The Egyptian Journal of Otolaryngology

ORIGINAL ARTICLE Open Access

Expression of serotonergic (5HT) receptors in patients with chronic rhinosinusitis with nasal polyposis and in normal nasal mucosa

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Abstract

Expression of serotonergic (5HT) receptors in patients with chronic rhinosinusitis with nasal polyposis and in normal nasal mucosa: a case-control study.

Background Chronic rhinosinusitis with nasal polyposis is one of the challenging conditions regarding treatment and management. Many recent studies introduced new modalities for treatment like targeted immunomodulating drugs rather than antihistamines, local and systemic steroids, and endoscopic sinus surgery. Understanding the pathology behind the disease by studying its immunologic pathways and substances that take part in the inflammatory process can help in the introduction of new treatment options that can improve outcomes and decrease the costs of treatment.

Objective The aim of our study is to demonstrate the presence of 5-HT receptors in nasal polyps and inferior turbinate mucosa in patients with chronic rhinosinusitis with nasal polyposis and then compare this expression of 5-HT receptors with inferior turbinate mucosa of the normal control group.

Methods A case-control study was conducted on 80 patients. Specimens from nasal polypi and turbinate mucosa of patients with chronic rhinosinusitis (cases) and specimens from normal turbinate mucosa (controls) were stained with serotonin receptor Immunohistochemical staining by automated immunostainer in the pathology department laboratory in Ain Shams University Hospital with ratio 1:200–400 as recommended by the manufacturing company. Then, compared as regards stain distribution and intensity of mucosal lining, glands, and blood vessels.

Results There was a significant difference between polyp cases and controls as regards lining epithelium and mucosal gland stain distribution and stain intensity. Also significant difference between the polyp cases and controls as regards blood vessel strain distribution. However, no significant difference was found as regards blood vessel stain intensity. There was a significant difference between turbinate cases and controls as regards lining epithelium stain distribution, and stain intensity. There was no significant difference between turbinate cases and controls as regards gland stain distribution. However, a significant difference was found between turbinate and controls as regards gland stain intensity. There was a significant difference between turbinate cases and controls as regards blood vessel stain distribution; however, no significant difference was present as regards stain intensity. There was no significant difference between polyp and turbinate cases as regards lining epithelium and blood vessel stain distribution and stain intensity. There was no significant difference between polyp and turbinate cases as regards

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gland stain distribution; however, a highly significant difference between polyp and turbinate cases as regards gland stain intensity.

Conclusion Serotonin receptors are highly expressed in patients with chronic rhinosinusitis with nasal polyposis in both turbinate and polypoidal tissues which proves that serotonin has a strong role in the formation and growth of nasal polypi and allergic reactions. Hence serotonin modulating drugs can be studied as a new therapy for chronic rhinosinusitis with nasal polyposis.

Keywords Chronic rhinosinusitis, Serotonin receptors, Nasal polypi, Allergic rhinitis

Background

Nasal polyposis is an inflammatory disease of the nose and paranasal sinuses mucosa. Its prevalence is 1–4% in the general population and is known to cause symptoms of rhinorrhea and nasal obstruction [1].

Nowadays, nasal polyposis is treated with systemic or local steroids or by removal of polypoidal tissue by endoscopic sinus surgery. But sometimes symptoms can persist after the administration of steroids, and the disease can rapidly reappear even with surgery. Hence, experimental and clinical studies to understand the mechanisms leading to the development of nasal polyposis and different treatment options are continually being conducted [2].

Understanding chronic rhinosinusitis with nasal polyposis pathogenesis is important in the prevention and management of chronic symptoms and in the development of medical treatments to help affected patients [3].

Studies that include the use of molecular biomarkers and inflammatory endotypes are an important focus of research nowadays. The recent evolution of targeted therapies and biological therapeutics can rapidly improve care and outcomes in the treatment of chronic rhinosinusitis. Recent findings have improved the understanding of chronic rhinosinusitis phenotypic and endotypic heterogeneity, and the development of novel therapeutic interventions. These kinds of specific studies have the potential to aim and identify specific inflammatory pathways to increase efficacy, cost reduction, and limitation of side effects of treatment [4].

Although the inflammatory processes behind chronic rhinosinusitis with nasal polyposis are not fully understood, recent significant progress has shown that the inflammatory process consists of distinctive subtypes that are highly heterogeneous. Research on chronic rhinosinusitis has recently increased, and many different biomarkers related to polyp formation have been identified: eosinophil cytokines, metalloproteinases, interleukins like IL-4, IL-5, IL-13, IL-25, IL-33, nasal microbiome, sweet, or bitter taste receptors. However, we still need to find biomarkers involved in the intrinsic biomolecular mechanism for endotyping understanding to be applicable, predictable, and easily determined [5].

