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ORIGINAL PAPER

Olfactory Function in SCA10

Mariana Moscovich[1,2] · Renato Puppi Munhoz[3] · Adriana Moro[1] · Salmo Raskin[4] · Karen McFarland[2] · Tetsuo Ashizawa[5] · Helio A. G. Teive[1] · Laura Silveira-Moriyama[6,7,8,9]

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Abstract

Although the main clinical manifestations of spinocerebellar ataxias (SCAs) result from damage of the cerebellum, other systems may also be involved. Olfactory deficits have been reported in other types of ataxias, especially in SCA3; however, there are no studies on olfactory deficits in SCA type 10 (SCA10). To analyze olfactory function of SCA10 patients compared with that of SCA3, Parkinson's, and healthy controls. Olfactory identification was tested in three groups of 30 patients (SCA10, SCA3, and Parkinson's disease (PD)) and 44 healthy controls using the Sniffin' Sticks (SS16) test. Mean SS16 score was 11.9 ± 2.9 for the SCA10 group, 12.3 ± 1.9 for the SCA3 group, 6.6 ± 2.8 for the PD group, and 12.1 ± 2.0 for the control group. Mean SS16 score for the SCA10 group was not significantly different from the scores for the SCA3 and control groups but was significantly higher than the score for the PD group ($p < 0.001$) when adjusted for age, gender, and history of smoking. There was no association between SS16 scores and disease duration in the SCA10 or SCA3 groups or number of repeat expansions. SS16 and Mini Mental State Examination scores were correlated in the three groups: SCA10 group ($r = 0.59$, $p = 0.001$), SCA3 group ($r = 0.50$, $p = 0.005$), and control group ($r = 0.40$, $p = 0.007$). We found no significant olfactory deficits in SCA10 in this large series.

Keywords Cerebellar degeneration · Movement disorders · Olfaction · Spinocerebellar ataxia · Smell

Introduction

Spinocerebellar ataxias (SCAs) are a genetically and clinically heterogeneous group of autosomal dominant ataxias due to cerebellar and extra-cerebellar lesions involving primarily the brainstem [1]. To date, more than 40 different gene *loci* have been associated with these conditions (OMIM Phenotypic Series entry number PS164400). Spinocerebellar ataxia type 10 (SCA10) is caused by an unstable expansion of a pentanucleotide repeat (ATTCT) in the ataxin 10 (*ATXN10*) gene on chromosome 22 [2, 3]. The classical description of SCA10 (first reported in Mexican patients) includes ataxia and epilepsy, but in Brazilian patients the most common phenotype is "pure cerebellar ataxia," [4, 5] although recent descriptions of additional clinical features such as sensory polyneuropathy, pyramidal signs, and cognitive and neuropsychiatric impairments have been reported [6]. Epilepsy has been observed in only 3.75% of Brazilian SCA10 patients

✉ Mariana Moscovich
marimoscovich@hotmail.com

[1] Movement Disorders Unit, Neurology Service, Internal Medicine Department, Hospital de Clínicas, Universidade Federal do Paraná, Curitiba, PR, Brazil

[2] Department of Neurology, UKSH, Campus Kiel, Christian-Albrechts-University, Kiel, Germany

[3] Movement Disorders Centre, Toronto Western Hospital, University of Toronto, Toronto, ON, Canada

[4] Group for Advanced Molecular Investigation (NIMA), School of Health and Biosciences, Pontifícia Universidade Católica do Paraná (PUCPR), Curitiba, Paraná, Brazil

[5] Department of Neurology, Houston Methodist, Weill Cornell Medical College, Houston, TX, USA

[6] Postgraduate Program in Medicine, Universidade Nove de Julho, Uninove, São Paulo, Brazil

[7] Reta Lila Weston Institute of Neurological Studies, UCL Institute of Neurology, 1 Wakefield Street, London WC1N 1PJ, UK

[8] Departamento de Neurologia, Universidade Estadual de Campinas, UNICAMP, Campinas, Brazil

[9] Departamento de Neurologia, Universidade de São Paulo, USP, São Paulo, Brazil

[7]. Spinocerebellar ataxia type 3 (SCA3) is caused by an unstable CAG trinucleotide repeat expansion in the ataxin 3 (*ATXN3*) gene on chromosome 14. SCA3 is associated with high phenotypic variability, but the core phenotype is progressive gait ataxia with early speech impairment. Other hallmarks include ophthalmoplegia, bulging eyes, parkinsonism, dystonia, and neuropathy [8, 9].

