European Archives of Oto-Rhino-Laryngology (2019) 276:1241–1245
https://doi.org/10.1007/s00405-019-05364-1

MISCELLANEOUS

Olfactory dysfunction in spondyloarthritis

Esin Yalcinkaya[1] · Mustafa Mert Basaran[2] · Hakan Erdem[1] · Murat Kocyigit[3] · Aytug Altundag[4] · Thomas Hummel[5]

Received: 28 October 2018 / Accepted: 25 February 2019 / Published online: 5 March 2019

Abstract

Objective Spondyloarthritis (SpA) is a group of disorders characterized by inflammatory arthritis including ankylosing spondylitis, psoriatic arthritis, reactive arthritis and arthritis-related inflammatory bowel diseases. Recently it has been shown that arthritic disorders are accompanied by olfactory dysfunction. We aimed to specifically investigate the association between spondyloarthritis and olfactory impairment.

Materials and methods Fifty individuals with SpA and 50 healthy volunteers were included in the study. Olfactory function was evaluated using the "Sniffin' Sticks" test battery. Additionally, effects of age, gender, activity of the disease, HLA-B27 status, medications, and the duration of disease were included in the analysis.

Results SpA patients showed significantly lower scores for odor threshold (*T*), odor discrimination (*D*) and odor identification (*I*) than healthy controls (all $p < 0.001$). In addition, olfactory loss was negatively correlated with the presence of HLA-B27 (Human Leukocyte Antigen), but not with the current activity of the disease (Bath Ankylosing Spondylitis Activity Index). Neither medication nor duration of the disease had a significant effect on the results.

Conclusion SpA is associated with olfactory loss. Future studies will show whether olfactory function relates to the prognosis of SpA.

Keywords Smell · Hyponosmia · Inflammation · Spondyloarthritis · Bechterew

✉ Thomas Hummel
thummel@mail.zih.tu-dresden.de

Esin Yalcinkaya
esinkbbesin@gmail.com

Mustafa Mert Basaran
mbasaran88@gmail.com

Hakan Erdem
herdem67@yahoo.com

Murat Kocyigit
muratdr63@yahoo.com

Aytug Altundag
aaltundagkbb@yahoo.com

[1] Otorhinolaryngology Department, Medicana International Hospital, Ankara, Turkey

[2] Otorhinolaryngology Department, Ufuk University, Ankara, Turkey

[3] Kanuni Sultan Süleyman Education and Research Hospital, Istanbul, Turkey

[4] Otorhinolaryngology Department, Acibadem Taksim Hospital, Istanbul, Turkey

[5] Smell and Taste Clinic, Department of Otorhinolaryngology, TU Dresden, Dresden, Germany

Introduction

Ankylosing spondylitis, reactive arthritis, psoriatic arthritis, and enteric arthritis are a group of inflammatory arthritis called spondyloarthropathies (SpA) [1]. While the etiology of spondyloarthropathies is still unclear it is considered as an autoimmune disease that involves a combination of genetic and environmental factors. Genetic effects are partially explained by a strong association with the gene for human leukocyte antigen (HLA) B27, which encodes a major histocompatibility complex (MHC) type 1 surface antigen [2, 3]. Although not proven, the possible role of bacteria as environmental factors has been discussed [4].

Sacroiliitis is a typical early clinical manifestation. The earliest clinical symptom is often pain which is generally felt in the buttocks, lower lumbar regions or lower extremities. The pain becomes persistent and bilateral worsening at night. Affected joints show irregular erosion and sclerosis. Tissue is gradually replaced by fibrocartilage which becomes ossified. Peripheral joints and extra-articular structures can be affected. The most common extra-articular involvement is acute anterior uveitis causing pain, photophobia and increase

in lacrimation. Enthesitis, dactylitis, enteric mucosal lesions, and even aortic insufficiency, congestive heart failure are rare complications but can be found [5]. HLA-B27 is positive mostly at the early stages; however, positivity ranges from 70 to 95% [6].

A number of studies already showed the relationship between olfactory function and inflammatory diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, Wegener granulomatosis, Sjogren syndrome) [7]. Thus reduced olfactory function in many inflammatory diseases could be due to a (hypothetically) congested nasal mucosa in association with general inflammatory changes; such congestion would inhibit transportation of molecules to olfactory receptor neurons. In addition, inflammatory mediators may also affect olfactory neuroepithelial cells [7].

Because olfactory function in SpA has not yet been studied, the purpose of our study was to investigate olfactory function in relation to the activity and duration of SpA as well effects of different therapeutics and HLA-B27 status.