Serotonin (5-Hydroxy Tryptophan or 5HT) is a vasoactive agent and a potent neurotransmitter that is involved in different psychological and behavioral responses, such as pain, mood changes, sleep patterns, and appetite. Additionally, serotonin has an immunomodulating effect through serotonergic receptor stimulation [6].

Kubera et al. in 2005 reported that lymphocytes and macrophages needed serotonin in low concentrations for basal production of TNF-α and IL-6 both play a role in the allergic inflammatory process and nasal polyposis [7].

Serotonin contributes to the mechanism of allergic inflammation. The majority of serotonin's immunomodulatory functions have been identified, including cell migration, the phagocytosis process, lymphocyte production of cytokines, and monocyte production of superoxide anion [8].

In 1985, P. Tonessen and N. Mygind conducted a double-blind study to examine the reaction of 14 healthy individuals whose nasal mucosa was stimulated with serotonin and histamine. In addition to measuring the number of nasal secretions and the frequency of sneezes, active rhinomanometry was used to quantify the nose's airway resistance. Serotonin markedly increased nasal secretions, causing sneezing and itching that resembled histamine's effects. They discovered that the human nose can become inflamed in response to serotonin stimulation [9].

In 2006, a study by Kushnir-Sukhov and colleagues showed that mast cell adhesion and migration in human and rodent mast cells is induced by serotonin via the 5-HT1A receptor. The important effects of 5-HT receptors on the immune system and inflammation suggest that 5-HT receptors could be involved in nasal polyp development [10, 11].

In 2017, Yayla et al. studied the expression of serotonin receptors in nasal polyps and in inferior turbinate mucosa of non-allergic patients undergoing septoplasty. They found that serotonin receptors were highly expressed in polypoidal tissues suggesting a role for serotonin in the formation of nasal polypi [12].

Aim of the work

The aim of our study is to demonstrate the presence of 5-HT receptors in nasal polyps and inferior turbinate mucosa in patients with chronic rhinosinusitis with nasal polyposis and then compare this expression of 5-HT receptors with inferior turbinate mucosa of the normal control group. This will be done by comparing the 5HT receptor's intensity and distribution as regards lining epithelium, mucosal glands, and blood vessels.

Methods

A case-control study was held in the Otorhinolaryngology Department, Faculty of Medicine, Ain Shams University.

Inclusion criteria

All adult patients (of both sexes and between 20 and 60 years of age) with chronic rhinosinusitis with nasal polyposis were diagnosed clinically and radiologically according to Lund-Mackay CT scan Scoring (of score 8 and more).

Exclusion criteria

Acute sinusitis, chronic granulomatous inflammations, and administration of oral or nasal steroids within the last 4 weeks.

The current study consists of a study group that includes 40 patients diagnosed with chronic rhinosinusitis with nasal polyposis from which biopsies from nasal polypi and turbinate mucosa will be taken. The control group includes 40 patients not diagnosed with chronic rhinosinusitis with nasal polyposis undergoing septoplasty and partial inferior turbinectomy (compensatory turbinate hypertrophy associated with nasal septum deviation) for treatment of nasal obstruction.

The sample size was calculated using PASS 110 and based on a study carried out by Yayla et al. 2017. Group sample sizes of 40 cases and 40 controls achieve 95% power to detect a difference of 3.1 between the null hypothesis that both group means are 4.6 and the alternative hypothesis that the mean of group 2 is 1.5 with estimated group standard deviations of 0.2 and 5.0 and with a significance level (alpha) of 0.05000 using a two-sided two-sample *t*-test.

All patients will be subjected to the following protocol after obtaining their written consent.

Full history taking and otorhinolaryngological examination of patients diagnosed with chronic rhinosinusitis with nasal polyposis according to the European Position Paper on Rhinosinusitis and Nasal Polyps 2020 (EPOS2020 guideline) (Fokkens WJ, Lund VJ, Hopkins C, et al. 2020*)*, and to fulfill inclusion criteria including both sexes of age group between 20 and 60 years old. Endoscopic examination of the nasal cavity and grading of nasal polyposis (all grades will be included). Computed tomography (CT scan) of paranasal sinuses and grading according to Lund-Mackay CT Scoring only patients score 8 and more will be included. Biopsy was obtained from the patients during functional endoscopic sinus surgery (FESS) from polyps and turbinate mucosa in the examined group of patients and from turbinate mucosa in the control group using Blakesley forceps [13].

