Parkinsonism and Related Disorders xxx (2017) 1–7

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Olfactory dysfunction and dementia in newly diagnosed patients with Parkinson's disease

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ARTICLE INFO

Article history:
Received 1 December 2016
Received in revised form
13 February 2017
Accepted 17 February 2017

Keywords:
Parkinson's disease
Dementia
Olfactory dysfunction
Prospective study

ABSTRACT

Introduction: Studies report that up to 90% of patients with idiopathic Parkinson's disease (PD) have olfactory dysfunction (hyposmia). Hyposmia has also been connected to cognitive impairment and dementia in PD, but no studies of newly diagnosed patients followed longer than three years exists. The present study investigates the prevalence of olfactory dysfunction at PD diagnosis, how it evolves over time and whether hyposmia increases the risk of dementia in Parkinson's disease.

Methods: Olfactory function was assessed with Brief Smell Identification Test (B-SIT) in 125 newly diagnosed patients with PD. They were followed for a maximum of 10 years (median six years) with extensive investigations at baseline, 12, 36, 60 and 96 months. Patients with B-SIT<9 were considered hyposmic.

Results: Hyposmia was found in 73% of the patients at diagnosis. During the follow up period of ten years 42 (46%) patients with hyposmia at baseline developed dementia compared to seven (21%) of the normosmic patients. Cox proportional hazards model showed that hyposmia at baseline (controlled for age, gender, UPDRS III and Mild Cognitive Impairment) increased the risk of developing dementia (hazard ratio (95%CI): 3.29 (1.44–7.52), p = 0.005). Only one of 22 patients with normal cognition and normal olfaction at baseline developed dementia.

Conclusions: Olfactory dysfunction was common at the time of PD diagnosis and increased the risk of dementia up to ten years after PD diagnosis regardless of baseline cognitive function. Normal olfaction together with normal cognition at baseline predicted a benign cognitive course up to ten years after diagnosis.

1. Introduction

Cross-sectional studies report that up to 90% of patients with Parkinson's disease (PD) are affected by mild to severe hyposmia [1,2]. Olfactory dysfunction has been suggested as an early clinical marker for PD [3,4] and to distinguish PD from Progressive Supranuclear Palsy (PSP), essential tremor and vascular PD [5]. Olfactory dysfunction has been shown to increase the risk of Alzheimers dementia (AD) in people with Mild Cognitive Impairment (MCI) [6], and in older populations [7]. It has also been connected to cognitive impairment [8–12] and dementia in PD [13]. Early research claims that after an initial olfactory decline in early stages of PD, olfactory function remains fairly stable [14]. Later studies suggests that there is likely to be additional olfactory loss at later stages in PD patients with cognitive decline [15]. Recent work has shown self-reported olfactory complaints to be an independent predictor of AD [7]. Self-reported olfactory complaints in relation to dementia in PD (PDD) have not yet been investigated.

Several studies have investigated olfaction in PD. Most studies are cross-sectional and the few existing prospective studies included patients at various disease stages. Longitudinal studies of olfaction in newly diagnosed patients with PD are needed to determine if olfactory dysfunction is a useful clinical marker for PDD, and to study olfactory change over time [11].

The aim of the present study was to investigate olfactory function and its progression five years after PD diagnosis; and to evaluate olfactory dysfunction as a possible clinical marker for later development of Parkinson's disease dementia (PDD) in a group of

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http://dx.doi.org/10.1016/j.parkreldis.2017.02.017
1353-8020/

newly diagnosed patients with PD followed up to 10 years.

2. Methods

2.1. Participants

The data was collected from the NY (new) Parkinsonism in UMeå (NYPUM)-study, a population based prospective study of 175 newly diagnosed patients with Parkinsonism (145 patients with PD, 14 patients with Multiple System Atrophy (MSA) and16 patients with PSP). The patients were included between January 1, 2004 and April 30, 2009 from the catchment area of Umeå University Hospital (northern Sweden) with around 142000 inhabitants, and followed up to ten years with extensive investigations at baseline, one, three, five and eight years. In the present study, only PD patients who fulfilled the criteria for PD according to Unified Parkinson's Disease Rating Scale (UKPDSBB) [16] at their last follow-up were included. Inclusion also required a pathological presynaptic dopamine uptake and a completed Brief Smell Identification Test (B-SIT). The study was approved by the Ethics Committee of the Faculty of Medicine at Umeå University. Written, informed consent was obtained from all participants.

