Parkinsonism and Related Disorders xxx (2014) 1–4

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

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

Olfactory performance in spinocerebellar ataxia type 7 patients

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ARTICLE INFO

Article history:
Received 17 October 2013
Received in revised form
20 January 2014
Accepted 31 January 2014

Keywords:
Spinocerebellar ataxia
SCA7
Smell
Olfactory impairment

ABSTRACT

A large body of evidence has shown olfactory deficits in many neurodegenerative diseases. However, the nature of the olfactory impairment remains poorly understood partly because the majority of studies have only explored smell identification capabilities. The purpose of the present study was twofold. First we wanted to test if patients with spinocerebellar ataxia type 7 (SCA7), a progressive neurodegenerative disorder characterized by cerebellar ataxia and visual loss, also have olfactory deficits. Secondly, we wanted to test the nature of the olfactory deficits by testing not only the identification level but also olfactory threshold and discrimination. Based on the olfactory dysfunction found in different neurodegenerative diseases and functional neuroimaging data showing cerebellar activation during olfaction, we hypothesized that SCA7 patients would show an olfactory impairment. To test this hypothesis we studied twenty-eight genetically confirmed SCA7 patients and twenty-seven matched controls using the Sniffing Sticks Test and the University of Pennsylvania Smell Identification Test (UPSIT). The results show that SCA7 patients' ability to discriminate and identify odors is significantly impaired, although their odor detection thresholds were at normal levels. These results suggest that SCA7 neurological damage affects olfactory perception but spares the patients' olfactory sensory capabilities.

1. Introduction

Olfactory deterioration has been found in different ataxia populations, including spinocerebellar ataxias types 2, 3, 10, Friedreich ataxia, and sporadic ataxia [1–6]. However, an important limitation of these studies is that many of them only measured olfactory identification, making it difficult to dissociate if the olfactory problem is a consequence of limited sniffing capacity or a consequence of impaired olfactory processing.

Here we wanted to test if Spinocerebellar ataxia type 7 (SCA7), which is a genetic neurodegenerative disease characterized by ataxia, pyramidal syndrome and progressive macular dystrophy [7] also showed olfactory impairments; and second, we wanted to characterize the nature of the olfactory impairment, if present. For these purposes, we evaluated the olfactory performance of a large number of SCA7 patients in three domains: olfactory threshold, odor identification and odor discrimination.

2. Subjects and methods

2.1. Subjects

Twenty-eight SCA7 patients with molecular diagnosis and 27 controls with no history of neurological injury, psychiatric disease or smoking history participated in this study. The SCA7 patients and the controls were matched for age, education, sex and area of residency to avoid cultural biases (all of the participants were recruited from the communities of Tlaltetela, Tuzamapan and Cosautlán de Carvajal, from the state of Veracruz, México) (Table 1). All participants were informed about the nature of the research, and gave written informed consent. All procedures were approved by the health and ethics committees of the National Autonomous University of Mexico and were in accordance with the declaration of Helsinki [8].

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http://dx.doi.org/10.1016/j.parkreldis.2014.01.024
1353-8020/

Table 1
Patients and control subjects general characteristics.

	M	F	Age (years)	Disease evolution (years)	SARA	CAG-length	Schooling	MMSE*
Control group	17	10	38.3 ± 15.5				7.1 ± 3.5	26.4 ± 1.0
SCA7 patients	17	11	42.6 ± 14.3	8 ± 4.3	19.2 ± 7.6	47.8 ± 7.1	6.8 ± 3.3	25.7 ± 1.3

M/F: male and female ratio; SARA: Scale for Assessment and Rating of Ataxia [9]; MMSE: Mini Mental State Examination [10]. *Two items that required visual processing (read aloud a phrase and copy interlocking pentagons), were eliminated from the scoring in both groups, leaving the maximum score at 28 points.

2.2. Olfactory tests

- Sniffin' Sticks Test (Bughart medizintechnik Inc.)

