Rhinology, 49, 112-116, 2011

Reduced olfactory bulb volume in total laryngectomy patients: a magnetic resonance imaging study*

Bayram Veyseller[1], Fadlullah Aksoy[1], Yavuz Selim Yıldırım[1], Fatma Gülüm İvgin Bayraktar[2], Defne Gürbüz[3], Yıldıray Savaş[3], Orhan Özturan[1]

[1] Bezmiâlem Vakif University, Department of Otorhinolaryngology and Head and Neck Surgery, Fatih, Istanbul, Turkey
[2] Haseki Research and Training Hospital, Department of Otorhinolaryngology and Head and Neck Surgery, Istanbul, Turkey
[3] Haseki Research and Training Hospital, Department of Radiology, Istanbul, Turkey

SUMMARY

Objectives: *The olfactory bulb (OB) is a remarkably plastic structure with highly active afferent neurons, which is partly reflected by its volume. Although deterioration of olfaction after total laryngectomy is reported by many patients, this problem has not received widespread attention. There has been no study that has addressed this loss olfactory ability as a function of OB volume. The aim of this study was to determine OB volume changes after laryngectomy.*
Study Design: *Twenty one patients post-total laryngectomy and 17 subjects with normal olfactory function underwent magnetic resonance imaging (MRI) for volumetric measurement of the OB. The history of all participants was taken in detail to exclude other possible causes of smell dysfunction. Volumetric measurement of the OB was performed by manual segmentation of the OB into coronal slices. Olfactory function was assessed with the orthonasal olfaction test.*
Results: *There was no statistically significant difference in volume between the right and left sides of the OB in the study and control groups. However, the study group had smaller OB volumes than the control group. In our assessment of orthonasal olfaction, patients who were post-total laryngectomy had worse orthonasal olfactory function than the control group. There were significant correlations between OB volumes and orthonasal test scores.*
Conclusions: *Our MRI study showed that post-total laryngectomy patients had higher rates of olfactory bulb atrophy than the control subjects. Laryngectomy is associated with measurable decreases in olfactory function and this study hopes to further clarify this association by demonstrating that patients with total laryngectomy have reduced OB volumes when compared to the normal population.*

Key words: olfactory bulb volume, laryngectomy, anosmia, hyposmia, plasticity

INTRODUCTION

The inability of patients after laryngectomy to detect smoke or other odorous danger signals can threaten their personal safety. Moreover, olfactory dysfunction adversely impacts their quality of life [(1)]. Although deterioration of olfaction after total laryngectomy has been reported by many patients, this problem has not received widespread attention [(2)]. The olfactory nerve contains the only sensory components in the body (afferent) capable of providing a sense of smell or olfaction. The olfactory system consists of the olfactory epithelium, bulbs, and tracts, along with the cortical olfactory areas, collectively known as the rhinencephalon. The olfactory bulb (OB) is a collection of the sensory afferent neurons of the olfactory receptor cells within the olfactory neuroepithelium. The OB is considered to be the first important relay station in the olfactory pathway, providing the link between the peripheral olfactory system and cortical structures. The OB remains highly plastic throughout adult life, reflecting the level of afferent neural activity [(2)].

One of the most outstanding characteristics of olfactory deprivation demonstrated in animals is the resulting reduction in OB volume, directly due to a decreased number of cells [(3)]. Immediately after total laryngectomy, which includes a complete separation of the nasal and digestive passageways, patients frequently report marked hyposmia or anosmia. At least, two thirds of patients who have undergone laryngectomy report severe impairment of olfactory ability, while anosmia was clinically determined in the remaining third [(4,5)].
Many hypotheses have been proposed to explain laryngectomy induced hyposmia. The 2 main mechanisms that have been studied as possible causes of hyposmia after laryngectomy are the loss of nasal airflow and the disruption of the complex neurosensor feedback mechanisms consequent to multiple peripheral nerve injuries connected with the surgical procedure [(4-6)].

*Received for publication: January 1, 2010; accepted: May 8, 2010

DOI:10.4193/Rhino10.001

Improvements in magnetic resonance imaging (MRI) techniques and volumetric magnetic resonance analysis offer an ideal way of reliably evaluating OB volume. Considering the plasticity of the olfactory bulb structure, bulb volume may reflect the functional state of the human olfactory system. Accordingly, OB volume has been previously studied in patients with post-traumatic olfactory deficits, congenital anosmia, neurodegenerative diseases, and in subjects with a normal sense of smell [7-12]. We are not aware of any reported study that evaluated olfactory bulb volume changes in patients who underwent total laryngectomy. To address this, we performed a systematic evaluation of olfactory bulb volume changes in post-total laryngectomy patients, using MRI and volumetric magnetic resonance analysis.