Olfactory dysfunction has been well documented in a number of neurological disorders with marked neurodegenerative changes [10–12], in particular Parkinson's disease (PD) [10, 11]. Some studies have investigated olfactory function in different types of hereditary cerebellar ataxias, and although the findings were controversial, some level of olfactory impairment was generally detected [12–16]. However, the majority failed to include cognitive evaluations or to adjust the score in olfactory tests for overall cognitive deficits [13–17], which are known to affect olfactory performance [5, 18]. In addition, the small number of subjects enrolled in most of these studies limits interpretation of the results. We assessed olfactory identification in a large sample of individuals with SCA10 and compared the results with those for SCA3 patients, PD patients, and controls adjusting for age, sex, and smoking history, and also hypothesized that SS16 results can be correlated with MMSE scores.

Methods

Subjects

Subjects were prospectively recruited at the Ataxia Outpatient Clinic in the Movement Disorders Unit in the Neurology Service of the Hospital de Clínicas, Federal University of Paraná (UFPR). The unit is one of the major referral centers for SCAs in southern Brazil. Informed consent was obtained from all participants, and the protocol was approved by the local (UFPR) ethics committee. Subjects were excluded if they had significant cognitive impairment, detected using a conservative cutoff of 18 in the Mini Mental State Examination (MMSE) [19], or a history of head trauma or sinonasal disease that could significantly impair olfaction. Patients with young-onset PD or a confirmed or suspected diagnosis of genetic parkinsonism were also excluded.

Genetically Confirmed SCA All cases in the SCA10 and SCA3 groups had clinically and/or genetically confirmed diagnoses. SCA10 was confirmed genetically by the presence of an ATTCT pentanucleotide repeat expansion with more than 32 repeats in the ATXN10 gene on chromosome 22q13, and SCA3 was confirmed by the presence of a CAG trinucleotide repeat expansion with more than 51 repeats in the ATXN3 gene on chromosome 14q24.3-q31. Cases included in the study who had not previously had a genetic diagnosis were symptomatic first-degree relatives of individuals with genetically confirmed SCA10 or SCA3. Genomic DNA was isolated from peripheral blood using standard protocols, and mutations were screened and confirmed using established methods [7, 20, 21]. During the testing process, none of the patients or controls were on medication that might interfere with the test results.

Control Group Forty-four individuals matching the SCA10 and SCA3 patients in terms of age, gender, and history of smoking were included in the control group. Controls were selected from the SCA10 and SCA3 patients' non-consanguineous spouses and caregivers.

Sporadic Parkinson's Disease Group Clinical diagnosis of PD was determined by a movement disorders specialist using the Queen Square Brain Bank Criteria [22]. Because of the natural history of PD and SCAs, subjects in the PD group could not be matched to the other groups.

Clinical Variables

The validated Brazilian Portuguese translations of the 16-item Sniffin' Sticks (SS16) smell identification test [23], Scale for the Assessment and Rating of Ataxia (SARA) [24, 25], and Mini Mental State Examination (MMSE) [19] were used.

Statistical Analyses

IBM SPSS Statistics v.20.0. Armonk, NY, IBM Corp, was used for statistical analysis. Univariate analyses were performed using one-way ANOVA (age) or the non-parametric Kruskal-Wallis test (SS16 scores). Categorical variables (gender and smoking) were analyzed by chi-square test. Analysis of covariance considering ranks was used to compare olfaction among the groups adjusting for age, gender, and smoking. Spearman's correlation coefficient was estimated to evaluate association between SS16 and MMSE scores. Receiving operating curve (ROC) was considered to analyze SS16 as a discriminator between health and SCA disease. *P* values less than 0.05 were considered for statistical significance.