The Sniffin' Sticks Test was used to investigate olfactory performance using pen-like odor dispensing devices [11]. It tests three olfactory functions: odor threshold, odor discrimination and odor identification.

General procedures. Subjects were blindfolded with sleeping masks during the three parts from tests to prevent visual identification of the odorant-containing pens. Pen caps were removed only during odor presentation and positioned approximately 2 cm for 3 s, in front of both nostrils. The pens were presented one at a time.

2.3. Odor threshold testing

Subjects were first acquainted with the odor of the highest concentration of *n*-butanol, (4%). Then, using a triple-forced-choice paradigm [12], three pens (triplets) were randomly presented to each subject; two contained the solvent (without odor) and the third contained the odorant (*n*-butanol) in different dilutions. The subjects' task was to identify the pen with the odorant. The triplets presentation started with the lowest concentration of the odorant (1.22 ppm of *n*-butanol). If the subject did not detect the odor, then the next triplet with the pen that contained a higher concentration was presented and *vice versa*; if the subjects detected the odor, then the next triplet with the pen that contained a lower concentration was presented (staircase reversal method). This task was completed once six reversals were reached. The mean of the last four reversals was used to estimate the detection threshold [13]. Sixteen triplets, with different dilutions of *n*-butanol, comprised the odor threshold testing.

2.4. Odor discrimination testing

Using a triple-forced-choice paradigm [12], where two pens had the same smell and one contained a different smell, subjects were asked to identify the one that smelled differently. Sixteen triplets were presented to the subjects in this task.

2.5. Odor identification testing

Using a four-forced-choice paradigm [12], subjects had to identify, from a list of four odor names, the odor from each of sixteen different pens.

- University of Pennsylvania Smell Identification Test (Sensonics Inc.)

A Spanish version of the University of Pennsylvania smell identification test (UPSIT) was used. This test consists of 40 different odorants microencapsulated and positioned in strips at the bottom of pages of a test booklet. The test score ranges from 0 to 40, and can differentiate between anosmia, which is defined as the complete inability to perceive odors, and multiple levels of hyposmia, defined as the partial inability to perceive odors. In this method, the experimenter scratched the test booklet and brought it near the subject's nose to allow him or her to sniff the odorant. The subjects had to choose, among four possible choices, which odor best described the perceived odor [13].

3. Results

A Student's *t* test between the control group and the group of SCA7 patients on scores of olfactory detection threshold, from Sniffin' Sticks Test, showed no significant difference ($t(53) = 0.869$, $p = 0.389$) (Fig. 1a). The same analysis for odor discrimination (Fig. 1b) and odor identification (Fig. 1c), from Sniffin' Sticks Test, showed SCA7 patients made significantly fewer the correct responses than controls ($t(53) = 6.239$, $p < 0.001$) and ($t(53) = 4.297$, $p < 0.005$ respectively). Likewise, the UPSIT scores (Fig. 1d) showed patients correctly identified significantly fewer odors than controls ($t(53) = 3.619$, $p < 0.001$). Subsequently, we conducted an analysis of variance on the results obtained only from the group of SCA7 patients. We divided the patients into three different groups based on their score on the scale for the assessment and rating of ataxia (SARA) score: Mild (SARA ≤14); Moderate, outpatients that needed support and decreased visual acuity (SARA ≤26); and Severe, non-ambulatory and total blindness (SARA ≥27). The analysis of variance showed no significant differences among the three patient groups in each area tested: detection threshold, $F(2, 25) = 0.57$, $p = 0.568$ (Fig. 2a); discrimination, $F(2, 25) = 1.69$, $p = 0.204$ (Fig. 2b); identification, $F(2, 25) = 2.47$ $p = 0.104$ (Fig. 2c) and UPSIT, $F(2, 25) = 0.2$, $p = 0.821$ (Fig. 2d). Finally, using Pearson correlation analysis, no correlation was found between CAG length and any other measure.