2.2. Clinical assessments

Unified Parkinson's Disease Rating Scale (UPDRS) [16] and the Hoehn and Yahr staging (stage one to five) [17] were used to measure the severity of parkinsonism. UPDRS was assessed before the start of Parkinson medication (drug naïve) at baseline and ON medication at follow-up. Patients were divided into groups based on predominant motor features (Postural Impairment and Gait Disorders (PIGD), tremor or indeterminate phenotype) [18]. To assess global cognition Mini-Mental State Examination (MMSE) was used [19]. The Montgomery and Åsberg Depression Rating Scale (MADRS) was used to measure the level of depression; scores between eight and 17 were considered to be mild depression and scores 18 or over as severe depression [20]. A patient were considered a smoker if they were currently smoking or had previously smoked for more than 10 years. Dopamine transporter (DAT) Single-photon emission computed tomography (SPECT)-imaging using ^{123}I-Ioflupane ([^{123}I]FP-CIT) measured presynaptic dopamine uptake and was evaluated in a clinical routine setting with visual tree stage grading (normal, borderline or pathological).

2.2.1. Cognitive decline

A battery of standardized neuropsychological tests were used for PD-MCI and PDD diagnostics at zero, one, three, five and eight years. To assess MCI the MDS Task Force Guidelines criteria were applied [21]. The neuropsychological assessment included a minimum of two tests from each cognitive domain except for language and therefore a modified level two criteria was used, in accordance with previous research [22]. Tests used and procedures are described in Appendix a in the supplement. Fourteen patients did not perform the full neuropsychological testing at baseline and had their MCI classification based on self-perceived cognitive decline together with MMSE (cutoff $\leq$ 29 according to Hoops et al. [23]). Only four patients without the full neuropsychological testing were classified as having MCI at baseline.

PDD were diagnosed by neurologists experienced in neurodegenerative disorders according to published criteria [24]. The PDD diagnosis required the onset of motor symptoms one year prior to the onset of dementia, and cognitive deficiency severe enough to affect activities of daily living that could not be attributed to motor or other dysfunctions. Structural magnetic resonance imaging were performed in all patients to exclude non PDD causes of dementia. PDD was in periods in between the neuropsychological testing diagnosed by decline in MMSE, cognitive decline reported by patient and/or family member and functional impairment in basic activities of daily living due to cognitive decline.

2.2.2. Olfactory function

Olfactory function was tested at baseline and at 12, 24, 36, 60 and 96 months with the twelve-item Brief Smell Identification Test (B-SIT) and with a survey on subjectively reported olfactory complaints. The B-SIT is a smell identification test that contains a booklet with 12 different scented strips (cinnamon, turpentine, lemon, smoke, chocolate, rose, fuel, banana, thinner, pineapple, soap and onion) which releases odour when scratched upon [25]. Each odour have four alternatives and the participant is asked to pick one of the alternatives even if they do not recognize the smell. Patients were considered hyposmic if they identified eight or less odors [25]. Results of four or under were considered as severe hyposmia [13]. All patients except two were drug naïve at the baseline investigation. Patients had been off dopaminergic medication a minimum of 12 h at all follow-up assessments of olfactory function.

2.3. Study size

Of the 145 patients with PD, nineteen did not perform the olfactory testing and were therefore not included in this study. In addition, one patient was excluded due to impaired eyesight which made the interpretation of the neuropsychological results difficult. Patients not performing the olfactory test were older (83.4 vs 71.1 years, $p < 0.001$) and were followed for a shorter period of time (36.0 vs 96.0 months, $p < 0.001$) than patients performing the olfactory test. Of the 125 patients with PD included in the present study 86 patients were followed for a minimum of seven years (33 died, four was followed through telephone contact and two moved out of the county). At ten years, 29 patients have so far been eligible for follow-up. At the one year follow-up 113 patients performed the B-SIT, at the three year follow up 92 patients performed the B-SIT and at the five-year follow-up 77 patients performed the B-SIT (see Fig. 1).

2.4. Statistics

Group comparisons on baseline data were performed between hyposmic and normosmic PD with the Mann-Whitney *U* test for continuous variables and Chi-square test for binary variables. Comparisons of B-SIT scores at baseline, one, three and five years follow-up between patients that developed dementia (PDD) at follow-up and cognitively stable patients and between PD hyposmic and PD normosmic were made with linear mixed models using interaction terms for group and time (baseline, one, three and five years) and adjustments for gender, age, and UPDRS III. The first order autoregressive covariance structure was used in all models.

Incidence rates for dementia were calculated and Kaplan-Meier curves were performed. PDD onset was endpoint and time were months passed between inclusion in the study and time of PDD onset. The time of PDD onset was estimated as the midpoint between the latest assessment without PDD and the assessment when PDD was diagnosed. Patients were also divided in to four groups based on olfactory and cognitive function, one group were both hyposmic and had MCI at baseline, one group were only hyposmic, one group only MCI and one group had normal cognitive function and smell.

Cox proportional hazards models with PDD as endpoint were performed in three stages: univariate, controlled for age, gender and UPDRS III at baseline and finally by adding MCI status at

Please cite this article in press as: M.E. Domellöf, et al., Olfactory dysfunction and dementia in newly diagnosed patients with Parkinson's disease, Parkinsonism and Related Disorders (2017), http://dx.doi.org/10.1016/j.parkreldis.2017.02.017