MATERIALS AND METHODS

Study design

This cross-sectional clinical study was performed at the Department of Otolaryngology, Head and Neck Surgery and at the Department of Radiology in the Haseki Training and Research Hospital, İstanbul, Turkey. This investigation was carried out according to the Declaration of Helsinki on Biomedical Studies Involving Human Subjects (WMA; 1997). This study was approved by the ethics committee of the Haseki Training and Research Hospital. All subjects provided written consent after being informed about the procedures and aim of the study.

Patients

In total, 21 selected patients participated. Two female and 19 male patients were studied (mean age, 54.5 years; range, 40 74). All of these patients were smokers (mean, 20 cigarettes per day; range 10 - 40). Patients with a history of any olfactory disorder before laryngectomy were excluded. All participants received an otolaryngological investigation, including a volumetric MRI scan and orthonasal olfaction tests. MRI evaluations were performed in the post-operative period, at a mean period of 23 months after total laryngectomy. Additionally, subjects received an extensive review of their clinical histories to exclude other possible external causes for smell dysfunction. Furthermore, all subjects underwent a complete neurological examination and mental state examination to exclude any possible cognitive or neurodegenerative disease.

The control group consisted of 17 subjects with normal olfactory function, 5 women and 12 men (mean age 53.2 years; range 44-65). All subjects in the control group were also smokers (mean 7 cigarettes per day; range 5-20).

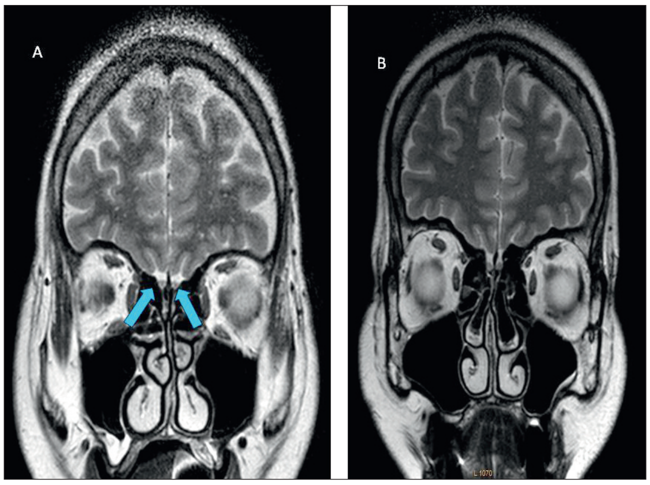

Figure 1. T2-weighted coronal image with decreased olfactory bulb volume (arrows)(A) and control image (B).

Olfactory test

The orthonasal olfactory test, defined by the Connecticut Chemosensory Clinical Research Center (CCCRC), was applied to post-total laryngectomy patients, as modified by Leon at al. [13,14].

As in the CCCRC orthonasal test, scores were grouped as follows: 0 to 1.75, anosmia; 2.00 to 3.75, severe hyposmia; 4.00 to 4.75, moderate hyposmia; 5.00 to 5.75, mild hyposmia; and 6.00 to 7.00 normal.

Magnetic resonance imaging

OB volume was calculated using MRI (Figure 1) [15]. All examinations were performed on a 1.5-Tesla system (Philips Achieva) using 8-channel head coil MR sequences that included sagittal T1W SE, and axial T2W TSE and T2W GRE, with slice selection gradients oriented coronally and perpendicularly to the frontal skull base or the cribriform plate. Coronal T1W SE, T2W TSE, and coronal T2W TSE images were produced with a slice thickness of 3 mm with no gaps. All volumetric measurements were performed by an experienced radiologist who was blinded to the olfactory test data; a manual segmentation was performed of the right and left side of the OB, creating coronal T2W slices.

Table 1. Results of summary statistics table study and control group.

	n	Mean	SD	Median	Minimum	Maximum	10 - 90 P
Right OB study	21	60,048	16,8656	57,000	25,000	95,000	37,200 - 79,400
Right OB control	17	70,647	10,8336	68,000	56,000	91,000	58,000 - 87,200
Left OB study	21	56,762	15,8616	56,000	33,000	89,000	36,600 - 77,800
Left OB control	17	73,235	13,3395	71,000	57,000	104,000	57,400 - 96,000
Mean OB study	21	58,381	15,7717	58,000	31,000	92,000	39,600 - 77,600
Mean OB control	17	71,882	11,2299	68,000	60,000	96,000	60,200 - 89,800
Orthonasal study	21	3,012	1,4064	3,000	0,500	5,500	1,150 - 5,100
Orthonasal control	17	5,456	1,0504	5,500	2,750	6,750	4,050 - 6,500

