

## Evaluation of olfactory functions in patients with laryngopharyngeal reflux

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### Abstract

**Objective:** To evaluate olfactory functions in patients with laryngopharyngeal reflux.

**Methods:** The study consisted of control and reflux groups. Each group consisted of 50 patients. Reflux group received the diagnosis of reflux based on reflux symptom index, and reflux symptom scores. The olfactory test of Connecticut Chemosensory Clinical Research Center (CCCRC) was conducted on these 2 groups, and the results were compared.

**Results:** No statistically significant difference was found between the demographic characteristics such as gender and smoking rates while there was statistically significant difference between the groups in terms of age variable. The covariance analysis was used to eliminate the effect of age variable. The mean scores calculated after covariance analysis were compared. It is known that the higher score of CCCRC test is 7 points. Accordingly, CCCRC scores of the control and reflux groups were  $5.84 \pm 0.13$ , and  $5.20 \pm 0.11$ , respectively. This difference between two groups was statistically significant ( $p < 0.001$ ).

**Conclusion:** Laryngopharyngeal reflux disease has a negative effect on olfactory functions without total loss in olfactory functions.

**Keywords:** Reflux, reflux symptom index, scoring of reflux findings, smell test.

### Özet: Larengofarengal reflü hastalarında koku fonksiyonlarının değerlendirilmesi

**Amaç:** Çalışmanın amacı larengofarengal reflü hastalarında koku fonksiyonlarını değerlendirmektir.

**Yöntem:** Çalışma, kontrol ve reflü grubu olmak üzere 2 gruptan oluşmaktaydı. Her grupta 50'şer hasta mevcuttu. Reflü grubuna reflü tanısı koyarken reflü semptom indeksi ve reflü bulgu skorlamasından faydalanıldı. Bu 2 gruba Connecticut Chemosensory Clinical Research Center (CCCRC) koku testi uygulanıp sonuçlar karşılaştırıldı.

**Bulgular:** Grupların demografik özelliklerine bakıldığında cinsiyet ve sigara kullanımı oranları açısından istatistiksel fark bulunmazken yaş değişkeni açısından istatistiksel fark vardı. Yaş değişkeninin etkisini ortadan kaldırmak için kovaryans analizi yapıldı. Kovaryans analizi sonrası hesaplanan ortalama skorlar karşılaştırıldı. CCCRC testinin en yüksek skorunun 7 olduğu bilinmektedir. Buna göre kontrol grubunda CCCRC skoru  $5.84 \pm 0.13$  iken reflü grubunda  $5.20 \pm 0.11$  olarak hesaplandı. İki grup arasındaki bu fark istatistiksel olarak anlamlı idi ( $p < 0.001$ ).

**Sonuç:** Larengofarengal reflü hastalığı koku fonksiyonlarında total kayba yol açmadan koku fonksiyonları üzerinde negatif etkisi bulunmaktadır.

**Anahtar sözcükler:** Koku testi, reflü, reflü bulgu skorlaması, reflü semptom indeksi.

Laryngopharyngeal reflux (LFR) is the detection of gastric contents in laryngopharyngeal cavity.<sup>[1]</sup> This pathology is thought as a different entity by some authors, some others consider this condition as an extraesophageal form of gastroesophageal reflux. Still, the studies have demonstrated that pathophysiologies of laryngoesophageal, and gastroesophageal refluxes are quite different.<sup>[1]</sup> LFR was estimated to be in 4–10 % of patients referred to ENT special-

ists.<sup>[2]</sup> Its main symptoms are throat clearing, hoarseness, chronic coughing, postnasal discharge, halitosis, dysphagia, and feeling of foreign substance in the throat. In LFR, direct laryngoscopy may reveal mucosal edema, redness, ventricular obliteration, interarythenoid hypertrophy, and laryngeal granulomas.<sup>[1]</sup>

Smell is an olfactory function provided by specialized cells of the upper respiratory tract mucosa. As demonstrat-

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ed in recent population-based studies, olfactory dysfunction is seen at a higher frequency than estimated.<sup>[3]</sup> Bramerson et al. indicated that decreased olfactory function in the population is seen at a higher incidence of 16%, and 5% of the population is anosmic.<sup>[4]</sup> Although olfactory function has an impact on many events as human behaviors and sexual functions, loss of smell is not considered to be important by the patients and physicians.

Laryngopharyngeal reflux is an important etiological factor in the development of many upper respiratory tract diseases.<sup>[5]</sup> Its potential effects on nasal, laryngeal, and otologic disorders have been investigated in the literature.<sup>[6-9]</sup> However, a limited number of studies are available on olfactory functions. Our aim in this study is to evaluate the effect of LFR on olfactory functions using the olfactory test of Connecticut Chemosensory Clinical Research Center (CCCRC).