4. Discussion

In this study we tested the olfactory capabilities of a large group of SCA7 patients. Our results showed a significant decrease in their olfactory discrimination and identification capabilities, despite showing normal olfactory thresholds. The olfactory impairments, however, did not show any correlations with the degree of the

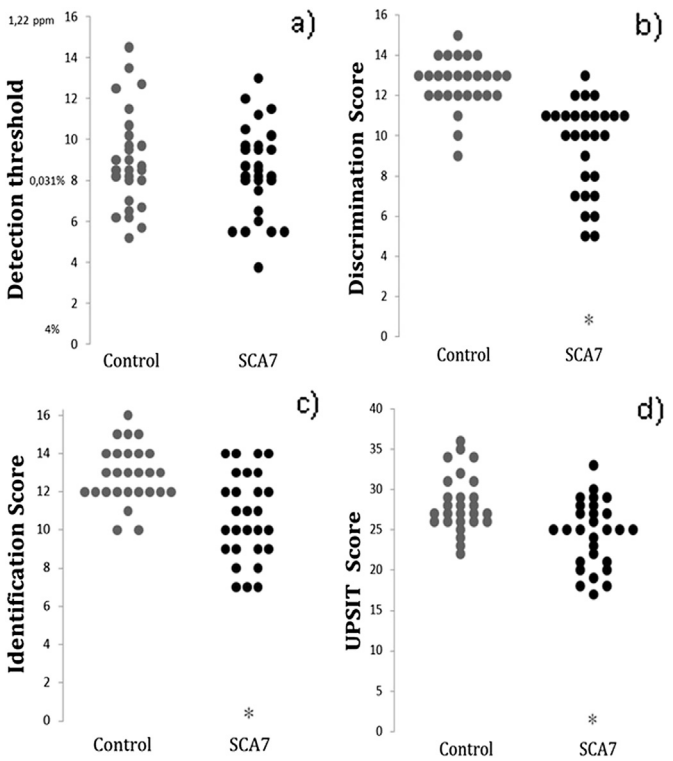

Fig. 1. Number of correct Sniffin' Stick Test and UPSIT responses. The SCA7 patients group (black circles) showed similar odor detection capacity as a control group (gray circles). However, the patients showed a significant decrease in the performance to discriminate and identify odors. *$p < 0.05$.

Please cite this article in press as: Galvez V, et al., Olfactory performance in spinocerebellar ataxia type 7 patients, Parkinsonism and Related Disorders (2014), http://dx.doi.org/10.1016/j.parkreldis.2014.01.024