Materials and methods

Ethics

This study was approved by the Institutional Review Board of Ankara University and was conducted in the otorhinolaryngology clinic of the Medicana Hospital, Ankara. Informed written consent was taken from the all participants. The investigation conformed to the Declaration of Helsinki.

Participants

We included 50 patients with SpA (31 men, 19 women; age range 21–58 years, mean age of 41.8 years) and 50 healthy volunteers (31 men, 19 women; age range 20–60 years, mean age 42.4 years). Each participant underwent a clinical examination and a detailed history was taken, providing the following parameters: age, gender, activity of the disease, HLA-B27 status, medications, and duration of disease. Exclusion criteria were major nasal septal deviation, chronic rhinosinusitis, nasal polyposis, pregnancy, smoking, severe hypertension, severe diabetes, asthma or autoimmune diseases other than SpA. Dementia was excluded based on Mini Mental State Examination [8] with all participants scoring 29 points and higher.

Assessment of SpA patients

SpA diagnosis and evaluation were made by a trained rheumatologist. Patients diagnosed with SpA for 2 months to 30 years were included. Participants were evaluated according to ASAS classification criteria [9] (Table 1).

Olfactory function

Orthonasal olfactory function was measured by means of the validated extended Sniffin' Sticks test battery (Burghart messtechnik, Wedel, Germany) which consists of three separate subtests: phenylethylalcohol (PEA) odor thresholds (THR), odor discrimination (DIS), and odor identification (ID) [10]. Results of the three subtests are summed up for a composite TDI score. The test demonstrated a high test-re-test reliability [11]. The test is based on pen-like odor-dispensing devices. For odor testing the cap of the pen was removed for approximately 3 s and the felt-tip was presented approximately 2 cm in front of the subjects' nostrils. Testing started with the threshold subtest, where 16 dilutions were used. The participants received three odorized pens, with one containing the odor (phenyl ethyl alcohol, PEA—a rose-like smell) and the others containing solvent, propylene glycol, alone. Triplets were presented in increasing odor concentrations, starting with the lowest one. After identifying the correct (odor containing) pen twice in a presented triplet, a reversal of the staircase was started until the participant could no longer correctly identify the odor containing pen. The threshold score was the mean of the last four out of seven staircase reversals. For the DIS, also 16 triplets were presented, with two pens containing the same odor and the third a different one, which the participant should identify. The last subtest performed was the ID, where 16 pens with different odors were presented. Individuals were asked to choose the object that described the odor the best using multiple forced choice from flash cards where the name of the objects were written.

For odor presentation, the pen cap was removed by the experimenter for approximately 3 s and the tip of the pen was placed approximately 1–2 cm in front of the nostrils.

Table 1 Comparison of odor scores between SpA and healthy controls

Odor scores	SpA (mean ± SD; $n = 50$)	Control (mean ± SD; $n = 50$)	p value
Odor discrimination (numbers correct)	11.6 ± 2.4	15.4 ± 0.9	< 0.001
Odor identification (numbers correct)	9.7 ± 2.5	14.2 ± 0.9	< 0.001
Odor threshold (dilution steps)	4.2 ± 1.5	8.2 ± 1.2	< 0.001

Statistical analyses

Continuous variables are presented as mean ± SD; categorical variables are shown as percentage. Data were tested for normal distribution using the Kolmogorov–Smirnov test. The Student's *t* test was used for the comparison of continuous variables and the χ^2 test for categorical variables. For comparison of more than two groups analyses of variance were used. Spearman statistics were used for correlational analyses. All tests of significance were two-tailed. Statistical significance was defined as $p < 0.05$. The SPSS statistical software (version 25.0 for Windows, SPSS Inc., Chicago, IL, USA) was used for all statistical calculations.

Results

SpA patients exhibited lower olfactory scores than healthy controls (*T*: 11.64 ± 2.4 vs 15.40 ± 0.9, *D*: 9.72 ± 2.5 vs 14.22 ± 0.9, *I*: 4.22 ± 1.5 vs 8.20 ± 1.2, all $p < 0.001$) (Table 2). In the SpA group, 45 patients were hyposmic, and only 5 patients with SpA had normal olfactory scores. In contrast, all healthy controls (HC) had normal olfactory scores.

