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Olfactory testing combined with dopamine transporter imaging as a method to detect prodromal Parkinson's disease

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ABSTRACT

Objective Olfactory dysfunction is an early and common symptom in Parkinson disease (PD). Previously, the authors demonstrated that idiopathic olfactory dysfunction in first-degree relatives of PD patients is associated with an increased risk of developing PD within 2 years. The aim of the present study was to determine the value of combined olfactory testing and SPECT scanning in predicting future PD in the same population of relatives over a 5-year period.

Methods In a cohort of 361 non-parkinsonian, non-demented first-degree relatives of PD patients, a combination of olfactory processing tasks was used to select groups of hyposmic (n=40) and normosmic (n=38) individuals for a 5-year clinical follow-up evaluation and sequential SPECT scanning, using a dopamine transporter ligand to assess nigrostriatal dopaminergic function at baseline and 5 years from baseline. A validated questionnaire, sensitive to the presence of parkinsonism, was used in the follow-up of the remaining 283 relatives.

Results Five years from baseline, five out of the 40 hyposmic relatives fulfilled clinical diagnostic criteria for PD. None of the other 349 relatives available for follow-up developed PD. All hyposmic individuals developing PD had an abnormal baseline SPECT scan.

Discussion In conclusion, idiopathic hyposmia in first-degree relatives of PD patients is associated with an increased risk of developing clinical PD of 12.5% over a 5-year period. The present data suggest that a two-step approach using olfactory testing followed by SPECT scanning in hyposmic individuals has a very high sensitivity and specificity in detecting PD. The usefulness of this two-step approach needs to be confirmed in larger populations.

INTRODUCTION

Parkinson disease (PD) is characterised by degeneration of nigrostriatal dopaminergic neurons. Imaging studies in PD suggest that the onset of dopaminergic loss antedates the clinical diagnosis by 4–6 years.^{1–3} This time-window offers the opportunity to apply neuroprotective treatments^{4,5} and slow down the disease process early, delaying the appearance of motor signs. Subclinical reductions in dopamine transporter (DAT) binding have indeed been detected in at-risk individuals who later developed PD.^{6,7} However, considering radiation exposure and cost-effectiveness, DAT imaging is not a suitable screening strategy for PD in the general population. It is therefore important to identify risk factors for PD that can be used in conjunction with

imaging techniques to identify participants in the prodromal phase of PD.

Recently several groups have demonstrated that hyposmia is a risk factor to develop PD in both selected and unselected populations.^{8–10} However, the absolute risk of future PD associated with olfactory dysfunction is not high, likely due to a lack of specificity of hyposmia for PD. A two-step approach, combining olfactory testing and DAT single-photon emission CT scanning, might significantly increase specificity.

Two-year follow-up data of a prospective study using combined olfactory testing and SPECT scanning in a cohort of first-degree relatives of PD patients were reported previously.⁹ The aim of the present study was to determine the value of combined olfactory testing and SPECT scanning in predicting future PD in the same cohort of PD relatives over a 5-year period. An additional goal was to determine whether the increased rate of loss of DAT binding that was observed 2 years from baseline in hyposmic, but non-parkinsonian relatives would progress over time.

MATERIALS AND METHODS

Study population/participants

The present study involved 361 non-parkinsonian, non-demented first-degree relatives of patients with sporadic PD, who were selected as previously described.⁶ All participants gave written informed consent; the study protocol was approved by the Health Council of The Netherlands and local medical ethical committees of the VU University Medical Center and the Academic Medical Center.

Study design

At baseline, all 361 participants were submitted to a combination of an odour detection, discrimination and identification task.⁶ As described previously,⁸ 40 hyposmic and 38 normosmic participants were selected for SPECT scanning based upon their olfactory test scores. These two groups did not differ with regard to baseline demographics.⁸

Five years after baseline, 74 out of the 78 individuals who were scanned at baseline were available for clinical follow-up, four of whom did not have a follow-up SPECT scan for various reasons (see figure 1). A total of 280 relatives, including 277 of the 283 relatives not selected for baseline SPECT scanning and three relatives who switched from the hyposmic and normosmic groups, completed a questionnaire sensitive to the presence of parkinsonism as part of the 5-year follow-up evaluation.

