Parkinsonism and Related Disorders 25 (2016) 45–51

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

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

Olfactory impairment predicts cognitive decline in early Parkinson's disease

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ARTICLE INFO

Article history:
Received 14 December 2015
Received in revised form
30 January 2016
Accepted 14 February 2016

Keywords:
Parkinson's disease
Olfaction
Mild cognitive impairment
Non-motor symptoms
Cerebrospinal fluid

ABSTRACT

Objective: To evaluate the association between baseline olfaction and both cross-sectional and longitudinal cognitive assessments, motor symptoms, non-motor symptoms (NMS), and CSF biomarkers in early Parkinson's disease (PD).

Methods: Parkinson's Progression Marker's Initiative (PPMI) participants underwent baseline olfactory testing with the University of Pennsylvania Smell Identification Test (UPSIT). Serial assessments included measures of motor symptoms, NMS, neuropsychological assessment, and CSF biomarkers. Up to three years follow-up data were included.

Results: At baseline, worse olfaction (lowest tertile) was associated with more severe NMS, including anxiety and autonomic symptoms. Those in the lowest olfactory tertile were more likely to report cognitive impairment (37.4%) compared to those in the middle (24.4%) and highest olfactory tertiles (14.2%, $p < 0.001$). $A\beta_{1\text{-}42}$ was significantly lower, and tau/$A\beta_{1\text{-}42}$ ratio was higher in those with worse olfaction. In longitudinal analyses, lower UPSIT score was associated with greater decline in MoCA score ($\beta = 0.02$ [0.01, 0.03], $p = 0.001$) over time, as were composite measures of UPSIT score and either $A\beta_{1\text{-}42}$ or tau/$A\beta_{1\text{-}42}$ ratio. In a Cox proportional hazards model, a composite measure of olfaction and $A\beta_{1\text{-}42}$ was a significant predictor of conversion from normal cognition to mild cognitive impairment (MCI; i.e., MoCA < 26), with subjects most impaired on both measures being 87% more likely to develop incident MCI (HR = 1.87 [1.16, 3.01], $p = 0.01$).

Conclusions: Worse baseline olfaction is associated with long-term cognitive decline. The addition of AD CSF biomarkers to olfactory testing may increase the likelihood of identifying those at highest risk for cognitive decline and progression to MCI.

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1. Introduction

Defining biomarkers for the diagnosis and prognosis of Parkinson's disease (PD) remains a major unmet need. Olfactory impairment is common in PD, with a prevalence ranging from 50 to 90% [1,2]. It is often one of the first manifestations of the disease [3], and pathologically, the olfactory bulb and lower brainstem are involved with synuclein pathology early on, with later spread through the rostral brainstem and eventually to the cerebral cortex [4]. These observations, along with the ease and low cost of

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http://dx.doi.org/10.1016/j.parkreldis.2016.02.013
1353-8020/Published by Elsevier Ltd.

assessment, make it an attractive biomarker.

Several studies have shed light on the relationship between olfaction and other non-motor symptoms (NMS) in PD, which are important causes of morbidity. Cross-sectional studies have shown associations between olfactory impairment and depression, anxiety, apathy, REM behavior sleep disorder (RBD) and autonomic symptoms [5–7]. General measures of cognition, including Mini-Mental Status Examination, were not associated with hyposmia in some studies [8], while others have demonstrated associations between olfaction and specific cognitive domains, including episodic verbal learning and verbal memory [9–12]. Worse baseline olfaction predicted self-reported cognitive impairment several years later in a retrospective cohort study [13], and a small longitudinal study identified severe hyposmia as an independent risk factor for development of dementia within 3 years [14].

While a marker of high sensitivity in PD, olfaction lacks specificity, and how it might be used in combination with other putative biomarkers is of interest. Cerebrospinal fluid biomarkers, including CSF tau (higher) and $A\beta_{1\text{-}42}$ (lower) have been associated with cognitive impairment in PD and dementia with Lewy bodies (DLB) in cross sectional studies [15,16], and reduced CSF $A\beta_{1\text{-}42}$ was an independent predictor of cognitive decline in two mixed stage PD cohorts [17,18].

In the present longitudinal, exploratory study, we aim to characterize olfaction in an early PD cohort, examine the association between baseline olfaction and measures of disease severity and other NMS, and determine if olfaction alone or in combination with CSF biomarkers predicts cognitive decline and conversion to mild cognitive impairment (MCI).