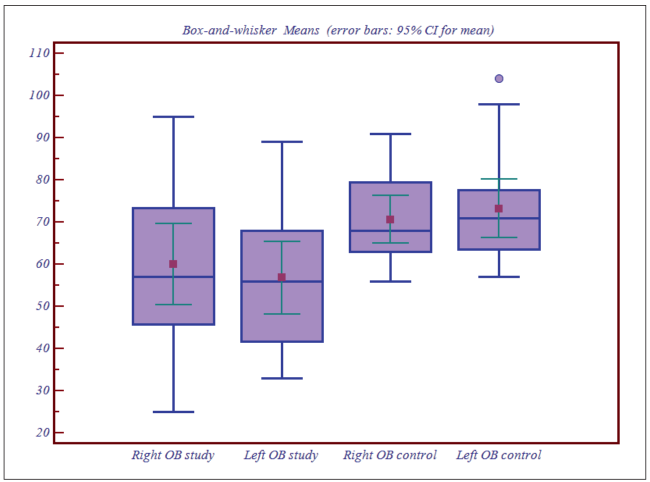

Figure 2. Box plot showing the distribution of OB volume measurements in the study and control groups.

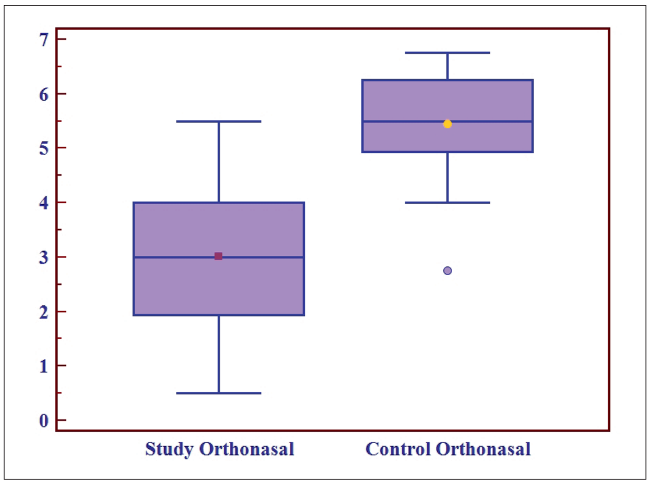

Figure 3. Box plot showing distribution of olfaction test results in the study and control groups.

To exclude any deposits of parenchymal or meningeal post-traumatic hemosiderin, we performed and examined T2W GRE images of the entire brain. Also, standard T2W TSE images of the entire brain were used with no gaps between cross sections to exclude organic brain disorders.

Statistical analyses

Data were analysed using the MedCalc®Turkey program (v. 10.4.8). Student's *t*-test was used to compare dependent groups. The paired sample *t*-test was used for comparing independent groups. Correlation analyses were performed according to Pearson. A p-value of < 0.05 was deemed to indicate statistical significance.

RESULTS

The volume of the subjects' OBs within the study group varied widely. The mean volume of the left OB for 21 patients was 56.76 mm3 (SD, 15.86; range, 33-89). The mean volume of the right OB was 60.05 mm3 (SD, 18.67; range, 25-95). The average volume of the right and left OBs together was 58.38 mm^3 (SD, 15.77; range, 31-92).

The mean volume of the OB in the control group was 70.64 mm^3 (SD, 10.83; range, 56-91) on the right side and 73.23 mm^3 (SD, 13.33; range, 57-104) on the left side. The average volume of the right and left OBs together was 71.88 mm^3 (SD, 11.22; range, 60-96; Table 1).

OB volume measurement

There was no statistically significant difference in OB volumes between the right and left sides in the study or the control group (p = 0.1424, p = 0.2607, respectively).

The difference in OB volumes between study and control groups was statistically significant ($p < 0.05$; Figure 2), where the study group presented with smaller OB volumes than the control group.

Olfactory function testing

Results of the orthonasal olfactory testing are summarized in Table 2. The mean score (averages of butanol threshold and identification scores) was 3.01 out of 7 (SD, 1.4; range, 0.5-5.5) for the post-total laryngectomy group and a score of 5.45 (SD 1.05, range 2.75-6.75) for the control group. A score of 3.01 for study group in the CCCRC scoring system indicated "severe hyposmia" and a score of 5.45 for the control group indicated "mild hyposmia."

All patients in the study group had olfactory dysfunction, as assessed by the orthonasal olfactory test battery. Five patients were anosmic, 10 were severely hyposmic, 3 were moderately hyposmic, and 3 were mildly hyposmic. In the control group, 1 patient was severely hyposmic, 3 were moderate hyposmic, 5 were mildly hyposmic, and 8 were normal (Table 2).

There was a significant difference ($p < 0.001$; Figure 3) when patients post-total laryngectomy were compared with control subjects within each CCCRC score group. Assessment of orthonasal olfaction showed that the patients who had undergone total laryngectomy had worse orthonasal olfactory function than the control group.