Patients and controls were significantly different in terms of age (35.6 ± 9.5 vs 43.8 ± 12.6, $p < 0.001$, respectively). However, the differences in olfactory function between the two groups remained significant even when removing all subjects older than 45 years, rendering the two groups similar in terms of age. Same results were also attained in data after adjusting for age (Table 4). When splitting the group of SpA patients into two, with BASDAI scores less or higher than 4, we found that SpA patients with low degree of inflammation had decreased olfactory function (Table 2). However, there was no significant correlation between olfactory scores and the BASDAI score as a measure of the degree of inflammation (Table 3). In 22 of the 50 patients HLA-B27 status had been recorded: 11 patients had a HLA-B27 positive result, and 11 were HLA-B27 negative. In our study, olfactory function was found to be significantly higher in HLA-B27 positive patients compared to HLA-B27 negative ones (Table 2), but lower than controls (Table 3) (all for *T, D, I,* $p < 0.001$). We also compared olfaction scores between different medical therapy groups. We classified medical therapy options as three groups: biologic agents ($n = 33$), non steroidal anti-inflammatory drugs (NSAID) ($n = 12$), disease modifying antirheumatic drugs (DMARD) ($n = 5$). There was no significant difference between the groups with regard to olfactory function (Table 2). There was also no significant relationship between duration of disease and olfactory scores (Table 4).

Table 3 Correlation analysis of BASDAI score in SpA patients

Variables	BASDAI scores in SpA patients $N = 50$	
	r	*p* value[a]
Odor discrimination (*D*)	0.27	0.06
Odor identification (*I*)	0.20	0.17
Odor threshold (*T*)	0.00	1.00
Age, years	−0.01	0.98
Duration of disease, years	−0.30	0.03

[a]Spearman test was used

Table 2 Comparison of Odor Scores of SpA Subgroups

Subgroups in SpA patients $n = 50$	*T* Mean ± SD value	*p* value	*D* Mean ± SD value	*p* value	*I* Mean ± SD value	*p* value
HLA-B27 $n = 22$						
Positive	6.0 ± 0.7	< 0.001	12.8 ± 2.1	0.042	11.3 ± 2.4	0.012
Negative	2.9 ± 1.5		10.7 ± 2.4		7.9 ± 3.2	
BASDAI $n = 50$						
≥ 4	4.9 ± 1.9	0.36	12.7 ± 2.4	0.026	10.2 ± 3.2	0.028
< 4	3.9 ± 1.2		11.1 ± 2.3		9.4 ± 2.1	
Duration of disease $n = 50$						
≥ 4	4.2 ± 2.4	0.88	11.6 ± 2.6	0.90	9.8 ± 2.3	0.87
< 4	4.2 ± 2.1		11.7 ± 1.9		9.5 ± 3.2	
Therapy $n = 50$						
Biologic agent	4.1 ± 1.5	0.08	11.2 ± 2.4	0.70	9.8 ± 2.3	0.19
NSAID	4.5 ± 1.5		12.4 ± 2.5		8.8 ± 2.9	
DMARD	4.3 ± 2.1		12.6 ± 2.4		11.8 ± 2.5	

Table 4 Comparison between HLA subgroups and healthy controls

Groups:	SpA patients		Healthy controls $N=50$	p value
Variables	HLA-B27 (neg) $N=11$	HLA-B27 (pos) $N=11$		
Odor discrimination (D)	10.7 ± 2.4	12.8 ± 2.1	15.4 ± 0.9	<0.001
Odor identification (I)	7.9 ± 3.2	11.3 ± 2.4	14.2 ± 0.9	<0.001
Odor threshold (T)	2.9 ± 1.5	6.0 ± 0.7	8.2 ± 1.2	<0.001
Gender, male	45%	63%	64%	0.51
Age, years	34.9 ± 9.8	32.3 ± 4.7	43.8 ± 12.6	0.003
BASDAI	4.38 ± 1.68	4.06 ± 1.99	–	0.69

Discussion

Approximately 5% of the general population is anosmic, and about 15% have reduced olfactory function [12, 13]. However, in our study group 90% of the patients were hyposmic, and in the healthy group no one showed olfactory dysfunction.

Spondyloartropathies are defined as inflammatory artropathies with sacroiliac involvement. Immune mediated mechanisms involving human leucocyte antigen (HLA)-B27, inflammatory cellular infiltrates, cytokines (tumour necrosis factor α and interleukin 10), and genetic and environmental factors are thought to play key roles in etiopathology. Genetic effects are partially explained by the gene for HLA B27, which encodes a MHC type 1 surface antigen [2]. A wide range of genes or genetic regions has been associated with SpA susceptibility [14, 15]. Interleukin-23 (IL-23) and IL-17 play an important role in SpA [16]. HLA-B27 misfolding can activate IL-23 [14]. Activation of IL-23 can lead to increased release of IL-17, IL-6, and IL-22 with chemokines causing entheseal inflammation in peripheral and axial locations [4].

