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Olfactory Impairment in Familial Ataxias

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Abstract

The main clinical manifestations of the spinocerebellar ataxias (SCAs) result from the involvement of the cerebellum and its connections. Cerebellar activity has been consistently observed in functional imaging studies of olfaction, but the anatomical pathways responsible for this connection have not yet been elucidated. Previous studies have demonstrated olfactory deficit

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AUTHORS' CONTRIBUTIONS

M Moscovich: conceptualized study, analyzed data in study, drafted manuscript, revised manuscript R P Munhoz: drafted manuscript, revised manuscript H A Teive: revised manuscript S Raskin: revised manuscript M J Carvalho: revised manuscript E R Barbosa: revised manuscript R Ranvaud: revised manuscript J Liu: revised manuscript K McFarland: revised manuscript T Ashizawa: revised manuscript A J Lees: revised manuscript L Silveira-Moriyama: designed study, interpreted data in study, analyzed data in study, drafted manuscript, revised manuscript.

in SCA2, Friedreich's ataxia (FA) and in small groups of ataxia of diverse etiology. We used a validated version of the 16 item smell identification test from Sniffin' Sticks (SS-16) was used to evaluate 37 patients with genetically determined autosomal dominant ataxia, and 31 with familial ataxia of unknown genetic basis .This data was also compared to results in 106 Parkinson's disease (PD) patients and 218 healthy controls. The SS-16 score was significantly lower in ataxia than in the control group ($p<0.001$, 95%CI for $\beta = 0.55$ to 1.90) and significantly higher in ataxia than in PD ($p<0.001$, 95%CI for $\beta = -4.58$ to -3.00) when adjusted for age ($p=0.001$, 95%CI for $\beta = -0.05$ to -0.01), gender ($p=0.19$) and history of tobacco use ($p=0.41$). When adjusted for general cognitive function we found no significant difference between the ataxia and control group. Our study confirms previous findings of mild hyposmia in ataxia, and further suggests this may be due to general cognitive deficits rather than specific olfactory problems.

Search Terms

Movement disorders; Smell; Cerebellar ataxia; Cerebellar degeneration; Cognition

Introduction

Olfactory dysfunction is documented in a number of neurological disorders with marked neurodegenerative changes found in the brain at post-mortem, including Alzheimer's disease (AD), Parkinson's disease (PD), progressive supranuclear palsy, multiple system atrophy (MSA), corticobasal degeneration, and parkinsonism-dementia complex of Guam.[1–6] Ataxias result from the involvement of cerebellar structures and extra-cerebellar lesions, especially those due to brainstem involvement.[7] Spinocerebellar ataxias (SCA) are a genetically and clinically heterogeneous group of autosomal dominantly inherited progressive ataxia disorders. Up to now, almost 31 different gene *loci* have been found.[8–10]

A few reports have investigated olfactory function in cerebellar ataxias, showing a mild but significant olfactory impairment in patients with varied forms of ataxias.[11–14] Functional magnetic resonance imaging (MRI) studies show odor-induced cerebellar activity that is independent of sniffing.[15] The functional role of the cerebellum in olfaction and pathways through which olfactory information reach the cerebellum are unknown.[16]

We aimed at investigating if smell was impaired in a large sample of patients with familial ataxias, including fourteen patients with SCA10, a condition in which smell testing has never been described before.

Methods

All subjects were recruited in Brazil between 2004 and 2011. Subjects were recruited at the University of Sao Paulo and the Federal University of Parana (between 2009 and 2011). The protocol used to test the sense of smell and evaluate cognitive function was identical and the researchers are part of a collaborative network.

Patients with a diagnosis of hereditary episodic ataxia and X linked ataxias, participants with an active upper respiratory tract infection, MMSE scores below 18 and those with a previous history of head trauma were excluded. Consent was obtained from all participants and the protocol was approved by the local ethics committees.

Subjects

Smell testing was performed in sixty-eight patients including those with SCA diagnoses confirmed by genetic test (one SCA 1,two SCA 2, seventeen SCA 3,one SCA 6,one SCA 7,fourteen SCA 10 and one SCA 13) and also thirty-one familial ataxia patients without genetic confirmation.