## Materials and Methods

### Study design

The prospective randomized study has been conducted in accordance with the principles of the Helsinki Declaration and approved by the local Institutional Review Board (2014/03). Written informed consent was obtained from all patients who admitted to our university between March 2014 and September 2014 and they constituted the study group.

After ENT examinations were performed in the reflux group participated in the study, the patients completed reflux symptom index (RSI), and reflux finding scoring (RFS) which was developed by Belafsky and Koufman to evaluate LFR. The patients who obtained 13 and 7 points from RSI and RFS tests, respectively, were considered as LFR patients, and olfactory test was applied. As olfactory test, the modified CCCRC test was used. Instead of essence of peanut butter used for the smell identification phase of the CCCRC olfactory test, the essence of arachis oil was used. In the control group, also ENT examination and olfactory test were applied.

In both groups, the patients with chronic sinonasal infection, allergic rhinitis, active upper respiratory tract infection, septal deviation, nasal polyps and history of head trauma, the patients who lost their sense of smell after upper respiratory tract infection, cases with intracranial malignancies or malignant diseases of the olfactory tract, those receiving RT because of head and neck malignancies, patients with a history of drug use because of chronic diseases, or had nasal

surgery for any indication, and those with psychiatric or neurological diseases were excluded from the study.

The CCCRC test includes butanol threshold test and odor identification test using common odors; these tests were conducted as described previously.

### Butanol threshold test

For each trial, two glass bottles were presented to the subject. One contained water and the other a dilute concentration of butanol. The bottles were of identical appearance and were presented simultaneously. Subjects were instructed to occlude one nostril and place the tip of the first bottle immediately beneath the other nostril. The second bottle was then sampled in a similar manner, and the subject had to choose which of the bottles contained something other than water. If the choice was incorrect, the next stronger concentration of butanol was presented along with a bottle containing only water. Once the subject correctly identified the same butanol concentration five times in a row, the score was recorded for that nostril. The other nostril was then tested separately, and the scores for both nostrils were averaged to arrive at the final score. The strongest butanol concentration (bottle 0) was 4% butanol in deionized water. Each subsequent dilution (bottles 1–9) was a 1:3 dilution with deionized water. Possible scores ranged from 0 to 9, but all scores 7 and higher were scored as 7 per the CCCRC test.

### Identification test

Common household odorants: Peanut butter, soap, mothballs, Vicks, chocolate, coffee, cinnamon and baby powder were within opaque jars. The subjects then chose from a printed list containing the correct items as well as an equal number of distractor items. The forced choice items included the following: Vicks, burnt paper, wood shavings, coffee, baby powder, peanut butter, spearmint, cinnamon, soap, chocolate, mothballs, grape jam, ketchup, black pepper, and rubber. The ability to sense Vicks indicates intact trigeminal nerve function. It was easily identified by all subjects and was not included in the final score. Possible scores ranged from 0 to 7 items were correctly identified. Scores for both nostrils were averaged to arrive at the final score.

Scores for the butanol threshold test and identification tests were subsequently averaged to arrive at a composite score for orthonasal olfactory ability. Based on the mean total CCCRC test results, patients were evaluated as normosmic (6.00–7.00 pts), mildly hyposmic (5.00–5.75 pts), moderately hyposmic (4.00–4.75 pts), severely (hyposmic (2.00–3.75 pts), and anosmic (0–1.75 pts).

## Statistical analysis

The data were analyzed using the IBM Statistical Package for Social Sciences v19 (SPSS Inc., Chicago, IL, USA). A normal distribution of the quantitative data was checked using Shapiro-Wilk test. Parametric tests were applied to data of normal distribution and non-parametric tests were applied to data of questionably normal distribution. Mann-Whitney U-test was used to compare independent groups. The distribution of categorical variables in both groups was compared using Pearson chi-square and chi square with the Yates' correction tests. Covariance analysis was performed to reveal the impact of "age" variable between groups, and adjusted mean, standard errors, and results of comparison obtained were shared. Data were expressed as mean±SD (standard deviation) or median (interquartile range), as appropriate. All differences associated with a chance probability of 0.05 or less were considered statistically significant.