Clinical evaluation

Clinical evaluation of all individuals selected for SPECT scanning included a neurological examination and a specific assessment to detect parkinsonism as defined by the UK Parkinson's disease Society Brain Bank (UK-PDSBB) criteria.¹¹ Motor function was rated using the motor section of the Unified Parkinson's Disease Rating Scale (UPDRS); a score of ≥ 5 was considered a sign of motor dysfunction, not necessarily as part of a parkinsonian syndrome. Individuals who were using dopaminergic medication were tested off-medication, at least 12 h after their evening dose.

The mail questionnaire used consisted of a Dutch translation of a screening questionnaire for PD (for a description, see Ponsen et al⁸ and Duarte et al¹²) and an additional question to establish whether any physician had made a diagnosis of PD over the course of the follow-up period. Three or more positive

responses to the questionnaire, as well as a positive response to the additional question, were considered indicative of possible parkinsonism, and these individuals were submitted to a structured clinical work-up by a blinded movement disorders specialist not involved in the baseline screening.

SPECT scanning

SPECT scanning was performed as described previously,^{6 8 13} using the well-validated DAT tracer [¹²³I]β-CIT.¹⁴ For the present study, we used an updated image reconstruction method, resulting in a 3D mode reconstruction (<http://www.neurophysics.com>). Analysis of bilateral striatal, bilateral putamen and bilateral caudate [¹²³I]β-CIT binding for each baseline and follow-up scan was performed as described previously.⁶ Baseline SPECT scans of one hyposmic relative and three