Genetically confirmed SCA

Of the 37 patients with confirmed SCA diagnoses, seventeen (45.9%) were female and seventeen (45.9%) were smokers. Mean age was 48.4 years [standard deviation (SD) 11 years], mean age of onset was 35.3 years (SD 10.7 years), and mean disease duration was 13 years (SD 8.5 years). In the SCA subgroup, the mean disease duration was 11 years (SD 5 years) on the SCA 3 group and 17.6 years (SD 10.6 years)for the SCA 10 group. The mean SARA score for the SCA3 group was 14.4 (SD 6.2) compared with 10.68 (SD 5.7) on the SCA 10 group. Genomic DNA was isolated from peripheral blood using standard protocols and mutations were screened and confirmed using previously established methods.[17–19]

Familial ataxia without genetic diagnosis

A total of thirty-one patients with familial ataxia of unknown etiology were tested. Fifteen (48.5%) were female and nine (27.3%) were smokers. All patients had a clinical diagnosis of familial ataxia, progressive ataxia with gait and stance impairment, speech disturbance and oculomotor abnormalities with no apparent medical causes such as vitamin deficiencies, infections, or exposure to toxins. Genetic testing was performed in 20 patients but none of the tested mutations was identified, and in others genetic testing was not performed due to socioeconomic reasons.

Mean age was 45 years (SD 10.9 years), mean age of onset was 34 years (SD 13 years), and mean disease duration was 10.9 years (SD 8.8 years).

Control Groups

For the comparison groups we used data from 106 PD patients and 218 control subjects tested for a previous study.[4] In the PD group, the mean age was 61.2 years (SD 11.0 years), 35 (33%) of subjects were female and 41 (38%) were smokers. Mean age of onset of the PD patients was 48.9 years (SD 13.4 years) and mean disease duration was 12.3 years (SD 9.0 years). In the control group, mean age was 50.9 years (SD 17.1years), 92 (42.2%) were female and 103 (47.2%) were smokers. (Table 1)

Clinical studies

Smell testing

A previously validated Brazilian-Portuguese translation of the 16 item smell identification test from Sniffin' Sticks (SS-16) [20] was used. Clinical assessment was conducted using the Scale for the Assessment and Rates of Ataxia (SARA) [21, 22] (scores ranging from 3 to 30) and a validated translation of the Mini-Mental Status Examination (MMSE) [23]

Statistical Analyses

In the ataxia group the association between the score in the SS-16 and other clinical variables (disease duration, SARA, MMSE) was done using multiple linear regressions (MLR) adjusting for age, gender and smoking as covariates. To investigate the difference in the average SS-16 score between groups when adjusting for other possible influencing factors such as age, gender, history of smoking and score in the MMSE, MLR analyses were used. When the three groups of patients were compared, indicator variables were used to

compare the ataxia group with control and PD groups. Because there was a significant effect of the MMSE on the SS-16 scores and a significant interaction between MMSE and the variable comparing ataxia and PD subjects, subsequent analyses were performed to investigate the relationship between the SS-16 and MMSE in the three groups of subjects using MLR and also partial correlations. Partial correlation coefficients between MMSE and SS-16 when adjusting for age and gender were compared between the groups ataxia and controls using the Z distribution using the online software Stattools (http://www.stattools.net/). Except where otherwise stated, all analyses were performed using the statistics software SPSS v19. Assumptions for the MLR analyses were checked by visual inspection of the residuals.

Results

In the ataxia group (n=67), the SS-16 score was significantly associated with the MMSE score (p=0.001, 95%CI for β = 0.18 to 0.63) when adjusted for age (p=0.95), gender (p=0.03, 95%CI for β = −2.55 to −0.15), smoking (p=0.11), SARA score (p=0.37), and disease duration (p=0.91). The variance inflation factor (VIF) for the covariates ranged between 1.11 to 1.38, indicating an absence of significant multicollinearity.

A multiple linear regression (MLR) including all 391 subjects demonstrated that the SS-16 score was significantly lower in the ataxia group than in the control group (p=0.001, 95%CI for β = 0.52 to 1.88) and significantly higher in the ataxia group than in PD group (p<0.001, 95%CI for β = −4.60 to −3.02) when adjusted for age (p<0.001, 95%CI for β = −0.05 to −0.01), gender (p=0.19) and history of tobacco use (p=0.31) (see figure 1); the VIF ranged between 1.08 and 2.91. When also adjusting for the MMSE (p<0.001, 95%CI for β = 0.17 to 0.37) in addition to age (p=0.042) and gender (p=0.04) the MLR showed the SS-16 score in the ataxia group to be higher than in the PD group (p<0.001, 95%CI for β = −5.45 to −3.80) and not different from that of controls (p=0.31); the VIF ranged between 1.08 and 2.41).

