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Clinical short communication

Olfaction and apathy in early idiopathic Parkinson's disease

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ABSTRACT

Background: Apathy remains a disabling symptom in Parkinson's disease (PD) with limited therapeutic success. Processing of emotions and smell share neuroanatomical and evolutionary pathways.
Objectives: To explore the association of apathy with smell dysfunction (SD) in early PD.
Methods: We analyzed patients with de-novo PD, with follow-up of at least 5 years from the Parkinson's Progression Markers Initiative. SD and apathy were defined using University of Pennsylvania Smell Identification Test and MDS-UPDRS part 1A. Odds ratios were calculated between apathy and olfaction groups. Kaplan-Meier survival analysis was grouped by presence/ absence of smell dysfunction. The Log Rank test was used to compare time to apathy.
Results: We found no association between presence of apathy in patients with and without SD (OR 1.01 [0.49–2.08]). There was no significant difference between PD patients with and without SD in time to apathy ($p = 0.72$).
Conclusions: SD does not portend greater risk of apathy in PD.

1. Introduction

The sense of smell, one of the most primitive human sensory modalities, is closely related to emotions [1]. Processing of emotions and smell share neuroanatomical commonalities, including the amygdala, insula, anterior cingulate cortex, and orbitofrontal cortex [2]. Apathy and smell dysfunction (SD) are both prevalent in people with Parkinson's disease (PD) [3]. Apathy is characterized by a lack of motivation and goal-oriented behavior, in the setting of reduced emotional expression. It is seen in 17–60% of people with PD and may be highly disabling [4]. To date, there are no reliable, evidence-based treatment modalities for apathy in PD [5]. Through this effort, we seek to assess the effect of SD on apathy risk in PD. Such an association would posit the possibility of a novel therapeutic approach to address apathy in PD.

2. Methods

We analyzed data on patients with early de-novo idiopathic PD, enrolled within 2 years of motor symptom onset in the Parkinson's Progression Markers Initiative (PPMI) study. The PPMI is a prospective multicohort study that identifies clinical, imaging and biologic markers of PD progression for use in clinical trials of disease-modifying therapies. Details on the PPMI methods and objectives have been published elsewhere [6]. We defined SD as a University of Pennsylvania Smell Identification Test (UPSIT) score performed at the baseline visit at or below the 10th percentile by age and gender. Apathy was identified using the Movement Disorders Society United Parkinson's Disease Rating Scale (MDS-UPDRS) part 1A item 1.5 with a score of 1 or more. Cognitive impairment was determined on the basis of criteria developed by the Movement Disorders Society as applied by the PPMI investigators and detailed in the original study [6]. To be included in the analysis, the PD patients needed to have a follow-up period of 5 years, not have apathy at the initial visit and have more than one visit. Cognitive assessment was done using the Montreal Cognitive Assessment (MoCA).

Odds ratios were calculated between apathy and olfaction groups (presence or absence of smell dysfunction). Kaplan-Meier survival analysis was grouped by presence or absence of smell dysfunction, and the Log Rank test was used to compare length of time until the onset of apathy. Cox regression analysis was conducted with apathy as the dependent variable, and age at the time of the first visit, Hoehn-Yahr (HY) stage at the time of the first visit, MDS-UPDRS part III score at the time of the first visit, presence of SD at the time of the first visit,

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depression at the time of the first visit, and the State-Trait Anxiety Inventory (STAI) at the time of the first visit as the independent variables and hazard ratios (HR) were calculated and confidence intervals at 95% are presented in brackets. Models were executed with and without depression and STAI to account for potential collinearity. All analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

A total of 486 PD patients were included in our analysis. There was no significant difference in UPSIT scores between patients with and without apathy at the beginning (23.4 and 23.5 respectively, $p = 0.89$) or at the end of the follow up period (22.9 and 23.6 respectively, $p = 0.5$). We found no association between the presence of apathy when comparing patients with and without SD (OR 1.01 [0.49–2.08]) (Table 1).