Specimens fixed in 10% buffered formalin, paraffin-embedded, sectioned, and processed for routine hematoxylin and eosin (H&E) stain, for histological examination and evaluation. 5HT immunohistochemical staining was performed by an automated immunostainer in the pathology department laboratory at Ain Shams University Hospital with a ratio 1:200–400 as recommended by the manufacturing company. Examination of immunohistochemically stained sections and evaluation of the distribution and intensity of the positive staining.

Data collected from study groups are subjected to statistical analysis. The collected data was revised, coded, tabulated, and introduced to a PC using Statistical Package for Social Science (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). Data was presented and suitable analysis was done according to the type of data obtained for each parameter.

i. *Descriptive statistics*

1. Shapiro-Wilk's test was used to evaluate the normal distribution of continuous data. Mean, standard deviation (± SD), and range were used for parametric numerical data, while median and interquartile range (IQR) were used for non-parametric numerical data.
2. Frequency and percentage of non-numerical data.

ii. Analytical statistics

1. Student's *t* test
2. Mann- Whitney test (*U* test)
3. Chi-square test
4. Wilcoxon signed rank test
5. McNemar test

P value: level of significance

- $P > 0.05$: non-significant (NS).
- $P < 0.05$: significant (S).
- $P < 0.01$: highly significant (HS).

Table 1 Comparison between the cases and control groups as regards personal characteristics

		Group				*P*	Sig
		Controls		Cases			
		Mean	±SD	Mean	±SD		
Age		29.90	4.93	29.80	4.39	0.924‡	NS
Sex	Male	23	57.5%	24	60.0%	0.82*	NS
	Female	17	42.5%	16	40.0%		
Smoking	No	23	57.5%	18	45.0%	0.26*	NS
	Yes	17	42.5%	22	55.0%		

‡ Student's *t* test

* Chi-square tests

Results

There was a significant difference between polyp cases and controls as regards lining epithelium and mucosal gland stain distribution and stain intensity. Also significant difference between the polyp cases and controls as regards blood vessel stain distribution. However, no significant difference was found as regards blood vessel stain intensity.

There was a significant difference between turbinate cases and controls as regards lining epithelium stain distribution, stain intensity. There was no significant difference between turbinate cases and controls as regards gland stain distribution. However, a significant difference was found between turbinate and controls as regards gland stain intensity. There was a significant difference between turbinate cases and controls as regards blood vessel stain distribution; however, no significant difference was present as regards stain intensity.

There was no significant difference between polyp and turbinate cases as regards lining epithelium and blood vessel stain distribution and stain intensity. There was no significant difference between polyp and turbinate cases as regards gland stain distribution, however, a highly significant difference between polyp and turbinate cases as regards gland stain intensity (Tables 1, 2, 3, 4, 5, 6, 7, 8, 9, 10).

There was no significant difference as regards sex, age, or smoking among study groups.

Discussion

Polyposis is described histologically as an inflammatory response defined by the migration of inflammatory cells, primarily neutrophils, and eosinophils, in the case of nasal polypi. Furthermore, research has demonstrated that oxidative stress and the immune system are important factors in the emergence and growth of nasal polypi. Many investigations were conducted to explore

Table 2 Comparison between polyp cases group and controls as regards stain characteristics of the lining epithelium

		Group				*P*	Sig
		Controls		Polyp group			
		N/Mean	%/±SD	*N*/Mean	%/±SD		
Lining epithelium stain distribution	Focal	29	72.5%	14	35.0%	0.001*	HS
	Diffuse	11	27.5%	26	65.0%		
Lining epithelium stain intensity	Faint	33	82.5%	15	37.5%	0.001**	HS
	Moderate	7	17.5%	16	40.0%		
	Strong	0	0.0%	9	22.5%		
Combined lining epithelium score		0.90	1.43	2.80	2.43	0.001‡	HS
Combined lining epithelium score	Negative	27	67.5%	15	37.5%	0.0001*	HS
	Moderate	8	20.0%	3	7.5%		
	Strong	5	12.5%	22	55.0%		

* Chi-square test

** Fisher exact test

‡ Mann-Whitney test

Table 3 Comparison between polyp cases group and controls as regards stain characteristics of glands