## Results

A total of 100 patients met the eligibility criteria for the study. Of the 100 patients (34 males, 66 females) whose charts were reviewed, the mean age was 35.7±12.9 years. The Control Group included 50 patients (20 males, 30 females) with a mean age of 29.64±10.20 (range: 21 to 59) years. The Reflux Group included 50 patients (14 males, 36 females) with a mean age of 41.76±12.50 (range: 18 to 74) years. Both groups differed significantly by means of age ( $p<0.001$ ); however, they did not differ from each other by means of gender ( $p=0.291$ ). The groups were also compared in terms of the number of smokers in the control ( $n=12$ ;

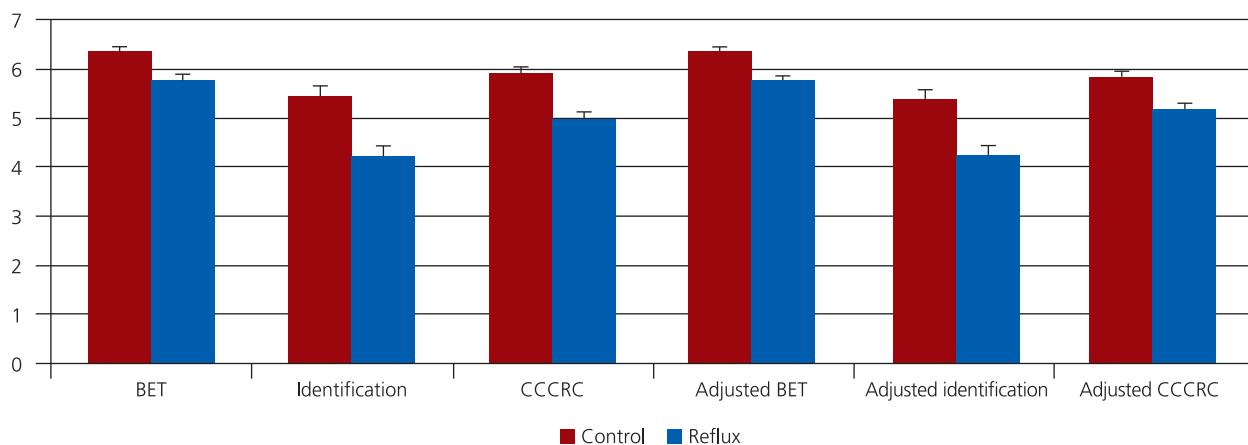
24%), and reflux ( $n=14$ ; 28%) groups. A statistically significant intergroup difference was not detected in terms of the number of smokers ( $p=0.820$ ).

Mean BET scores of the control, and reflux groups were 6.38±0.08, and 5.79±0.10 points, respectively ( $p<0.001$ ). After the elimination of the impact of age variable, corrected mean BET scores of the control and reflux groups were 6.7±0.09, and 5.77±0.09 points, respectively ( $p<0.001$ ).

Mean scores of the identification tests were 5.48±0.16 points in the control group, and 4.23±0.21 points in the reflux group ( $p<0.001$ ). After the elimination of the age variable, the calculated adjusted mean identification scores were 5.41±0.18 and 4.24±0.19 points in the control and reflux groups, respectively ( $p<0.001$ ).

The mean total CCCRC scores were also compared between groups. Mean total CCCRC scores in the control and reflux groups were 5.93±0.10 (range: 4 to 7) and 5.01±0.13 (range: 2.5 to 7) points, respectively ( $p<0.001$ ). After eliminating the impact of age, adjusted mean total CCCRC scores were calculated as 5.84±0.13 and 5.20±0.11 points in the control and reflux groups, respectively ( $p<0.001$ ) (Fig. 1).

The groups were divided into 5 subgroups within themselves to grade the loss of smell. Based on the mean total CCCRC test results, patients were evaluated as normosmic (6.00–7.00 pts), mildly hyposmic (5.00–5.75 pts), moderately hyposmic (4.00–4.75 pts), severely (hyposmic (2.00–3.75 pts), and anosmic (0–1.75 pts). The indicated percentages of individuals in the control group were evaluated as normosmic (62%), mildly hyposmic (32%), and moderately hyposmic (6%). Severely hyposmic and anos-



**Fig. 1.** Mean butanol threshold test, identification test, and Connecticut Chemosensory Clinical Research Center's test scores before and after the adjustments made for age variable.

mic individuals were not found in the control group. In the reflux group, the indicated percentages of the individuals were in the normosmic (22%), mildly hyposmic (22%), moderately hyposmic (32%), and severely hyposmic (12%) sub-groups. Any anosmic individual was not found in the reflux group.

## Discussion

Literature studies on the upper respiratory tract and pharynx are available. In a study performed by Habesoglu et al., the authors induced experimental reflux in 18 rats under general anesthesia, then soft palates of the rats were histologically examined under light microscope. Hyperplasia of submucosal glands, inflammation, subepithelial edema, muscular atrophy, vascular dilatation, and dilated ducts of secretory glands were compared between groups, and a significant difference was found between reflux and control groups regarding the cited variables.<sup>[6]</sup>

