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Rhinological manifestations of Sjögren's syndrome: a cohort-matched, prospective, cross-sectional, observational study

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Main Article

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Abstract

Objective. To assess the prevalence of abnormal rhinological findings in a Sjögren's syndrome population.

Methods. A cohort-matched, prospective, cross-sectional, observational study was conducted. Sixty-seven subjects (30 patients and 37 controls) were enrolled. Rhinological assessment including smell threshold was evaluated using a standardised, validated clinical test as part of a larger study.

Results. Smell thresholds were −4.4 and −5.4 in the Sjögren's syndrome and control groups, respectively ($p = 0.001$). Hyposmia (threshold values of less than −4.5) was demonstrated in the Sjögren's syndrome group (47 per cent). Smell was negatively correlated with age ($p = 0.040$). Nasal septal perforation was noted in 3 Sjögren's syndrome patients (10 per cent) and nasal mucosal dryness in 10 patients (33 per cent), but none of the control group were affected.

Conclusion. Hyposmia in Sjögren's syndrome was demonstrated using the Smell Threshold Test. Nasal septal perforation and nasal mucosa dryness were also noted in patients with Sjögren's syndrome. A diagnosis of Sjögren's syndrome should be considered and investigated in smell deprivation and/or nasal septal perforation patients.

Introduction

Sjögren's syndrome is a chronic autoimmune condition, affecting women more than men (9:1), characterised by dry eyes and mouth resulting from lymphocytic infiltration of the exocrine glands. It is estimated to affect 1 per cent of the population.[1] Sjögren's syndrome is classified into primary and secondary (when it co-occurs with another well-defined connective tissue disease). The American-European Consensus Group criteria, introduced in 2002, have become widely accepted as the basis for diagnosis and classification.[2] Four of six criteria (ocular and oral symptoms and signs, histopathology, and autoimmune antibodies) are needed to satisfy the diagnosis of primary Sjögren's syndrome.

There have been contradictory reports on Sjögren's syndrome nasal physical findings and/or olfactory functions.[3–6] This study aimed to assess the degree of smell impairment and nasal findings in patients with Sjögren's syndrome as part of a larger study. This paper presents the olfactory and physical nasal findings in a Sjögren's syndrome population compared with controls.

Materials and methods

This was a cohort-matched (gender and sex), cross-sectional, observational study. Ethical approval was granted by the North Wales research and development committee. Patients and controls gave their informed consent to be enrolled in the study according to the Declaration of Helsinki.

Patients (all adults) with Sjögren's syndrome (primary and secondary), who had ocular and oral symptoms and signs, were initially identified from the rheumatology department diagnostic database. Names were then checked with the database from the diagnostic serology and pathology service to confirm that they had positive serology and pathology for anti-La and/or anti-Ro antibodies, and/or positive lip biopsy histology, to fulfil four out of the six American-European Consensus Group diagnostic criteria for Sjögren's syndrome.[2] Exclusion criteria were: previous head injury, stroke, radiotherapy to head and neck, chemotherapy, nasal polyposis, chronic rhinosinusitis, nasal surgery, anosmia from another cause prior to diagnosis with Sjögren's syndrome, major head and neck surgery, salivary gland surgery, or other autoimmune rheumatological diseases.

Controls (adults) were selected to match the Sjögren's syndrome group in terms of age and gender. The exclusion criteria for controls were the same as for the Sjögren's syndrome group.

A concise rhinological history was taken, followed by anterior rhinoscopy examination using a headlight and nasal speculum.