In the current study, olfactory function was found to be significantly lower in SpA patients compared to controls. However, among SpA patients olfactory function was higher in HLA-B27 positive patients compared to HLA-B27 negative ones. HLA B27 gene encodes MHC type 1 surface antigen and the MHC locus is known to be associated with olfactory functions [2]. Therefore, it could be hypothesized that HLA-B27 is associated with some protective effect on the olfactory system. In addition, the olfactory scores were also higher in patients with high BASDAI scores (≥ 4 vs < 4). Still, there was no correlational association between the severity of SpA disease expressed as BASDAI score and olfactory performance.

The main finding of this study was that olfactiory function in SpA patients is significantly worse compared to healthy controls. Considering that inflammation of the olfactory epithelium is typically associated with a decreased sense of smell [12], it may be concluded that the olfactory changes seen in SpA patients do not appear to be due to a hypothetical increased level of inflammation in the olfactory epithelium. Accordingly, the decrease of the sense of smell seen in other systemic inflammatory conditions may also not be due to nasal inflammation. In terms of olfactory sensitivity, genetic factors may be more dominant in these autoimmune diseases than inflammatory factors. In our study, there were 50 subjects in SpA group but in 22 of them HLA B27 gene positivity was studied. More studies with large series are needed to investigate the role of genetics in autoimmune, inflammatory diseases. As mentioned in the introduction, disorders of olfactory function can be seen in autoimmune and inflammatory diseases such as systemic lupus erythematosus (SLE), and rheumatoid arthritis [5, 7, 17–20]. It also has been shown that there is olfactory dysfunction in Sjogren's syndrome [21] and in patients with hereditary angioedema [22, 23]. Similarly to the present work Steinbach and colleagues reported a change of olfactory function in relation to disease activity [18].

However, they also did not report a correlation between olfactory function and disease activity. There are numerous reasons for olfactory dysfunction that may apply to SpA patients [17], for example drug toxicity due to tumor necrosis factor (TNF_{alpha}), or the use of methotrexate which may cause neuropathy [24]. Corticosteroids may cause hypokalaemia with alkalosis which also results in olfactory dysfunction [25]. Although not the major focus of the present study, in a preliminary analysis we did not see major differences between the three treatment regimens: biologic agents, NSAIDs, and DMARDs.

Hyposmia in SpA patients can also be related with depression and anxiety which is frequent in SpA patients [26], but was not assessed in the present study. In fact, recent studies clearly show the relation between depression and olfactory loss [27, 28].

In summary, the current study shows a decreased olfactory function in SpA patients. Because patients with smell difficulty are also known to have difficulty in taste and related nutrition, SpA patients should be informed about the situation. Additionally, the sense of smell protects from toxic gases or poisoning. Accordingly, SpA patients should be examined in terms of their smell and taste functions. In addition, the present study showed a positive association between HLA B27 status and olfactory test scores, but there was no

evidence for a correlation between inflammatory activation and olfactory scores. The role of genetics in olfactory function of patients with autoimmune inflammatory disease should be subject to further investigations.