There was no significant difference between PD patients with and without SD in time to onset of apathy when comparing the survival curves presented in Fig. 1 ($p = 0.72$). This multivariate analysis also included age (HR 1.02, [1–1.04]), HY stage at the time of the first visit (HR 0.99[0.64–1.53]), MDS-UPDRS part III score at the time of the first visit (HR 1 [0.98–1.02], presence of SD at the time of the first visit (HR 0.79 [0.43–1.45]), depression at the time of the first visit (HR 1.48 [0.83–2.63]), and STAI score at the time of the first visit [1–1.02]). C-Index was 0.838 [CI95 0.69–0.95]. Removal of depression and STAI from the model did not lead to a significant change ($p = 0.180$) (age HR = 1.02 [1.00–1.04], HY stage HR = 1.05 [0.68–1.62], MDS-UPDRS part III HR 1.01 [0.98,1.03], SD HR 0.81 [0.44,1.48]. C-index = 0.892 [0.76–0.98]). For both these models, C-index indicated a good measure of fit.

4. Discussion

Specific smells may elicit distinct emotions. The sense of smell in humans has been linked to emotions and associated behavior through an evolutionary mechanism [7]. The brain circuitry associated with apathy shares a neuroanatomical pathway with olfaction [2]. Clinically, a relationship between apathy and smell has been shown to exist in patients with probable Alzheimer's disease. A mild association has previously been reported in PD patients. However, these were further along in their disease course, and with data confounded by dopaminergic medications [3,8]. Our analyses, conducted on a large sample size of de-novo PD patients within 5 years of symptom onset, indicates no clinical association between smell dysfunction and apathy.

In addition to the dopaminergic pathway, progressive degeneration of the serotonergic meso-cortico-limbic pathway is seen in PD patients with apathy, depression and anxiety. A correlation between hypomimia has been established with apathy, without increased prevalence of depression, anxiety, or cognitive impairment. It serves as an example with such shared pathophysiological mechanism, related to altered interactions between the basal ganglia, prefrontal cortex and the limbic system [10]. Such a clinical presentation, common among PD patients, has been described as a "neuropsychiatric lesional profile" in reference to common underlying serotonergic pathways in apathy, depression and anxiety [9]. In clinical practice [4] and in investigations, emotional dysfunction may be misconstrued as apathy, thereby confounding conclusions and misguiding proposed interventions [5].

Table 1
Demographic information stratified per the presence or absence of apathy.

	Apathy	No apathy
Age at first visit	61.15	61.64
Female sex	32.86%	35.34%
Montreal cognitive assessment	27.05	27.61
MDS-UPDRS part III at first visit (mean)	21.34	19.81
Depression	83.69%	86.96%
STAI score (mean)	67.4	60.84
Smell dysfunction	60 (14.39%)	357 (85.61%)
Normal olfaction	10 (14.49%)	59 (85.51%)

The lack of association between apathy and smell dysfunction in PD in our analyses persisted even after controlling for other serotonergic manifestations namely depression and anxiety, thereby strengthening our conclusion. A factor that we could not account for was the use of serotonergic drugs that patients could have been using for the treatment of depression, as the PPMI database does not have information regarding their use [6]. We expect that controlling for depression and anxiety would, at least partially, offset the contribution of these missing data on serotonergic drug use. As previously mentioned, confounding effects of cognitive or emotional factors may not be addressed. Indeed, the prevalence of apathy is reduced by half to 20% once these factors are considered. Another factor to consider is the discrepancy between apathy reported by the patient and their care partners, with the latter perhaps reporting a higher severity due to the burden experienced [5].

Our analysis used available MDS-UPDRS data for the determination of apathy. Such an approach has been previously used for this purpose [[11,12]]. This relationship between olfaction and apathy has been previously investigated in PD patients with differing results, albeit in a different study population and using different tools. Hong and colleagues utilized the Cross Cultural Smell Identification Test (CCSIT) for olfaction and the neuropsychiatric inventory (NPI) to identify apathy. [13] Cramer performed a cross sectional study using the Brief Smell Identification Test (B-SIT) and the Apathy Evaluation Scale (AES). [3] The use of different apathy scales such as the AES [3] and the Neuropsychiatric Inventory (NPI) [13], might be at least partially, be responsible for the different conclusions than ours. In addition, the patient population in both studies was older, had a longer duration of disease, with worse motor symptoms. Our analysis was able to comment on the impact of impaired olfaction on the onset of apathy based on longitudinal data on patients with early PD.