Abdel-aziz et al. studied pepsin/pepsinogen ratios in middle ear fluid and blood samples of 31 children with otitis media with effusion, and pH monitorization was performed with the children. They detected that higher pepsin/pepsinogen levels in middle ear fluid may increase up to 540 times when compared with normal plasma concentrations. They found a correlation between pepsin levels in the middle ear effusion fluid, and the frequency of pharyngeal reflux episodes detected during pH monitorization. As an outcome of the study, they thought that pepsin may enter into middle ear through eustachian tube, and concluded that analysis of pepsin from middle ear effusion fluid samples may be a reliable diagnostic marker of LFR.<sup>[7]</sup> Toros et al. analyzed human-specific pepsinogen 1 antibodies in the middle ear effusion fluid samples, and published results similar to those of Abdel-aziz et al.<sup>[10]</sup> In a similar study Tasker et al. reported that pepsin/pepsinogen levels measured in the middle ear effusion fluid might increase up to 1000 times when compared with their serum levels.<sup>[11]</sup>

Hellgren et al. evaluated risk factors (i.e. smoking, atopy, asthma, coughing, obesity, and GERD) related to newly onset noninfectious rhinitis in a total of 3307 female and male individuals, and demonstrated significant correlation between GERD and adult-onset NIR.<sup>[12]</sup> Weaver et al. screened 152 studies performed between 1966 and 2001 in order to reveal the correlation among 3 supraesophageal diseases (sinusitis, otitis media, and laryngeal malignancy). In this meta-analysis, they found a weakly positive correlation between GERD, sinusitis, and laryngeal malignancy,

and a negative correlation between GERD and chronic otitis.<sup>[13]</sup>

Phipps et al. achieved improvement in 15 out of 19 (79%) patients with nasopharyngeal reflux, and chronic sinusitis after treatment for GERD, and revealed the relationship between GERD and these diseases.<sup>[9]</sup> Barbero et al. achieved remission in 68% of the children who were candidates for sinonasal surgery but resistant to standard clinical treatment following 3 months of antireflux treatment.<sup>[14]</sup> Similar to the results obtained by Barbero et al. Halstead achieved 90% improvement with antireflux treatment in children with GERD and upper respiratory tract symptoms.<sup>[15]</sup> Contencin and Narcy et al. suggested that acid gastric reflux causes chronic rhinopharyngitis and related chronic nasopharyngeal processes with resultant tuba auditus or inflammation leading to formation of middle ear effusion.<sup>[16]</sup> Various studies performed have shown that GERD or LFR leads to inflammation of all upper respiratory tract and eustachian tube with resultant edema.

Among many most frequently used tests to evaluate olfactory functions cited in the literature University of Pennsylvania smell identification test (UPSIT), cross cultural smell identification test (CCSIT), Sniffin' Sticks test (SST), and CCCRC test may be enumerated. In a study performed by Veyseller et al., CCCRC olfactory test was performed on healthy Turkish volunteers, and smell identification scores were evaluated in consideration of age, gender, and smoking, and the authors assessed their applicability and suitability for the Turkish population. They emphasized that CCCRC olfactory test is a simple and practical test which is applicable for Turkish population.<sup>[17]</sup> Therefore, we also used CCCRC olfactory test in our study.

In recent studies on the correlation between reflux and smell, Günbey et al. evaluated olfactory functions of GERD patients using Sniffin' Sticks smell test.<sup>[18]</sup> Thirty-five GERD patients and 45 healthy controls were included in the study. As a result, when odor threshold, identification, and odor discrimination scores were compared with those of the control group, they detected significantly lower scores in the control group. Although a statistically significantly positive correlation was found among parameters of odor parameters, chronic sinusitis, and chronic pharyngitis while they could not find a significant correlation between laryngeal findings and odor parameters.<sup>[18]</sup> Dinç et al. evaluated olfactory functions in LFR patients, and included 30 LFR patients and 30 healthy control subjects in their study. They found significantly

lower odor threshold, odor identification, and odor discrimination scores in the LFR group, and as a conclusion they reported that LFR disease may affect olfactory physiology, and it may be a cause of olfactory dysfunction.<sup>[19]</sup> As it is the case in these studies, we also found in our study that smell test scores were statistically significantly lower when compared with the control group scores.

Cilias of the olfactory mucosa increase their surface areas with resultant enhanced response to chemical stimuli, and increased absorption of smell molecules. Function of the cilias of the olfactory epithelium may be impaired dependent on the acid, and pepsin secretion in LFR. If the level of odorant-binding proteins which are transported in mucus from Bowman's gland into olfactory mucosa through a duct decreases secondary to ductal edema, olfactory perception may decrease. At the same time due to edema of the nasal mucosa, the volume of the smell which reaches to the olfactory area may also decrease. Our study results demonstrate that one or more than one of these factors are affected with resultant decrease in olfactory functions in patients with LFR. Further studies are needed to demonstrate the mechanisms affected.

## Conclusion

LFR disease exerts negative effects on olfactory functions without leading to total loss in olfactory functions. Further studies are needed to support the results of this study.

**Conflict of Interest:** No conflicts declared.

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