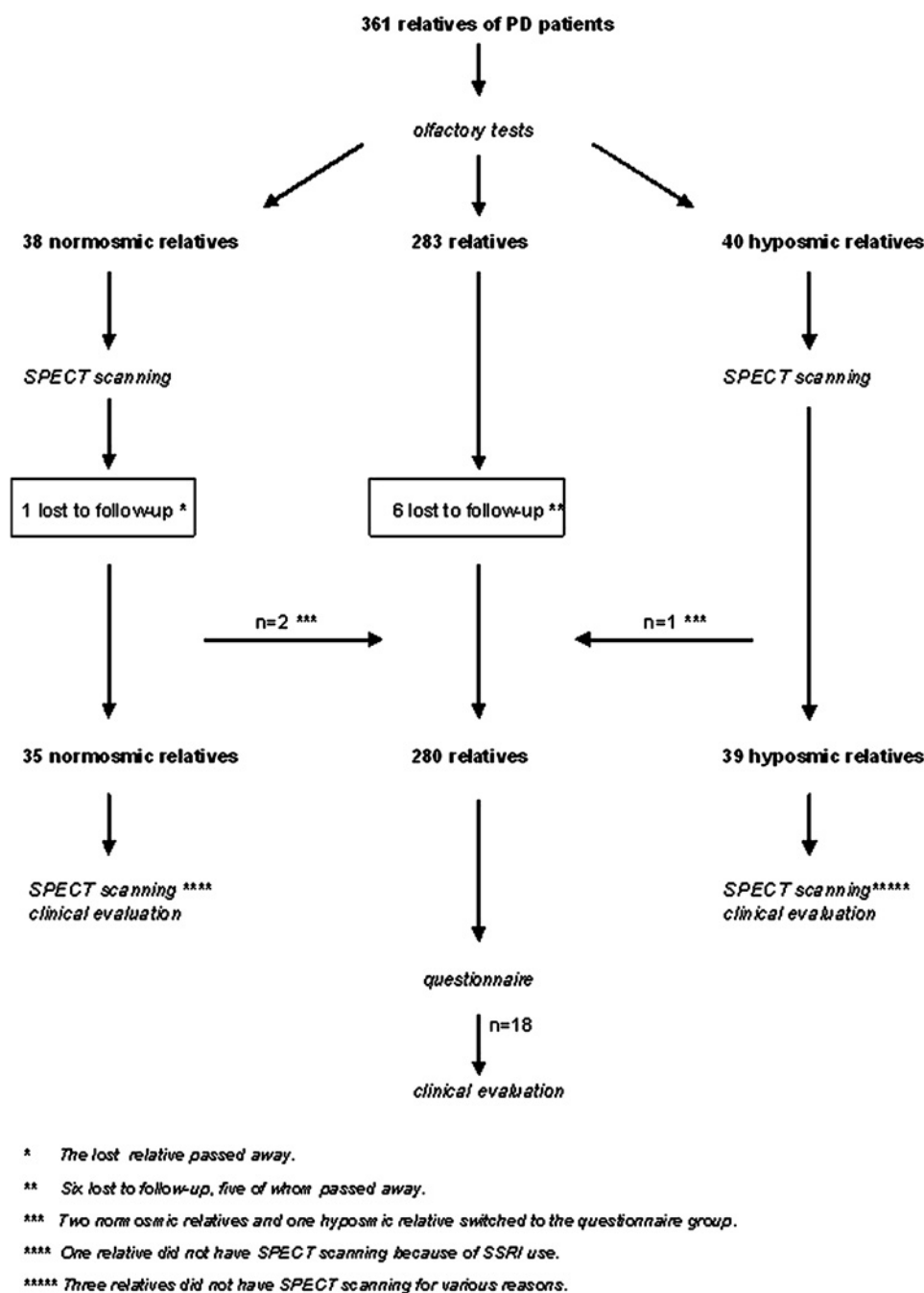


Figure 1 Flow chart illustrating the overall design of the study.

Research paper

normosmic relatives could not be analysed quantitatively due to technical problems.

For both baseline and follow-up SPECT scans, group means of each binding parameter were calculated and compared by means of the Student unpaired *t* test. In addition, for each baseline SPECT parameter, age-adjusted means and the 98% CI were determined in the group of normosmic relatives. Individual baseline values of hyposmic relatives were considered abnormal if they fell outside the 98% CI of the age-adjusted means of the group of normosmic individuals. Linear regression analysis was used to compare the average rate of decline in binding ratios, corrected for baseline values, over the 5-year follow-up period between groups (see also⁸).

RESULTS

Clinical evaluation

Five years from baseline testing, five relatives (12.5% out of 40 baseline hyposmic relatives) had developed clinical PD. Initial clinical (motor) symptoms appeared 9–52 months (median 15 months) after baseline testing. Five years from baseline, 'off'-medication UPDRS motor scores in these patients were 13, 16, 18, 29 and 52. Three of these relatives were using a dopamine-agonist and/or levodopa, and had a good response. Of the other 349 relatives available for follow-up, none fulfilled UK-PDSBB criteria for a parkinsonian syndrome, including the 280 relatives in the questionnaire group and the 69 non-parkinsonian relatives in the groups selected for SPECT scanning and clinical evaluation. In the questionnaire group, 18 relatives had three to seven (out of nine) positive responses to the screening questionnaire. Subsequent clinical neurological evaluation did not reveal a parkinsonian syndrome in any of them.

SPECT imaging

The mean SPECT binding ratios at baseline and 5 years later for the hyposmic and normosmic groups are listed in table 1. Five years from baseline, mean bilateral whole striatal, caudate and putamen binding ratios were not significantly different between normosmic and hyposmic relatives without parkinsonism. Of the hyposmic relatives with parkinsonism, all parameters were significantly different from the normosmic relatives and from the hyposmic relatives without parkinsonism. Compared with previously published data,^{6,8} the updated reconstruction method (see Materials and methods section) resulted in comparable, but slightly higher binding ratios.