Table 1. Sjögren's syndrome and control group characteristics

Parameter	Sjögren's syndrome group values	Control group values
Gender (*n* (%))		
– Male	3 (10)	2 (5.4)
– Female	27 (90)	35 (94.6)
Smoking (*n* (%))		
– Yes	2 (6.7)	6 (16.2)
– No	28 (93.3)	32 (83.8)
Results (*n* (%))		
– Smell test	30 (100)	37 (100)
– Anterior rhinoscopy	30 (100)	37 (100)
Age (years)		
– Mean (SD)	59.1 (11.25)	56.0 (11.7)
– Range	36–83	35–78

SD = standard deviation

The University of Pennsylvania Smell Threshold Test (Sensonics, Haddon Heights, New Jersey, USA) was performed according to standard manufacturer protocols as recommended. The test kit contained 20 bottles: 2 blank and 18 containing phenyl ethyl alcohol in concentrations from −10 ($\log_{10}$ 1/10 000 000 000) to −2 ($\log_{10}$ 1/100). The increments were in half log values. A threshold lower than −4.5 was considered to indicate hyposmia. High test–retest reliability ($r = 0.88$) was demonstrated (Appendix 1).[7,8]

Results

Thirty Sjögren's syndrome patients (27 females and 3 males) were included. Two female patients had secondary Sjögren's syndrome and 28 had primary Sjögren's syndrome. Thirty-seven controls (35 females and 2 males) were also enrolled. Mean age (± standard deviation) was 59 (± 11.25) years and 56 (± 11.7) years for the Sjögren's syndrome and control groups, respectively. Age range was 36–83 years in the Sjögren's syndrome group and 35–78 years in the control group. Two Sjögren's syndrome patients and six controls were smokers (Table 1).

All the Sjögren's syndrome patients satisfied the American-European Consensus Group criteria for Sjögren's syndrome. All had had dry eyes and dry mouth for at least three months. All had positive serology for anti-La and/or anti-Ro antibodies, typical minor salivary gland histology (lip biopsy), and a positive Schirmer test result. Associated diseases in the secondary group included systemic lupus erythematosus and rheumatoid arthritis. In the Sjögren's syndrome group, 12 patients had osteoarthritis, 8 were diagnosed with hypothyroidism and 1 with autoimmune thyroiditis, and 4 patients had fibromyalgia.

Nasal examination showed anterior nasal septal perforation in three patients with Sjögren's syndrome (10 per cent) but in none of the control group (Table 2). Dry nasal mucosa during examination was subjectively noted by the examiner in 10 patients with Sjögren's syndrome (33 per cent) but in none of the controls (Table 3).

The University of Pennsylvania Smell Threshold Test results are shown in Table 4. Smell threshold was reduced in the Sjögren's syndrome patients compared with the controls.

Table 2. Nasal septal perforation in Sjögren's syndrome and control groups

	Septal perforation? (*n*)		
Group	No	Yes	Total (*n*)
Sjögren's syndrome	27	3	30
Control	37	0	37
Total	64	3	67

Table 3. Nasal mucosa dryness in Sjögren's syndrome and control groups

	Nasal mucosal dryness? (*n*)		
Group	No	Yes	Total (*n*)
Sjögren's syndrome	20	10	30
Control	37	0	37
Total	57	10	67

Table 4. Smell threshold in Sjögren's syndrome and control groups

	Smell threshold result (*n*)		
Group	Hyposmia	Normal	Total (*n*)
Sjögren's syndrome	14	16	30
Control	7	30	37
Total	21	46	67

Table 5. Smell threshold test results

Group	Cases (*n*)	Mean threshold	SD	SE mean
Sjögren's syndrome	30	4.4040	1.00596	0.18366
Control	37	5.3749	1.28573	0.21137

SD = standard deviation; SE = standard error

There was both a statistically and a clinically significant difference between cases and controls on the Smell Threshold Test. The mean difference was a full 1 unit (95 per cent confidence interval of difference = 0.40 to 1.54, $p = 0.001$) (Table 5). This represents a countable difference in smell threshold testing (Figure 1).

Clinically, a smell threshold lower than 4.5 (disregarding the negative sign to ease description) is considered as hyposmia. The Sjögren's syndrome group showed hyposmia (mean smell threshold value of 4.4); in contrast, the mean smell threshold value was 5.4 in the control group. Hyposmia was diagnosed in 14 out of 30 patients (47 per cent) in the Sjögren's syndrome group and in 7 out of 37 individuals (19 per cent) in the control group. This difference is statistically significant (Pearson $\chi^2 = 5.93$, 1 degree of freedom; $p = 0.015$). Therefore, there is strong evidence to suggest a difference in smell threshold between Sjögren's syndrome cases and the control group. Anosmia (smell threshold value of 2 or less) was detected in two female patients and one female control. Smell threshold negatively correlated with age ($r = -0.252$; $p = 0.040$).