		Group				*P*	Sig
		Controls		Polyp group			
		N/Mean	%/±SD	*N*/Mean	%/±SD		
Glands stain distribution	Focal	20	50.0%	11	27.5%	0.039*	S
	Diffuse	20	50.0%	29	72.5%		
Glands stain intensity	Faint	13	32.5%	9	22.5%	0.024*	S
	Moderate	26	65.0%	22	55.0%		
	Strong	1	2.5%	9	22.5%		
Combined gland score		2.05	1.72	3.05	2.17	0.035‡	S
Combined gland score	Negative	13	32.5%	9	22.5%	0.194*	NS
	Moderate	14	35.0%	10	25.0%		
	Strong	13	32.5%	21	52.5%		

* Chi-square tests

‡ Mann-Whitney test

Table 4 Comparison between polyp cases group and controls as regards stain characteristics of blood vessels and overall stain expression

		Group				*P*	Sig
		Controls		Polyp group			
		N/Mean	%/±SD	*N*/Mean	%/±SD		
Blood vessel stain distribution	Focal	36	90.0%	26	65.0%	0.007*	HS
	Diffuse	4	10.0%	14	35.0%		
Blood vessel stain intensity	Faint	12	30.0%	10	25.0%	0.449*	NS
	Moderate	24	60.0%	22	55.0%		
	Strong	4	10.0%	8	20.0%		
Combined blood vessel score		1.70	1.40	2.60	2.10	0.09‡	NS
Combined blood vessel score	Negative	12	30.0%	10	25.0%	0.026*	S
	Moderate	24	60.0%	16	40.0%		
	Strong	4	10.0%	14	35.0%		
Overall expression score		1.50	1.00	2.80	2.00	0.003‡	HS
Overall expression	Negative	10	25.0%	6	15.0%	0.003*	HS
	Mild	14	35.0%	8	20.0%		
	Moderate	15	37.5%	12	30.0%		
	Strong	1	2.5%	14	35.0%		

* Chi-square tests

‡ Mann-Whitney test

alternative treatments for nasal polyposis, and a variety of anti-inflammatory and antioxidant medications were considered as potential cures [14].

It has been demonstrated that basophils, mast cells, enterochromaffin cells, and peripheral tissues all release serotonin. Inflammatory circumstances cause an increase in extracellular serotonin levels. Consequently, it is possible to think of serotonin as an immunomodulatory [15].

In our study, 5HT receptors were highly expressed in the polypoidal and mucosal inflammatory cells in the chronic rhinosinusitis with nasal polyposis group; this proves the significant role of 5HT in the inflammatory process of inflammatory nasal response and formation

Table 5 Comparison between turbinate cases group and controls as regards stain characteristics of the lining epithelium

		Group				*P*	Sig
		Controls		Turbinate group			
		N/Mean	%/±SD	*N*/Mean	%/±SD		
Lining epithelium stain distribution	Focal	29	72.5%	17	42.5%	0.007*	HS
	Diffuse	11	27.5%	23	57.5%		
Lining epithelium stain intensity	Faint	33	82.5%	16	40.0%	0.001**	HS
	Moderate	7	17.5%	22	55.0%		
	Strong	0	0.0%	2	5.0%		
Combined lining epithelium score		0.9	1.43	2.20	2.02	0.003 ‡	HS
Combined lining epithelium score	Negative	27	67.5%	16	40.0%	0.005*	HS
	Moderate	8	20.0%	6	15.0%		
	Strong	5	12.5%	18	45.0%		

* Chi-square tests

** Fisher exact test

‡ Mann-Whitney test

Table 6 Comparison between turbinate cases group and controls as regards stain characteristics of glands

		Group				*P*	Sig
		Controls		Turbinate group			
		N/Mean	%/±SD	*N*/Mean	%/±SD		
Glands stain distribution	Focal	20	50.0%	13	32.5%	0.112*	NS
	Diffuse	20	50.0%	27	67.5%		
Glands stain intensity	Faint	13	32.5%	24	60.0%	0.019**	S
	Moderate	26	65.0%	14	35.0%		
	Strong	1	2.5%	2	5.0%		
Combined gland score		2.05	1.72	1.30	1.84	0.033‡	S
Combined gland score	Negative	13	32.5%	24	60.0%	0.047*	S
	Moderate	14	35.0%	8	20.0%		
	Strong	13	32.5%	8	20.0%		

* Chi-square tests

** Fisher exact test

‡ Mann-Whitney test

of nasal polyps. This fact was also approved in Durk et al.'s 2005 study of the effect of 5HT in the inflammatory response in peripheral organs that 5-HT is present at high concentrations in mast cells, basophils, platelets, and enterochromaffin cells. It is released at high concentrations during IgE stimulation or platelet aggregation [8].