References

1. Akgul O, Ozgocmen S (2011) Classification criteria for spondyloarthropathies. World J Orthop 2:107–115
2. Thomas G, Brown M (2010) Genetics and genomics of ankylosing spondylitis. Immunol Rev 233:162–180
3. Brown MA, Kennedy LG, MacGregor AJ, Darke C, Duncan E, Shatford JL et al (1997) Susceptibility to ankylosing spondylitis in twins: the role of genes, HLA, and the environment. Arthritis Rheum 40:1823–1828
4. Sieper J, Braun J, Kingsley GH (2000) Report on the fourth international workshop on reactive arthritis. Arthritis Rheum 43:720–8
5. Sieper J, Braun J, Rudwaleit M, Boonen A, Zink A (2002) Ankylosing spondylitis: an overview. Ann Rheum Dis 61(Suppl III):iii8–iiii13
6. Liao Z, Gu J, Huang F, Lin Z, Zhao L, Yu B (2009) Verification of Berlin algorithm for diagnosing undifferentiated spondyloarthropathy patients in Chinese population. Jt Bone Spine 76:146–149
7. Tekeli H, Senol MG, Altundag A, Yalcinkaya E, Kendirli MT, Yasar H et al (2015) Olfactory and gustatory dysfunction in myasthenia gravis: a study in Turkish patients. J Neurol Sci 356(1–2):188–192
8. Folstein MF, Folstein SE, McHugh PR (1975) "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 12:189–198
9. Rudwaleit M, van der Heijde D, Landewe R, Akkoc N, Brandt J, Chou CT et al (2011) The Assessment of SpondyloArthritis International Society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general. Ann Rheum Dis 70(1):25–31
10. Hummel T, Kobal G, Gudziol H, Mackay-Sim A (2007) Normative data for the "Sniffin' Sticks" including tests of odor identification, odor discrimination, and olfactory thresholds: an upgrade based on a group of more than 3,000 subjects. Eur Arch Otorhinolaryngol 264(3):237–243
11. Haehner A, Mayer AM, Landis BN, Pournaras I, Lill K, Gudziol V et al (2009) High test–retest reliability of the extended version of the "Sniffin' Sticks" test. Chem Senses 34(8):705–711
12. Hummel T, Whitcroft KL, Andrews P, Altundag A, Cinghi C, Costanzo RM et al (2017) Position paper on olfactory dysfunction. Rhinol Suppl 54 26:1–30
13. Brämerson A, Johansson L, Ek L, Nordin S, Bende M (2004) Prevalence of olfactory dysfunction: The Skövde population-based study. Laryngoscope 114:733–737
14. Reveille JD (2012) Genetics of spondyloarthritis, beyond the MHC. Nat Rev Rheumatol 8:296–304
15. Robinson PC, Brown MA (2012) The genetics of ankylosing spondylitis and axial spondyloarthritis. Rheum Dis Clin N Am 38:539–553
16. DeLay ML, Turner MJ, Klenk EI, Smith JA, Sowders DP, Colbert RA (2009) HLA-B27 misfolding and the unfolded protein response augment interleukin-23 production and are associated with Th17 activation in transgenic rats. Arthritis Rheum 60:2633–2639
17. Steinbach S, Proft F, Schulze-Koops H, Hundt W, Heinrich P, Schulz S et al (2011) Gustatory and olfactory function in rheumatoid arthritis. Scand J Rheumatol 40:169–177
18. Shoenfeld N, Agmon-Levin N, Flitman-Katzevman I, Paran D, Katz BS, Kivity S et al (2009) The sense of smell in systemic lupus erythematosus. Arthritis Rheum 60:1484–1487
19. Tekeli H, Altundag A, Salihoglu M, Cayonu M, Kendirli MT (2013) The applicability of the "Sniffin' Sticks" olfactory test in a Turkish population. Med Sci Monit 19:1221–1223
20. Proft F, Steinbach S, Dechant C, Witt M, Reindl C, Schulz S et al (2014) Gustatory and olfactory function in patients with granulomatosis with polyangiitis (Wegener's). Scand J Rheumatol 43:512–518
21. Midilli R, Gode S, Oder G, Kabasakal Y, Karci B (2013) Nasal and paranasal involvement in primary Sjogren's syndrome. Rhinology 51:265–267
22. Perricone C, Shoenfeld N, Agmon-Levin N, de Carolis C, Perricone R, Shoenfeld Y (2013) Smell and autoimmunity: a comprehensive review. Clin Rev Allergy Immunol 45:87–96
23. Perricone C, Agmon-Levin N, Shoenfeld N, de Carolis C, Guarino MD, Gigliucci G et al (2011) Evidence of impaired sense of smell in hereditary angioedema. Allergy 66:149–201
24. Tektonidou MG, Serelis J, Skopouli FN (2007) Peripheral neuropathy in two patients with rheumatoid arthritis receiving infliximab treatment. Clin Rheumatol 26:258–260
25. Stanbury RM, Graham EM (1998) Systemic corticosteroid therapy—side effects and their management. Br J Ophthalmol 82:704–719
26. Malaty J, Malaty IA (2013) Smell and taste disorders in primary care. Am Fam Physician 88:852–888
27. Hyphantis T, Kotsis K, Tsifetaki N, Creed F, Drosos AA, Carvalho AF et al (2013) The relationship between depressive symptoms, illness perceptions and quality of life in ankylosing spondylitis in comparison to rheumatoid arthritis. Clin Rheumatol 32:635–644
28. Croy I, Symmank A, Schellong J, Hummel C, Gerber J, Joraschky P et al (2014) Olfaction as a marker for depression in humans. J Affect Disord 160:80–86