countries, where several of the odours used in the test are not familiar. It remains a possibility that some of the hyposmic vascular parkinsonism patients had subclinical or co-morbid Lewy body changes in addition to cerebrovascular disease.

The proportion of normal scores that we found in the patients with Parkinson's disease and the sensitivity of UPSIT for distinguishing between Parkinson's disease and vascular parkinsonism are in keeping with most reports showing olfactory dysfunction in 70–90% of Parkinson's disease patients.[1 2]

We conclude that, in contrast to Parkinson's disease, the majority of patients with vascular parkinsonism and without associated dementia have a preserved sense of smell. Testing olfactory function may help in the differential diagnosis between two important causes of parkinsonism in the elderly.

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