Previous studies with a relatively small sample size showed mild benefit with istradefylline, rivastigmine, and piribedil. Unlike benefits seen with motor symptoms, deep brain stimulation (DBS) may instead induce apathy after a few months in up to 54% of patients at 1 year after implantation [5]. This phenomenon has been postulated to be related to levodopa withdrawal and mesolimbic pathway denervation. Several non-pharmacologic interventions have been studied in the past, including exercise, behavioral therapy and cognitive stimulation, of which only exercise has demonstrated a mild benefit. Additionally, it is possible that some of these interventions target comorbidities that can simulate apathy, such as cognitive impairment or depression. Smell training has been proposed as an effective approach, most recently for patients suffering from hyposmia during COVID. This approach has a basis in evidence [14]. While our results based on group data argue against this perspective as a potential therapeutic approach for apathy, it is possible that such an endeavor requires specific smells evoking an emotional response for that individual [1].

Our analysis is not without limitations. While the MDS-UPDRS scale for determination of apathy has been used before, it relies on a single item with no objective grading. The Lille Apathy Rating Scale (LARS) might be a better way to establish the presence of apathy [5]. As mentioned above, this heterogeneity in tools to assess apathy likely contributes to the variability in conclusion. While the protocol acknowledges that patients will begin to have cognitive dysfunction and enforce a research proxy for every patient, there is no recording in the dataset as to who provided the information in each visit leading to heterogeneity in the source of information. Even though we controlled for potential confounding variables, the lack of a standardized interview and assessment for the evaluation of apathy is a potential limitation.

Apathy is a common and highly disabling feature in PD, with relatively few and mildly-effective pharmaco-therapeutic strategies and no proven non-pharmacological approaches. Appropriate recognition, management of confounders and larger clinical trials are needed, along

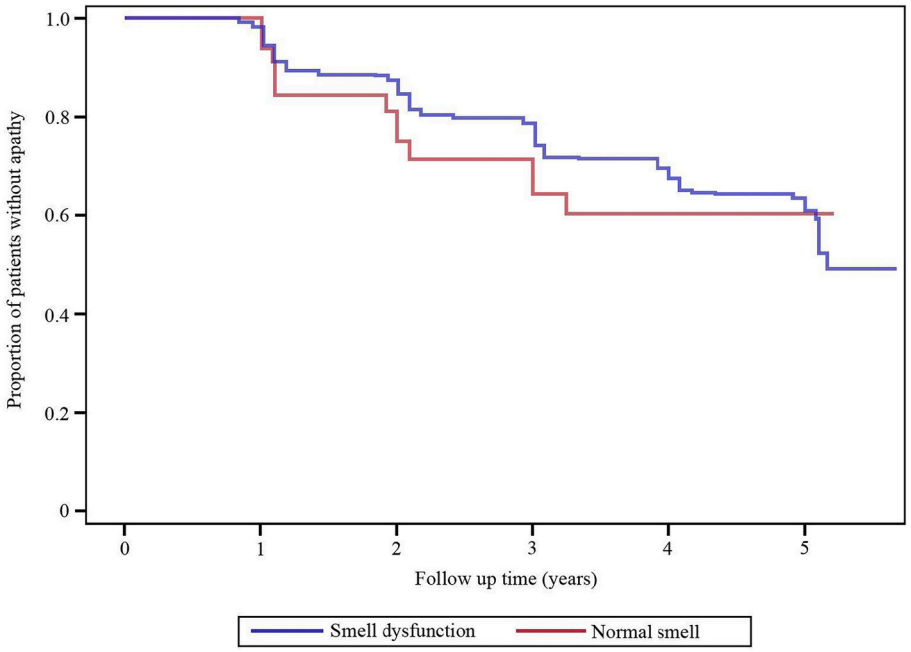

Fig. 1. Kaplan-Meier curves grouped by olfactory dysfunction compared to normal olfaction in Parkinson's disease. Events were defined as a new onset of apathy not present in the previous visit.

with exploration of novel therapeutics for adequate care of our patients.

Statements and declarations

This work was under the review of the Henry Ford Health System Internal Review Board (IRB) prior to its execution. Informed patient consent was not necessary for this work. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

Funding sources and conflicts of interest

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Author roles

AMN: data curation, methdology, writing-original draft.
KL: formal analysis, methdology, resources, software.
MSK: methodology, writing-review-editing, visualization.
AM: conceptualization, investigation, methodology, project administration, supervision, writing-review.

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