Results

Of the 30 individuals in the SCA10 group, 17 (56.7%) were female; mean age for the group was 48.5 ± 11.4 years, and 14 (46.7%) were smokers. Of the 30 patients in the SCA3 group, 16 (53.3%) were female; mean age was 51.3 ± 9.8 years and 10 (33.3%) were smokers. Mean disease duration in the SCA10 group was 14.2 ± 11 years, and the corresponding figure in the SCA3 group was 11.3 ± 6. In the group of healthy controls, 30 (68.2%) were female, mean age was 46.6 ±

11.1 years, and 21 (47.7%) were smokers. Comparisons of these three groups showed no significant difference in the three groups: age ($p = 0.201$), gender ($p = 0.384$), and history of smoking ($p = 0.427$). In the PD group ($N = 30$), 13 (43.3%) subjects were women mean age was 66.4 ± 8.8 years, and only 2 (6.7%) were smokers. Comparisons of the four groups showed significant difference for mean age ($p < 0.001$) and smoking ($p < 0.001$). No significant difference was observed for gender ($p = 0.196$).

Smell identification scores were significantly different comparing SCA10, SCA3 control group, and PD groups in the univariate analyses ($p < 0.001$) or when the results were adjusted for age, gender, and history of smoking ($p < 0.001$). Considering the post hoc adjusted analysis, SCA10, SCA3, and control were not significantly different (control × SCA10, $p = 0.973$; control × SCA3, $p = 0.729$; SCA3 × SCA10, $p = 0.727$). Otherwise, PD group had lower smell scores than the other three groups ($p < 0.001$ for all). SS16 scores for the three patient groups and controls are shown as a box plot in Fig. 1. SS16 scores was not a discriminator between ataxia (SCA10 or SCA3) and control status (area under the receiver operating characteristic curve 0.526, 95% CI 0.432–0.621).

Analysis of the correlation between SS16 and MMSE scores revealed that this was statistically significant in the control and ataxia groups but that there was no significant correlation in the Parkinson's group. These results are illustrated in Fig. 1 in the four scatterplots of SS16 and MMSE scores (SCA10: $r = 0.59$, $p = 0.001$; SCA3: $r = 0.50$, $p = 0.005$; control: $r = 0.40$, $p = 0.007$; PD: $r = 0.02$, $p = 0.926$).

Genetic data on the number of expansions was available for 17 SCA10 and 14 SCA3 patients. The average size of the ATTCT repeat expansion in the SCA10 patients was 2067 (ranging from 1335 to 3560 repeats), and the corresponding figure for the CAG repeat expansion in the SCA3 patients was 66.4 (ranging from 43 to 78 repeats). There was no correlation between SS16 score and number of repeats (SCA3: $r = -0.30$, $p = 0.303$; SCA10: $r = 0.09$; $p = 0.739$) or disease duration (SCA3: $r = 0.03$, $p = 0.866$; SCA10: $r = -0.35$; $p = 0.057$; PD: $r = -0.16$; $p = 0.409$).

Discussion

Our data show no significant olfactory deficits in the SCA10 or even SCA3 groups when adjusted for general cognitive function, agreeing with our previous study [5].

In the present study, the population sample consisted of homogeneous ataxia groups (SCA10, $N = 30$, and SCA3, $N = 30$), each of which was compared separately with the control group; while in our previous study [5], a heterogeneous group was used. The SS16 scores for this heterogeneous group were slightly lower than those for the control group ($p < 0.001$) and higher than those for the PD group ($p < 0.001$) when adjusted for age, gender, and history of smoking, but not when adjusted for cognitive function. No significant olfactory loss was observed in the present study, and the association between cognition and olfactory performance was corroborated.