The scatter-plot between MMSE and SS-16 in the three groups and subtypes SCA3 and SCA10 (see figure 2 and supplemental figure 1) shows a moderate correlation between the SS-16 and the MMSE. The partial correlation coefficient between MMSE and SS-16 when adjusting for age, gender and smoking was r=0.514 [p<0.001, degrees of freedom (df) = 62) in the ataxia group, r= 0.292 (p<0.001, df =213) in the control group, and r=0.028 (p=0.78) in the PD group, indicating that variations in the MMSE explain roughly 26% of the variation of the SS-16 in the ataxia group, 9% of the variation in the control group, and not a significant amount of the SS-16 variation in the PD group. Using the Z distribution there was a significant difference between the partial correlation coefficient in the ataxia and control groups (p=0.03, Z=1.8404) indicating that the variation in the MMSE explains a larger amount of the variation of the SS-16 in the ataxia than in the control group.

Although it is a possibility that olfaction only develops in later stages of disease, our current study fails to demonstrate such association, because there was no association between the SS-16 and disease duration (Pearon's correlation p value = 0.11). Regarding disease severity, there was an association between SS-16 ad SARA scores (Pearson's correlation −0.38, p=0.005) showing that more affected subjects have worse olfactory performance, but when adjusting for MMSE and age - and other factors that could potentially affect the olfactory abilities – there was no independent association between the SS-16 and SARA (p=0.37), although the MMSE remained an independent predictor (p=0.001).

Discussion

Our study provides independent confirmation of the smell deficit found in a large number of heterogeneous ataxia patients, as none of the patients in the current study were included in any of the previous reports. These findings add to a large picture of olfactory deficits in different neurodegenerative diseases. [2, 8–12] (Listed in Table 2)

The main clinical manifestations of spinocerebellar ataxias result from the involvement of cerebellar structures but they often present with extra-cerebellar features.[7, 8] The decrement of olfactory function observed in previous studies was always small and far less marked than that reported in PD or AD, for instance.[2, 11, 12, 24]

Abele et al [12] demonstrated a moderate impairment of olfaction in 8 patients with MSA and 11 patients with sporadic ataxia with unknown etiology, although, when controlled for age the authors did not adjust the results for MMSE scores. Connely et al [11] studied a group of 35 non demented patients with assorted degenerative ataxias (including SCA 3, 7, 2 and FA), showing a deficit in olfaction when compared to age and gender matched control subjects. Fernandez-Ruiz et al [13] reported olfactory impairments in 29 patients with autosomal dominant, recessive and sporadic ataxia in comparison to 29 age and gender matched controls, however, they did not correlate the UPSIT with the MMSE scores. Velazquez-Perez et al [25] found that UPSIT scores were lower in a group of 53 SCA 2 patients when compared to 53 controls but when demented subjects were excluded, there was no significant difference in UPSIT scores between groups. Recently, Braga-Neto et al [14] demonstrated olfactory dysfunction in 41 subjects with SCA 3 even when matched for age, gender and MMSE scores. They excluded all patients whose MMSE score was below 24 or individuals with less than 5 years of education.

The role of the cerebellum in olfaction has been proposed but never fully clarified and the anatomical pathways that lead to this connection have not yet been demonstrated, however, in 1997 Yousen et al [15] reported functional MRI findings in five adult man with normal sense of smell, showing that olfactory nerve mediated stimulation activated the orbitofrontal and cerebellar areas, suggesting that the cerebellum is involved in sensory discrimination and attention to tasks. Sobel et al [26] using a functional magnetic resonance imaging (fMRI) demonstrated that the cerebellum shows olfactory-related activation which was dependent on the odorant concentration, reinforcing the idea of a role for the cerebellum in olfaction. Nevertheless, the same study showed cerebellar activation during the sniffing of nonodorized air, which was hypothesized as part of a cerebellar role in the maintenance of a feedback mechanism regulating the sniffing magnitude. In another functional study, Qureshy et al [27] mapped the human brain during olfactory processing and reported a cerebellar activation during olfactory naming, suggesting the cerebellum may have a role in cognitive olfactory processing. Savic reported [28–31] in 4 different papers using fMRI or PET scan that the cerebellum is activated during odor discrimination, odor recognition memory and during passive smelling. Finally, Ferdon and Murphy [32] demonstrated in an fMRI study with ten young and ten elderly adults, that olfactory tasks caused activation of the cerebellar lobes, especially in superior semilunar lobule, inferior semilunar lobule and posterior quadrangular lobule.