At baseline, only the five hyposmic relatives who later developed clinical PD (as opposed to the 34 remaining hyposmic relatives) had at least one reduced [¹²³I]β-CIT binding ratio (ie, measurements for whole striatum, putamen or caudate) outside the 98% CI of the age-adjusted means of the normosmic relatives; three relatives with all six binding ratios reduced, one relative with reduced right striatal and right putamen binding ratios and

one relative with reduced left and right putamen binding ratios (putamen [¹²³I]β-CIT binding ratios are illustrated in figure 2). In the group of the normosmic relatives, only a single relative had (marginally) reduced left and right striatal and putamen binding ratios at baseline. However, 5 years from baseline, this relative had not developed parkinsonism and had normal binding ratios.

Five years from baseline, all five hyposmic relatives with clinical PD had reduced [¹²³I]β-CIT binding ratios compared with 2-year follow-up. A single normosmic relative, who had a normal baseline SPECT scan, now had marginally reduced right striatal and bilateral putamen binding ratios. However, this relative had not developed signs of parkinsonism (UPDRS motor score 2). The remaining relatives had normal binding ratios.

The average rate of decline in [¹²³I]β-CIT binding ratios over the 5-year follow-up period was not significantly different between the groups of normosmic and hyposmic relatives (table 1). There was a trend towards a higher rate of decline (*p*=0.093) in left putamen binding in the hyposmic group, compared with the normosmic group. This trend disappeared when the five hyposmic relatives who had already developed clinical PD were excluded from the analysis. No individual hyposmic or normosmic relative had a particularly rapid loss of binding.

DISCUSSION

In this 5-year follow-up study in first-degree relatives of PD patients, idiopathic hyposmia at baseline was associated with an increased risk of subsequently developing clinical PD of 12.5%. Furthermore, all hyposmic individuals who had developed PD within 5 years from baseline, had abnormal striatal DAT binding at baseline. No evidence was found for a subclinical dopaminergic degeneration in non-parkinsonian hyposmic relatives.

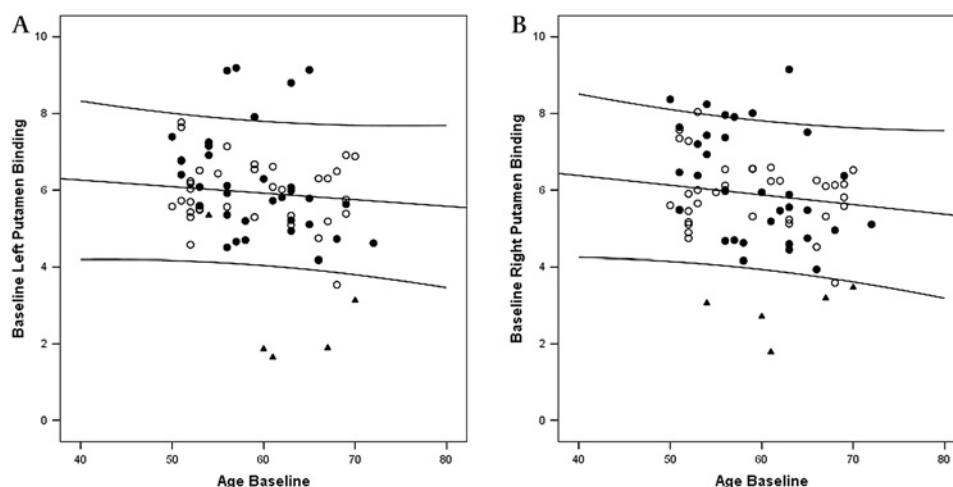
Compared with previous studies reporting an increased risk of developing clinical PD in the range of 2–7% for hyposmic individuals,^{9,10} the 12.5% risk found in our study is relatively high. We used, however, a selected population of first-degree relatives without a history of other disorders that might explain an olfactory impairment. An important conclusion from the available data is that across studies, even in selected populations, the absolute risk of hyposmia for the development of PD is not high. Most likely, this is related to the fact that olfactory impairments can occur as a result of many other conditions and disorders, some of which are quite prevalent such as viral infections. Evidently, olfactory testing cannot stand alone as a screening method to detect individuals at risk for PD.