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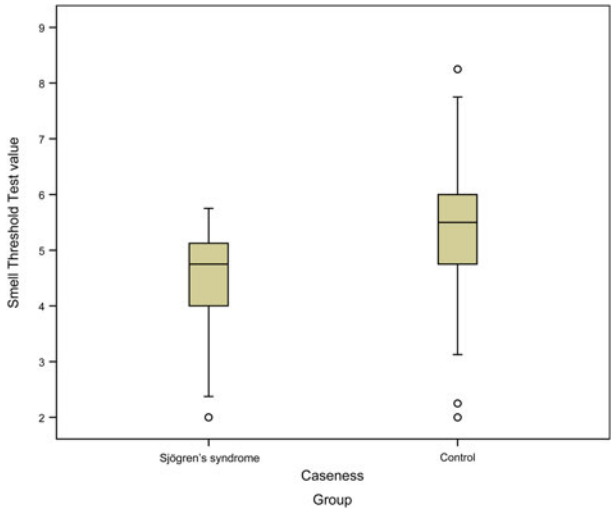

Fig. 1. Box plot of Smell Threshold Test results for both the Sjögren's syndrome and control groups.

Discussion

This study aimed to assess the degree of smell impairment and nasal findings in patients with Sjögren's syndrome as part of a larger study. It showed that patients with Sjögren's syndrome do indeed have abnormal smell perception leading to impaired smell sensation. There is relatively little literature on the effect of Sjögren's syndrome on smell perception. All Sjögren's syndrome patients recruited in the study fulfilled the American-European criteria for a Sjögren's syndrome diagnosis. Thirty patients took part in the study out of 50 identified and invited patients; this represents 60 per cent of patients with Sjögren's syndrome selected from the Rheumatology and Serology databases available at the time. Specific reasons for not taking part were not recorded, but the main reason was reluctance to travel long distances for testing. Nevertheless, 60 per cent represented a satisfactory acceptance rate.

None of the Sjögren's syndrome patients had clinically significant extraglandular disease caused by Sjögren's syndrome. However, there was some co-morbidity. Of the Sjögren's syndrome group, 12 patients had osteoarthritis, 8 patients were diagnosed with hypothyroidism and 1 with autoimmune thyroiditis, and 4 patients had widespread musculoskeletal pain and fatigue with features compatible with fibromyalgia.

Two of 30 patients in the Sjögren's syndrome group were smokers compared with 6 of 37 in the control group. This finding probably reflected the sensation of burning discomfort associated with smoking that is often reported by Sjögren's syndrome patients.[9] Although more subjects smoked in the control group than in the Sjögren's syndrome group, they scored better than the Sjögren's syndrome patients on smell. This may demonstrate the subtle damage to smell caused by Sjögren's syndrome.

A perforated nasal septum was noted in 10 per cent and nasal mucosal dryness in 33 per cent of patients in the Sjögren's syndrome group, who had no previous history of nasal surgery or trauma to their noses. They were unaware of the perforation. Examination showed the perforation edges to be smooth with no granulation tissue reaction. Nasal examination in the control group showed no nasal septal perforations.

This level of nasal involvement has not been reported in previous studies. In Doig and colleagues' 1971 study, 6.5 per cent of patients with secondary Sjögren's syndrome had nasal septal perforation.[10] Other previous studies looked at nasal findings in Sjögren's syndrome but did not report nasal septal perforation, although nasal dryness was reported.[3,11] In more recent Sjögren's syndrome articles, nasal dryness was reported in 20 per cent of patients, but there were no reports of nasal septal perforation.[4,5]

Nasal septal perforation might be caused by nasal dryness, which irritates the nasal mucosa, leading to nasal picking, crusting and the sensation of nasal blockage. Crustiness of the nasal septum due to dryness could lead to recurrent infection and perichondritis of the nasal septum, resulting in perforation. The nasal blockage sensation is not necessarily related to physical obstruction, but is often associated with nasal dryness.[11]

Smell perception in Sjögren's syndrome has not been widely documented in the past. Sjögren's syndrome diagnostic criteria were not well defined until the European criteria were developed, followed by the American-European Consensus Group criteria in 2002. This was very helpful in standardising patients for clinical studies, which could then be compared more realistically.