Besides the motor control and olfaction, the cerebellum has been well recognized to be involved in cognitive processing [33–36] These findings were consistent with a number of studies evidencing a cerebellar role during attention[37], memory [33, 38], language[39], and verbal fluency. [40]

Stoodley and Schmahmann [41] showed similar findings in a fMRI study with healthy subjects, showing cerebellar activation during cognitive functioning in the posterior lobe

areas, these findings were supported in different studies[35, 41, 42] and the posterior lobes were recognized as cognition regions.

Burk [33] studied cognition in SCA and FA patients reporting mild cognitive deficits in SCA1,SCA2 and SCA3 present on verbal memory tasks, supported by the hypothesis that these deficits are due to a disruption of cerebrocerebellar circuitries and not from the cerebellar degeneration per se.

The relationship between cognitive and smell test scores has previously been reported in control subjects [43], subjects with mild cognitive impairment and in patients with Alzheimer's patients , and in other neurodegenerative diseases such as PD[44] and Progressive Supranuclear Palsy [6]. Ours is the first study to show an association between olfaction and cognitive function in ataxias, but we suggest in future studies cognitive performance - measured by the crude score on the MMSE or more sophisticated neuropsychometric testing - should be taken into consideration when studying olfaction in neurodegenerative diseases, and ataxia in particular.

Quantitative correlation of clinical findings with MRI data was not possible in this study, future studies including voxel-based morphometry, diffusion tensor imaging, and functional MRI might help clarify this subject further. In studies with homogeneous groups of genetic ataxia patients, correlation with repeat length might also provide additional insights.

Our data, derived from the largest series of patients with a heterogeneous group of ataxia tested for smell deficit so far, confirm the presence of hyposmia in cerebellar ataxia, and further demonstrates that cognitive deficits in the ataxia group might be a confounding factor, and should be taken into consideration in future studies. Although the two deficits might be independent, it is also possible that cognitive difficulties party explain the smell deficit found in the ataxia group when compared to controls. .

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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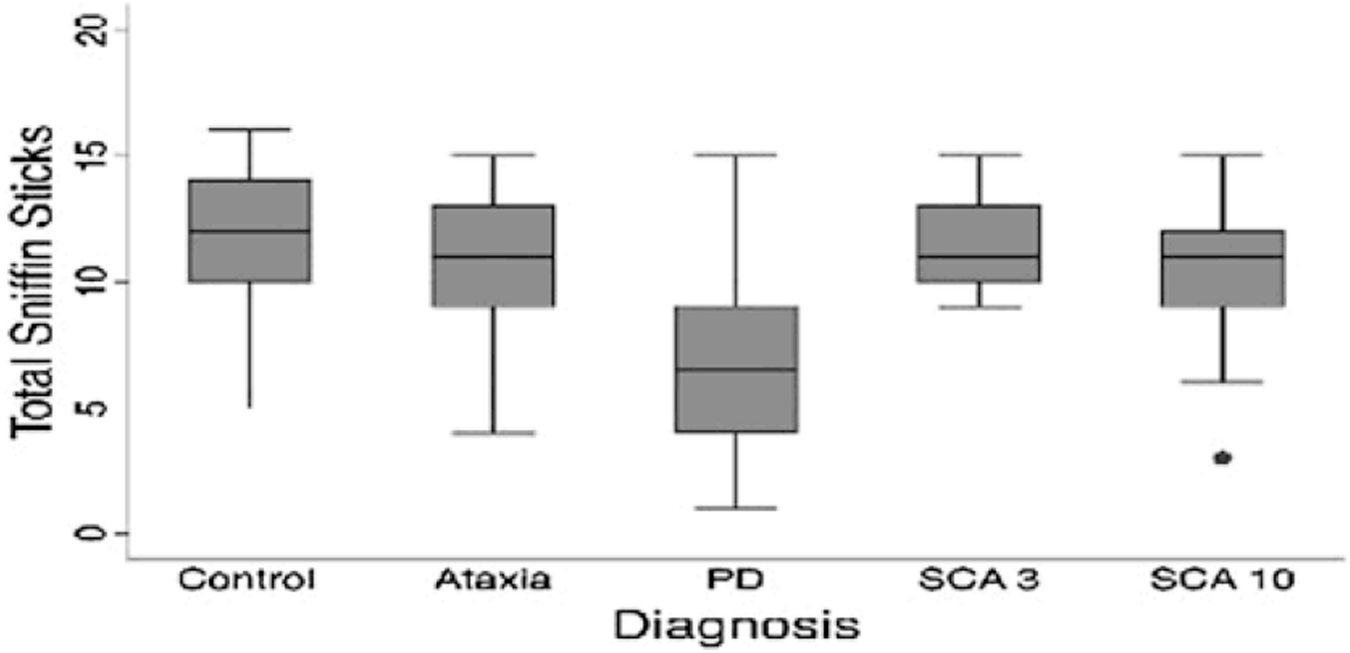