The results of the present study indicate that a two-step approach of initial olfactory testing followed by DAT SPECT scanning in hyposmic individuals strongly increases specificity while retaining the high sensitivity associated with olfactory testing alone. However, we should bear in mind that the number of cases developing PD in this study is too low to draw firm

Table 1 Specific to non-specific [¹²³I]β-CIT binding ratios (mean±SD) at baseline and 5-year follow-up

	Baseline		5-year follow-up		
	Normosmic relatives N=35	Hyposmic relatives N=39	Normosmic relatives N=34	Hyposmic relatives No parkinsonism N=32 Parkinsonism N=4	
Left striatum	7.79±0.9	7.55±2.2	7.50±1.3	7.60±1.0	3.48±1.1
Right striatum	7.77±1.0	7.53±2.1	7.43±1.5	7.47±1.1	3.29±0.4
Left putamen	5.94±0.9	5.76±1.8	5.96±1.1	5.90±1.0	2.05±0.7
Right putamen	5.90±0.9	5.74±1.7	5.71±1.2	5.74±1.1	1.88±0.1
Left caudate	8.87±1.0	8.96±2.7	8.41±1.5	8.77±1.2	4.89±1.6
Right caudate	8.91±1.0	8.90±2.6	8.48±1.7	8.70±1.3	4.89±0.7

Figure 2 Scatter plots of left (A) and right (B) putamen [^{123}I]β-CIT binding ratios at baseline. Open circles, normosmic relatives (n=35); filled circles, hyposmic relatives who remained non-parkinsonian (n=34); filled triangles, hyposmic relatives who developed clinical parkinsonism (n=5); solid lines, age-adjusted means and the 98% CI of [^{123}I]β-CIT binding values in the group of normosmic relatives.



conclusions. In considering the application of a two-step olfactory testing SPECT imaging approach to the general population for screening purposes, it is clear that this approach would require many SPECT scans in individuals not suffering from PD. Therefore, further improvements are necessary to develop a cost-effective method that would be feasible for large-scale screening. One way of doing so would be to expand the first screening step to include tests sensitive to other prodromal features of PD, such as REM sleep behaviour disorder¹⁵ or genetic susceptibility factors.^{16 17}

Two years from baseline in this same cohort of first-degree relatives of PD patients, non-parkinsonian hyposmic relatives showed an increased rate of decline in DAT binding compared with the normosmic relatives, possibly indicative of incipient nigrostriatal dopaminergic degeneration.⁸ This difference in the rate of loss of DAT binding could not be confirmed in the present analysis after 5 years of follow-up, possibly as a result of a decreased susceptibility to biological variation as the interval between SPECT scans increases.^{18–20}

A limitation of the present study is that baseline SPECT scanning was performed in only 78 out of 361 individuals, possibly missing some individuals with a subclinical degeneration of the nigrostriatal system. However, given the length of the follow-up period, it is unlikely that an individual with undetected subclinical dopaminergic degeneration at baseline would not have developed clinical signs of PD 5 years later. Another potential limitation of the present study is that we used a selected sample of relatives of PD patients, excluding participants with a history of other disorders or conditions known to influence olfactory function. This might explain the high predictive value of 12.5% of the current study compared with the value of 2% found in an unselected population.⁹

Important strengths of the current study are its prospective, longitudinal design and the two-step approach, combining olfactory testing with SPECT scanning. This increased the specificity in detecting individuals at risk for developing PD compared with olfactory testing alone. Furthermore, in spite of the long interval between baseline evaluation and follow-up, very few individuals were lost to follow-up.

In conclusion, idiopathic hyposmia in first-degree relatives of PD patients is associated with an increased risk of developing clinical PD within 5 years of 12.5%. A two-step approach using olfactory testing followed by SPECT scanning in hyposmic individuals appears to have a very high sensitivity and specificity in detecting PD in its prodromal phase. The usefulness of this two-step approach needs to be confirmed in larger populations.

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Competing interests None.

Ethics approval Ethics approval was provided by the Health Council of The Netherlands and local medical ethical committees of the VU University Medical Center and the Academic Medical Center.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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