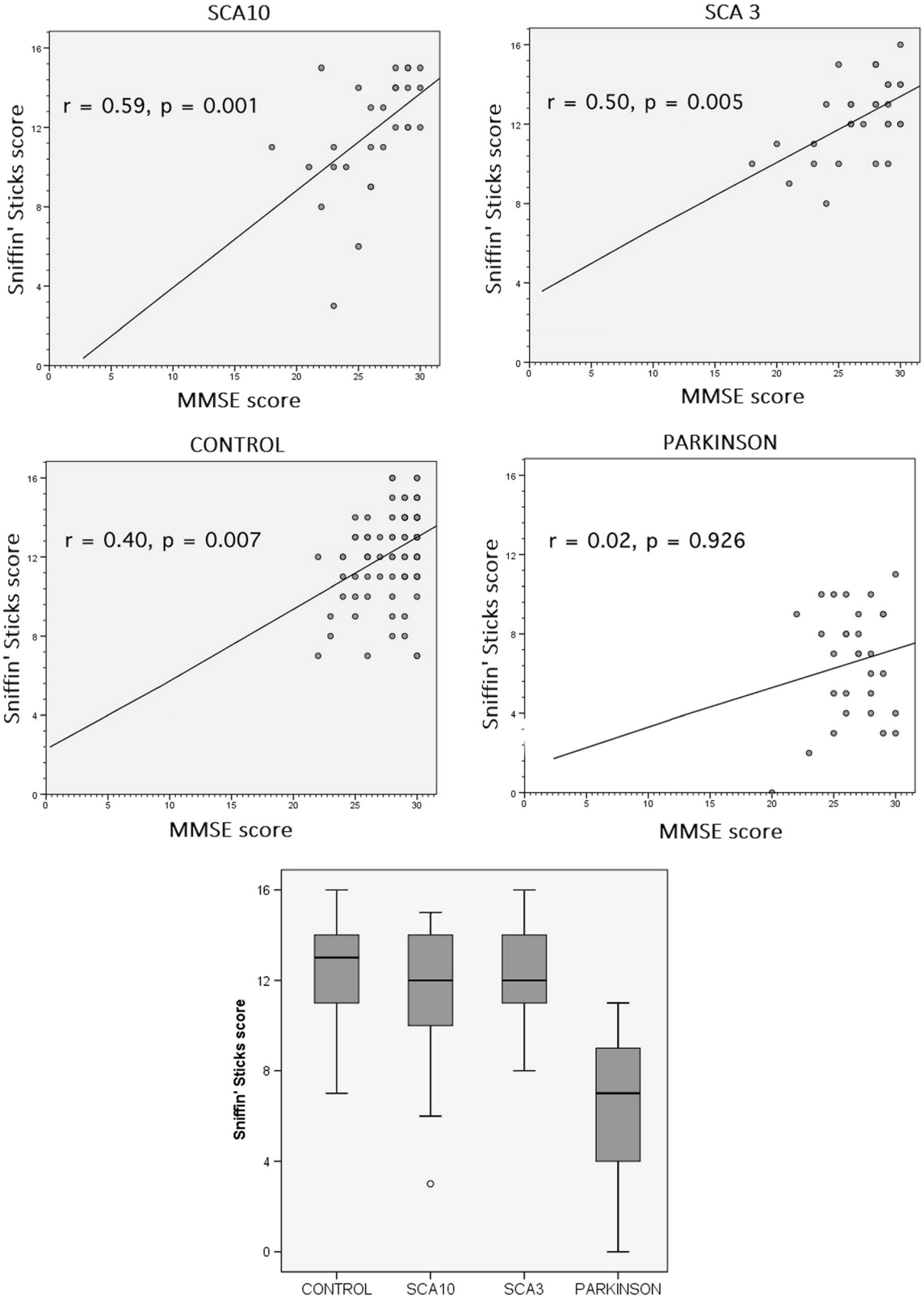
Although hyposmia is frequently observed in various neurodegenerative conditions, previous studies on olfaction in ataxia are inconclusive and contradictory [11, 17, 26, 27]. A correlation between cognitive function and smell test scores has already been described in healthy subjects [28], in subjects with mild cognitive impairment and neurodegenerative diseases such as PD [29], and in subjects with progressive supranuclear palsy [30].

The correlation between olfaction and cognition in ataxia has also been described by Velázquez-Pérez et al. [14], who studied olfaction in 53 SCA2 patients and 53 healthy controls. Olfactory scores were significantly lower in the ataxia group than in the controls, and a significant correlation between olfactory scores and MMSE scores was found ($p = 0.03$). However, after excluding 13 patients with MMSEs below 25, the only correlation found in the 40 remaining patients was between olfactory score and age ($p = 0.03$).