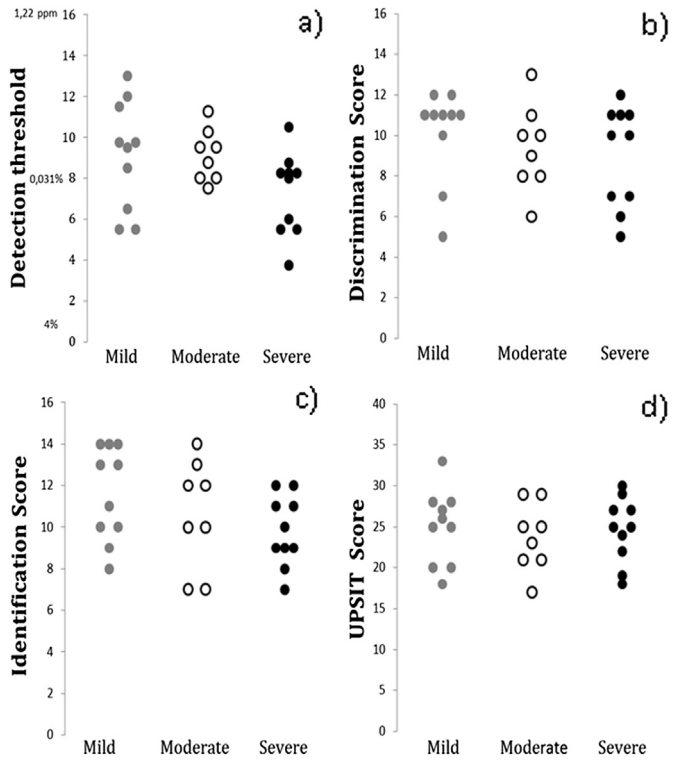

Fig. 2. Number of correct Sniffin' Stick Test and UPSIT response within the group of SCA7 patients, classified as mild (gray circles), moderate (white circles) and severe (black circles) by motor impairment degree. There were not significant differences between the SCA7 subgroups.

motor and visual acuity impairment (SARA scale score), CAG length, or any other clinical aspect of the disease.

Since the initial findings that showed an increase in cerebellar activity during an olfactory task [14], a number of studies have converged to suggest an olfactory impairment following cerebellar lesions [1–5]. However, the role of cerebellum in olfactory process remains unclear. One hypothesis suggests that even though cerebellar activations do not appear to be linked to a specific type of odorant, a slight difference between perceived intensities of two odorants is sufficient to produce a difference in the motor control of sniffing: sniff volume is inversely proportional to perceived concentration [14]. Therefore, it could be possible that an impaired sniffing ability in SCA7 patients could lead to olfactory impairments, starting with a deficit in olfactory threshold, as has been previously shown with Parkinson's disease patients [15]. However, our results did not support this conclusion. When we quantified the olfactory ability to detect just supra-threshold concentrations, SCA7 patients performed equivalently to the control group. These results suggest that the brain areas that degenerate in these patients play a greater role associated with olfactory perceptual functions than merely providing a feedback mechanism for the inhalation force.

Previous studies have tried to identify the possible neural bases of the olfactory deficits in polyglutamine diseases [5,16]. For example a recent study in SCA3 patients found that dopaminergic changes did not correlated with cognitive or olfactory scores [5]. Regarding SCA7, initial neuroimaging studies revealed a marked atrophy in the cerebellum and pons [17]. However, recent studies using voxel-based morphometry and tract-based spatial statistics have found significant bilateral gray matter volume reductions in the cerebellar cortex, pre and postcentral gyrus, and inferior and medial frontal, inferior parietal, parahippocampal and occipital cortices [18,19]. This widespread degeneration pattern in SCA7 makes difficult to attribute the olfactory deficit to the cerebellar degeneration, as other structures that are also affected, such as the medial frontal and parahippocampal cortices, are also implicated with olfactory processing. Furthermore, SCA7 patients also show functional connectivity detrimental changes between the parahippocampal cortex and the cerebellum [18,19], which may also contribute to the olfactory deficit. For example, functional changes in the parahippocampal area coincide with changes in the cerebellum [20,21] and functional connections between these areas are affected in major depression [22] which also results in olfactory dysfunction [23]. This suggests that more research is needed to understand the complex interrelations between the olfactory deficits, the neurodegeneration pattern, and the clinical manifestations including the affective state of these patients.

5. Conclusions

SCA7 patients exhibit hyposmia, consisting in a significant decreased ability to discriminate and identify odors. Olfactory threshold, however, remained intact. This suggests that the neurodegenerative pattern observed in this disease mainly affects higher order olfactory processing, while sparing a more basic function, like the olfactory detection threshold.

Acknowledgments

To Susana Garcia Rosales and all the patients and their families from Tlaltetela, Tuzamapan and Cosautlan de Carvajal communities who helped me with this research. Also, this work was supported by the Master Program in Neuroetologia at the Universidad Veracruzana and master scholarship from the Consejo Nacional de Ciencia y Tecnologia granted 262090, Programa de Fortalecimiento Académico de Posgrado de Alta Calidad I010/458/2013 C-703/2013 Universidad Veracruzana and DGAPA-PAPIIT IN221413.

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