Figure 1.
Box plot of the Sniffin Sticks score in the three patient groups and subtypes SCA3 and SCA10. The median (the horizontal line) is within the box containing the central 50% of the observations and the error bar contains the central 95% of the ordered observations. PD, Parkinson's disease.

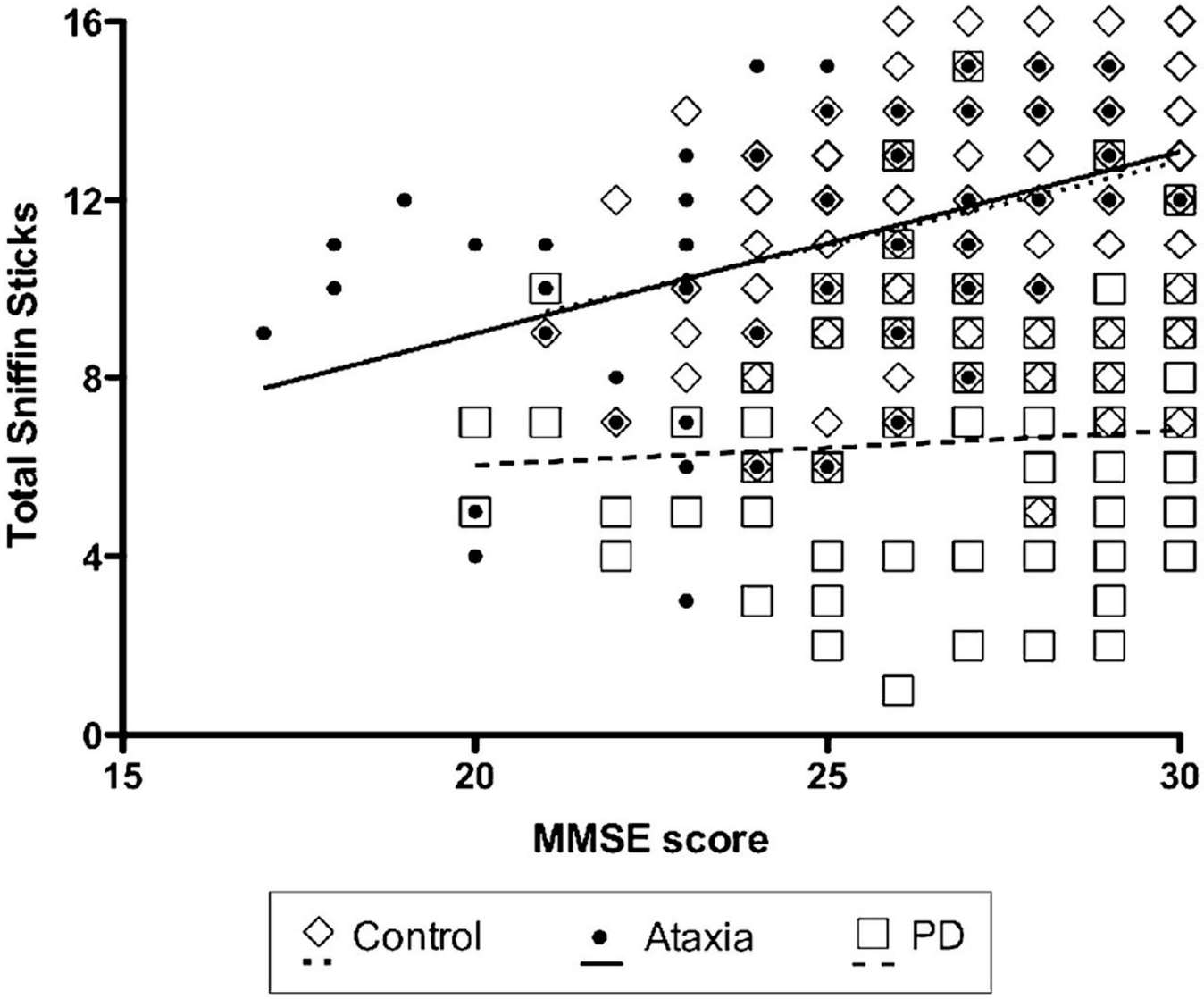

Figure 2.
Scatter plot of Sniffing Sticks and MMSE scores in the subjects who underwent both tests. Fit line showing the association between MMSE and Sniffing Sticks in each group. MMSE, Mini Mental State Examination

Table 1

Summary of clinical variables

		SCA	Familial but not genetically confirmed ataxias	PD	CONTROL
N		37	31	106	218
Age in years	Mean ± SD, range	48.4±11	45±10.9	61.2±11	50.9±17.1
Age of onset in years	Mean ± SD, range	35.3±10.7	34±13	48.9±13.4	N/A
Disease duration in years	Mean ± SD, range	13 ± 8.5	10.9±8.8	12.3±9	N/A
Disease severity	Mean ± SD, range	SARA12.3±5.5	SARA 12±7	UPDRS 25.5±14	N/A
History of smoking	N (%) positive	17 (45.9)	9 (27.3)	41 (38.7)	103 (47.2)
Gender	N (%) woman	17 (45.9)	15 (48.3)	35 (33)	92 (42.2)
MMSE	Mean ± SD, range	25±3.2	24±4	27.1±2.5	27.5±2.1
SS-16	Mean ± SD, range	11±2.6	10±4	6.5±2.7	11.9±2.3

SCA= Spinocerebellar ataxia SD = standard deviation; N = number of subjects; SS-16 = 16 item identification test from Sniffin Sticks (possible range 0 to 16). MMSE = Mini-Mental State Examination; PD = Parkinson's disease; SARA = Scale for the Assessment and Rating of Ataxia; UPDRS= Unified Parkinson's Disease Rating Scale

Table 2

Previous Studies

Paper	Number of cases	Test used	Method of analysis	Outcomes
Satya-Murti et al., 1988[43]	7 FA 9 other neurological disorder	BAEP + non standard test	Studied olfactory function	FA patients were significantly lower than the normal controls.