Smell testing is a specialised assessment and is not usually investigated routinely in Sjögren's syndrome patients. Additionally, both clinicians and patients tend to under-report smell involvement in Sjögren's syndrome because other systemic complications often take prevalence. Moreover, smell changes are usually subtle and gradual, and because they largely occur in people from middle to old age, the changes are often attributed to ageing. Lastly, ENT surgeons' assessment of hyposmia in Sjögren's syndrome is clinically limited.

Chemosensory perception can be divided into two categories. Identification and recognition is one category and threshold detection is another. Smell identification and recognition testing measures cognitive functions. In fact, a decline in identification and discrimination abilities correlates with reduced cognitive abilities, while threshold does not. Threshold elevation is more sensitive to peripheral sensory impairment, unlike chemosensory recognition and identification impairment, which is likely to be of central origin (e.g. Parkinson's disease and Alzheimer's disease).[12] For instance, human immunodeficiency virus infected patients had elevated smell threshold compared with controls, while no difference between the groups occurred in identification and discrimination testing.[13]

Unlike a few other studies using identification tests, we used smell threshold testing in our study.[4,14,15] This may explain the subtle difference in reporting. In this study, there was a significant difference between cases and controls in the Smell Threshold Test results. Indeed, frank clinical hyposmia was seen in 47 per cent and 19 per cent of Sjögren's syndrome and control groups, respectively. Smell threshold was negatively correlated with age ($r = -0.252$; $p = 0.040$), which supports previous reports.[16,17] We previously reported smell and taste hypofunction in primary Sjögren's syndrome impacting on patient quality of life.[6] Other studies have assessed olfactory functions in Sjögren's syndrome patients, which may be difficult to compare because of different methodology.[3,11,15] This study confirms the previous reports of impaired smell sensation in Sjögren's syndrome.

Study weaknesses

We did not perform endoscopic nasal examination as part of the nasal assessment for patients or controls. It was felt that

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anterior rhinoscopy would suffice, especially because patients and controls with nasal polyps and/or previous nasal surgery were excluded from the study group. We could have had a bigger group; however, there was a statistically significant smell threshold difference. Ideally, we could have obtained a better assessment of smell by performing identification or recognition, discrimination, and threshold assessments, an academic tool that is indeed exhaustive.[12,18] We did not objectively assess nasal mucosal dryness, as this was not the aim of the study; however, we have reported it here as another subjective nasal finding.

- Sjögren's syndrome affects 1 per cent of the population
- Sjögren's syndrome predominantly affects women more than men (9:1)
- Diagnostic criteria and classification are according to the American-European Consensus Group
- Smell threshold negatively correlated with age
- Sjögren's syndrome should be considered when investigating hyposmia

Conclusion

Hyposmia in Sjögren's syndrome (47 per cent) was demonstrated using the Smell Threshold Test. Nasal septal perforation (10 per cent) and nasal mucosa dryness (33 per cent) were noted in Sjögren's syndrome patients. A Sjögren's syndrome diagnosis should be considered and further investigated in patients presenting with hyposmia in ENT clinics.

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Competing interests. This study was part of a larger project (MD thesis) successfully submitted and examined by Cardiff University.

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Appendix 1. Smell threshold testing

Smell Threshold Test procedure

The Smell Threshold Test was administered in the research clinic room with a pre-set temperature corresponding to that indicated in the test kit (20–22°C).

The test kit was opened and placed on a table with its lid blocking the subject's view of the contents. The box contained 20 bottles: 2 blank bottles and 18 bottles with concentrations from −10 ($\log_{10}$ 1/10 000 000 000), to −2 ($\log_{10}$ 1/100). The increments are in half log values.