Correlation analyses of olfactory sensitivity in relation to the olfactory bulb volume was performed for both surgery and control groups. There were significant correlations between OB volumes and orthonasal test scores ($p < 0.001$).

DISCUSSION

Olfaction is both a passive process that occurs during normal breathing (passive smelling) and an active process (active

Table 2. Results of orthonasal olfactory testing grouped by category*.

Category	Total Laryngectomy Group	Control Group
Normal	0	8
Mild Hyposmia	3	5
Moderate Hyposmia	3	3
Severe Hyposmia	10	1
Anosmia	5	0
Total	21	17

*All data are reported as number of patients.

smelling or sniffing). Total laryngectomy has adverse effects on olfaction because of the permanent disconnection between the upper and lower airways. Total laryngectomy inevitably results in the loss of passive smelling and, for a majority of patients, loss of active smelling as well.

OB plasticity depends on 2 major neurobiological mechanisms. One is the continuous neural supply from the subventricular zone (SVZ). Here, neuroblasts migrate along the rostral migratory stream and replace interneurons (periglomerular cells, granular cells) in the OB, leaving the major relay neurons, mitral cells, substantially unaffected [(16)]. The second mechanism concerns continuous synaptogenesis that occurs primarily between incoming axonal projections of olfactory receptor neurons and dendrites of mitral/tufted cells at the glomerular level.

Age is an important factor influencing smell capacity and bulb volume, so control and study groups were standardized, but a prospective clinical trial with a larger number of subjects will be required.

In animals, one of the most important effects of olfactory deprivation is the reduction in OB volume as a result of hypoplasia [(3)]. Bulbar neuroplasticity is related to the input from the olfactory receptor neurons [(17)]. Furthermore, a continuous stream of neuroblasts to the OB from the SVZ has been described in the human CNS [(16)]. By maintaining constitutive neurogenesis that is sensitive to environmental influences, the resulting "neural recruitment" may in turn lead to a change in OB volume and to an improvement in sensory ability [(18)].

Although deterioration of olfaction after total laryngectomy is reported by many patients, this problem has not received widespread attention [(2)]. Moreover, olfactory rehabilitation has been given much less consideration than other sequelae of this operation, such as vocal and pulmonary problems. In several overviews of rehabilitation after laryngectomy, olfactory problems, as a consequence of the laryngectomy, were not even mentioned [(19,20)]. It was originally thought that the anosmia noted immediately after the operation was an inevitable result of the laryngectomy and that there could be no return of olfactory acuity for as long as 8 years after the operation [(21)]. However, others have reported an improvement in olfaction during the first 6 months after surgery and even the presence of a relatively normal sense of smell in some laryngectomies [(4,22)]. Atrophy of the olfactory neuroepithelium and/or bulb may play a role in the olfactory problems of the patients after laryngectomies [(23)].

While the pathophysiological feature of decreased olfaction in patients who have undergone laryngectomy is still unknown, several theories have been proposed. Patients who have undergone laryngectomy obviously lack nasopulmonary airflow, so they cannot "sniff" in the usual manner. It has been suggested that complex neural pathways critical for olfaction are interrupted by surgical denervation of the larynx [(24)]. Miani et al. proposed that degeneration of the olfactory epithelium was due to atrophy, inflammation, or disuse [(25)]. They noted more severe degeneration of the olfactory epithelium in biopsy samples taken from patients who underwent laryngectomy than the control group.

The results of this study demonstrate that OB volume reflects olfactory dysfunction. Our present results also support the findings discovered in experimental animals, where changes in OB volume were related to inputs from the olfactory epithelium. This relationship between structure and function is most likely due to the high plasticity found in the synaptogenesis of the OB [(3)].

CONCLUSIONS

When compared with normal subjects, patients who underwent laryngectomy show a high rate of olfactory bulb abnormality, as seen by MRI. These findings may indicate that laryngectomy leads to a reduced sensory input in the OB, resulting in structural changes at the level of the bulb and the symptoms of hyposmia or anosmia. Olfactory deprivation as a result of complete separation of the nasal and digestive passageways is likely to be the cause of decreased olfactory bulb volume. These findings require replication and extension, including longitudinal studies that examine OB changes in laryngectomy patients over time.

CONFLICT OF INTEREST

None; Funding source, financial disclosures: none; sponsor: none.

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Dr. Yavuz Selim Yıldırım
Haseki Egitim ve Arastirma Hastanesi
Kulak Burun Bogaz Klinigi
34089 Fatih
Istanbul
Turkey

Tel: +90-212-529 4400 Ext: 1286
Fax: +90-212-510 3701
E-mail: dryavuzselim@yahoo.com