In contrast, Braga-Neto et al., in a study comparing 41 SCA3 patients and 46 healthy controls [13], reported that ataxia patients can present with olfactory dysfunction independently of their cognitive status. In their study, SS16 scores were significantly lower in the SCA3 group than in the controls. In the present study, the ataxia patients were older and the MMSE scores for the SCA3 patients were higher.

During olfaction, identification and discrimination of odors require the participation of structures from the central nervous system in what are considered cognitive tasks [31]. Consecutive activation of the posterior lobe of the cerebellum during cognitive processing and stimulation of olfactory receptors, as described by Hummel and Kobal [32], may explain this association between cognition and olfaction. While the prevalence and severity of cognitive dysfunction vary considerably in different SCA populations, it is well known that SCA10 and SCA3 patients have some degree of cognitive impairment, which is likely to have influenced the results of the olfactory tests in the present study [6].

Several limitations can be identified in our study. Firstly, simple cognitive screening was used to assess the patients included in the study rather than in-depth cognitive testing. As the association between cognition and olfaction was positive, more comprehensive cognitive tests may be needed to understand this association better. Secondly, the group used for the purposes of comparison (PD group) was not completely matched to the other groups, as the diseases compared have a different age of onset. In the PD group, the patients were older than in the ataxia groups because of the natural history of the disease. Nevertheless, we chose to compare our SCA



groups with a group for which the presence of an olfactory deficit is well established and therefore expected to find a positive association between olfactory deficit and PD. Thirdly, it was not possible to perform a sinonasal scope examination to exclude any possible sinonasal disease, which maybe could interfere in our final results.

◀ **Fig. 1** Box plot of Sniffin' Sticks (SS16) test scores for the three patient groups and control and association between MMSE and SS16 test scores. Box plot of Sniffin' Sticks (SS16) test scores for the three patient groups and control. The median is the horizontal line inside the box, and the box contains the central 50% of the observations. The error bars contain the central 95% of the ordered observations. The four small boxes show scatterplots of SS16 and MMSE scores. The line of best fit shows the association between MMSE and SS16 test scores in each group (SCA10: MMSE × SS $p = 0.001$; SCA3: MMSE × SS16 $p = 0.005$; control: MMSE × SS16 $p = 0.007$; PD: MMSE × SS16 $p = 0.926$). SCA10, spinocerebellar ataxia type 10; SCA3, spinocerebellar ataxia type 3; MMSE, Mini Mental State Examination; PD, Parkinson's disease

SCA10 is a rare disease, and the case series in the present study is the largest to date in which olfactory deficits in SCA10 patients have been investigated and the results compared with those for other diseases. The cognitive impairment found in ataxia patients is an important factor in olfaction and should always be considered when interpreting test scores. Although the role of the cerebellum in olfaction has already been reported [33–36], assessment of olfactory deficits should always be adjusted for other variables.

Author Contributions M Moscovich conceptualized the study, analyzed the data in the study, drafted the manuscript, and revised the manuscript. R P Munhoz drafted the manuscript and revised the manuscript. H A Teive designed the study and revised the manuscript. S Raskin revised the manuscript. A Moro revised the manuscript. K McFarland revised the manuscript. T Ashizawa revised the manuscript. L Silveira-Moriyama designed the study, interpreted the data in the study, analyzed the data in the study, drafted the manuscript, and revised the manuscript.

Compliance with Ethical Standards

Informed consent was obtained from all participants, and the protocol was approved by the local (UFPR) ethics committee.

Conflict of Interest Dr. Moscovich, Dr. Munhoz, Dr. Moro, Dr. Raskin, and Dr. McFarland report no disclosure. Dr. Ashizawa is funded by NIH grant NS083564. Teive received personal compensation for educational activities with Allergan, Ipsen, Teva, and UCB and serves as an editor-in-chief of Arquivos de Neuro-Psiquiatria and editorial board member of *Movement Disorder Clinical Practice*, the *Journal of Neurology Research*, *Parkinson's Disease*, *Current Neurology and Neuroscience Reports*, and *Arquivos de Neuropsiquiatria*. Dr. Laura Silveira-Moriyama received travel grants from Teva and supervised scholarships from Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP) and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES).

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