2. Methods

Data used in this study came from the Parkinson's Progression Markers initiative (PPMI), a multicenter, observational cohort study following de novo (untreated at enrollment) PD patients and healthy controls. Participants underwent clinical assessments, imaging and blood and CSF collection at predetermined time points. The aims and methodology have been previously published [19]. Up-to-date information and further details on the study are available on-line (http://www.ppmi-info.org/). To be included in the PD arm, subjects had to meet clinical criteria for PD with a diagnosis within two years, confirmed by DAT imaging deficit. Enrollment was complete at the time of data acquisition and included a total of 423 patients with PD. Written informed consent was obtained from all study participants, and the study was approved by the institutional review board at each PPMI site.

Clinical Characteristics: Disease duration was calculated in months from the date of diagnosis. Education was reported in years by the study participant. Subscores of the Movement Disorder Society – Unified Parkinson's Disease Rating Scale (MDS-UPDRS) were collected at each visit, including MDS-UPDRS part III to capture severity of motor symptoms [20].

Olfaction: Odor identification was assessed using the University of Pennsylvania Smell Identification Test (UPSIT) with lower scores reflecting worse olfactory function [21]. Published normative values adjusted for age and sex were used to determine the percentile and olfactory classification for each subject. In order to group subjects into clinically meaningful categories, the PD patients were divided into olfactory tertiles based on raw UPSIT score. In doing so, the lowest olfactory tertile contained all participants classified as anosmic (based on published normative values adjusted for age and sex), while the middle tertile contained all participants with severe microsmia (Fig. e-2).

NMS assessments: Assessments of NMS included (i) the REM Sleep Behavior screening questionnaire, in which a positive screen was defined as a score >5 (consistent with possible RBD) [22], (ii) the Scales for Outcomes in Parkinson's Disease – Autonomic Questionnaire (SCOPA-AUT) to assess autonomic symptoms [23], (iii) the 15-item Geriatric Depression Scale (GDS-15) (cutoff $\geq$5 to indicate clinically significant depression) [24], and (iv) the State-Trait Anxiety Inventory (STAI; total of State and Trait subscales). Global cognition was assessed with the Montreal Cognitive Assessment (MoCA), and the recommended cutoff score of <26 was used to define MCI (PD-MCI level I category, abbreviated assessment) [25]. Question 1 on part 1 of the MDS-UPDRS was used to screen for patient reported cognitive impairment. Individual neuropsychological tests for specific domains have been previously described [26] and included the Benton Judgment of Line Orientation, Hopkins Verbal Learning Test-Revised delayed recall and recognition, Letter-Number Sequencing Test, Semantic Fluency and Symbol Digit Modalities Test.

2.1. CSF biomarkers

CSF was collected at each study site as described in the PPMI biologics manual (http://www.ppmi-info.org/). $A\beta_{1\text{-}42}$, total tau (t-tau) and phosphorylated tau (p-tau) were measured using the xMAP luminex platform (Luminex Corp) with INNO-BIA AlzBio3 immunoassay kit-based reagents (research use-only; Immunogenetics Inc) with a mean coefficient of variation below 10% between runs [27].

2.2. Statistical analysis

Statistical analysis was performed with Statistical Package for the Social Sciences (SPSS) statistics (version 22, SPSS, Inc., Chicago, IL). All statistical tests were two-sided. Statistical significance was set at $p < 0.05$. Since our study was exploratory rather than confirmatory, multiple testing adjustment was not performed [28]. Normality assumptions were checked where appropriate. Demographic characteristics and baseline motor, non-motor and CSF biomarkers were compared using chi-square, one way ANOVA and analysis of linear trend or Kruskal-Wallis tests for non-normally distributed data where appropriate. Because age and sex differed among the three olfactory tertiles, linear and logistic regressions were used to control for age and sex when comparing baseline clinical characteristics. Age and sex were also controlled for in all longitudinal analyses. Education was included as a covariate for analyses involving cognition.

Longitudinal analysis over a three year follow-up period was performed using linear mixed effects models, which accounts for correlations among repeated measures and for missing data (due to differing durations of follow up) [29]. Variables of interest based on published data, biologic plausibility, and/or identified as being significantly associated with olfaction at baseline were included in linear mixed effects models. Subject-specific random intercepts were used to account for the correlation between repeated measures. Fixed-effects in each mixed-effects model were UPSIT score, age, sex, time and baseline test score. Education was also included for the models involving the MoCA and neuropsychiatric tests. The relationship between olfaction and CSF biomarkers and decline in MoCA was first analyzed using the UPSIT and CSF biomarkers as continuous variables. There was no association between p-tau and olfaction or any of the cognitive endpoints, so it was not included in further analyses. Since CSF biomarkers $A\beta_{1\text{-}42}$ and T-Tau/$A\beta_{1\text{-}42}$ and olfaction were independently associated with decline in MoCA, we created a composite score as a way to classify risk for decline in MoCA based on a combination of olfactory status and CSF values. Because olfaction was divided into tertiles, we also divided the CSF biomarkers into tertiles. Those in the lowest olfactory tertile had a