Fernandez-Ruiz et al., 2003[13]	12 SCA2 5 SCA3 1 SCA 10 5 Sporadic 5 Recessive 1 FA 25 PD 27 HD	UPSIT	Compare UPSIT scores of the different groups.	Smell deficit in SCA 2, autosomal recessive ataxia and sporadic ataxia, but no in patients with SCA3
Abele et al., 2003[12]	8 MSA 1 late onset sporadic ataxia of unknown etiology	SS + (3 tests of olfactory function)	Studied olfactory function	No significant differences in olfactory function between patients with sporadic ataxia = MSA-C
Connely et al., 2003[11]	2 SCA2 5 SCA3 1 SCA7 4 unidentified forms of cerebral degeneration) 23 FA	UPSIT	Study olfactory function in patients with cerebellar disorder.	FA group were significantly lower than controls, Group with ataxia was also lower than control
Mainland et al., 2005[16]	7 focal unilateral cerebellar lesions	UPSIT	Examined the olfactory function in patients with unilateral cerebellar lesions.	Patients with unilateral cerebellar lesions were impaired at olfactory identification.
Velazquez-Perez et al., 2006[25]	53 SCA2	UPSIT + non standard test (detection threshold, discrimination threshold)	Analyzed olfactory threshold and their relation to other features.	Significant impairment in SCA 2:in olfactory threshold, quality, identification and discrimination
Braga Neto et al., 2011[14]	41 SCA 3 46 control	SS-16	Analyzed olfactory identification and correlate with MMSE and non-cerebellar symptoms	Significantly reduced in patients with SCA3 and that sex, MMSE scores and RLS also influence the SS-16 scores.

FA= Friedreich Ataxia; SCA= Spinocerebellar Ataxia; BAEP= Brainstem auditory evoked potentials; UPSIT= University of Pennsylvania Smell Test; MSA= Multiple system atrophy; MSA-C= Multiple system atrophy type cerebellar; SS= Sniffin'Sticks; RLS= restless leg syndrome; MMSE = Mini-Mental State Examination PD=Parkinson Disease HD=Huntington Disease