It has been established that in smell assessment, the increments of concentration were too small. Logarithmic units are better to handle these figures. (Other uses of logarithmic units include pH and hearing tests.)

The negative mark is indicative of the mathematical formula used as above. So, subjects with a threshold of −8 are performing better (can smell a lower concentration) than subjects with a smell threshold of −2.

The subject was told that the test was being conducted to establish the lowest concentration of an airborne chemical that they could detect by smell. The various concentrations of the chemical (phenyl ethyl alcohol) employed in this test are safe, and have been smelt by thousands of subjects without adverse effects.

The smell threshold was determined by the single staircase detection method. The initial odorant presentation was made at a −6 concentration, followed by the presentation of a blank bottle. The order of bottle presentation was that recommended by the manufacturer and listed on the recording chart, as below. For each trial, a correct response was signified by placing a '+' in the box corresponding to the concentration presented.

The test session lasted about 20 minutes.

Smell threshold test recording sheet

An incorrect response was signified by placing an 'O' in the box. If a miss occurred on any trial before five consecutive stimulus pairs were completed at the concentration, the next trial immediately began at the concentration one log step (i.e. two boxes), as in the sheet below (Appendix Figure 1). When five consecutive correct trials occurred at a given concentration level, the staircase was reversed and the subsequent pair of trials was presented at a concentration 0.5 log step lower (i.e. one box lower). From that point on, only one or two trials were presented at each step (i.e. if the first trial was missed, the second was not given and the staircase was moved to the next higher 0.5 log step concentration). If both trials were correct, the staircase was moved down one 0.5 log unit step. The two blank bottles were used intermittently throughout the testing. Testing was complete after seven threshold

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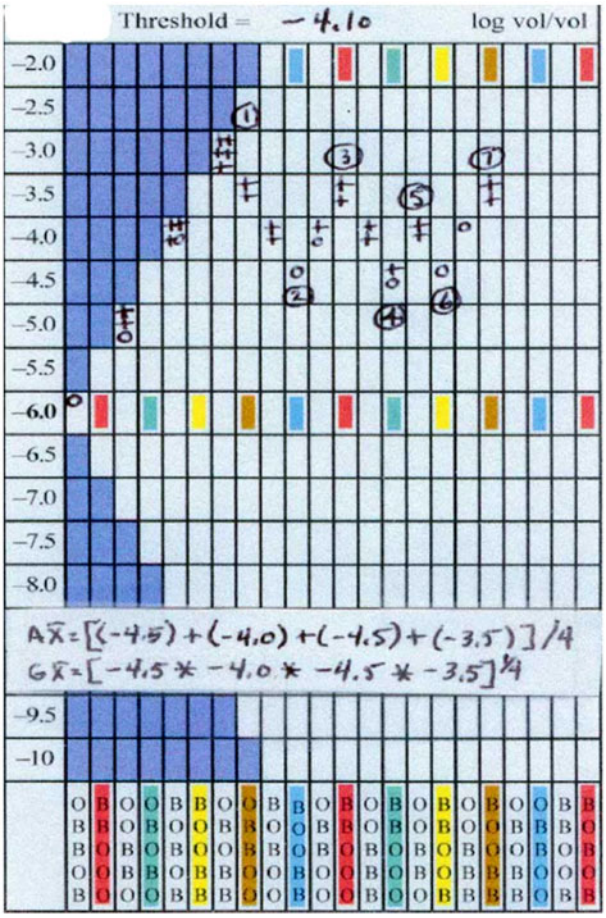

Fig. 1. Smell threshold test recording sheet.

reversals. The mean of the last four reversal points was calculated as the subject's mean smell threshold result.

Smell threshold calculation

As in the test recording sheet on the left, the arithmetic mean of the last four staircase reversals (i.e. (reversal number 7 + reversal number 6 + reversal number 5 + reversal number 4) / 4) of the seven reversals is most typically used as the threshold measure. So, according to the test recording sheet on the left, the smell threshold in this example would be −16.5 / 4 = −4.25. The normal value is –6. However, age has an effect and it influences the result accordingly.

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