According to the high distribution of 5HT receptors in mucosal glands, lining epithelium, and blood vessels in both polypoidal tissues and mucosal tissues of the patients' group in comparison to controls, we can strongly correlate allergic symptoms to the high expression of 5HT receptors according to total nasal symptoms score system. This correlation goes with the results of R.A. MacHaffie et al in 1960 and a more recent study by F. Soga et al. 2007 [16, 17].

There was a positive correlation between asthmatic patients and patients showing a high concentration of 5HT receptors which proves the significant effects of 5HT in asthmatic patients as postulated by Nau, F. et al. in 2015 who studied also the expression of 5HT

Table 7 Comparison between turbinate cases group and controls as regards stain characteristics of blood vessels and overall stain expression

		Group				*P*	Sig
		Controls		Turbinate group			
		N/Mean	%/±SD	*N*/Mean	%/±SD		
Blood vessel stain distribution	Focal	36	90.0%	27	67.5%	0.014*	S
	Diffuse	4	10.0%	13	32.5%		
Blood vessel stain intensity	Faint	12	30.0%	8	20.0%	0.344*	NS
	Moderate	24	60.0%	30	75.0%		
	Strong	4	10.0%	2	5.0%		
Combined blood vessel score		1.70	1.40	2.30	1.60	0.149‡	NS
Combined blood vessel score	Negative	12	30.0%	8	20.0%	0.118*	NS
	Moderate	24	60.0%	21	52.5%		
	Strong	4	10.0%	11	27.5%		
Overall expression score		1.50	1.00	1.90	1.30	0.254‡	NS
Overall expression	Negative	10	25.0%	7	17.5%	0.338*	NS
	Mild	14	35.0%	15	37.5%		
	Moderate	15	37.5%	13	32.5%		
	Strong	1	2.5%	5	12.5%		

* Chi-square tests

‡ Mann-Whitney test

Table 8 Comparison between polyp and turbinate cases group as regards stain characteristics of the lining epithelium

		Group				*P*	Sig
		Polyp		Turbinate group			
		N/Mean	%/±SD	N/Mean	%/±SD		
Lining epithelium stain distribution	Focal	14	35.0%	17	42.5%	0.581*	NS
	Diffuse	26	65.0%	23	57.5%		
Lining epithelium stain intensity	Faint	15	37.5%	16	40.0%	0.059**	NS
	Moderate	16	40.0%	22	55.0%		
	Strong	9	22.5%	2	5.0%		
Combined lining epithelium score		2.80	2.43	2.20	2.02	0.07*	NS
Combined lining epithelium score	Negative	15	37.5%	16	40.0%	0.38**	NS
	Moderate	3	7.5%	6	15.0%		
	Strong	22	55.0%	18	45.0%		

* McNemar test

** Wilcoxon signed ranks test

receptors in the bronchial airway of asthmatic patients [18].

Regarding endoscopic examination of the nasal cavity, Meltzer classification was used for determining the grade of the nasal polyps. It was noted that higher expression of 5HT receptors was associated with higher-grade nasal polyps [19].

Yayla et al.'s study in 2017 showed high expression (about 67-folds) of 5HT receptors in allergic nasal polyps in comparison to normal non-allergic nasal turbinate mucosa. Our results showed high expression of 5HT receptors in nasal polyps and moreover in the allergic nasal mucosa in comparison to the normal nasal mucosa of inferior turbinates [12].

Table 9 Comparison between polyp and turbinate cases group as regards stain characteristics of glands

		Group				*P*	Sig
		Polyp group		Turbinate group			
		N/Mean	%/±SD	*N*/Mean	%/±SD		
Glands stain distribution	Focal	11	27.5%	13	32.5%	0.804*	NS
	Diffuse	29	72.5%	27	67.5%		
Glands stain intensity	Faint	9	22.5%	24	60.0%	0.0001**	HS
	Moderate	22	55.0%	14	35.0%		
	Strong	9	22.5%	2	5.0%		
Combined gland score		3.05	2.17	1.30	1.84	0.001**	HS
Combined gland score	Negative	9	22.5%	24	60.0%	0.001**	HS
	Moderate	10	25.0%	8	20.0%		
	Strong	21	52.5%	8	20.0%		

* McNemar test

** Wilcoxon signed ranks test

Table 10 Comparison between polyp and turbinate cases group as regards stain characteristics of blood vessels and overall stain expression

		Group				*P*	Sig
		Polyp group		Turbinate group			
		N/Mean	%/±SD	*N*/Mean	%/±SD		
Blood vessel stain distribution	Focal	26	65.0%	27	67.5%	1.0*	NS
	Diffuse	14	35.0%	13	32.5%		
Blood vessel stain intensity	Faint	10	25.0%	8	20.0%	0.346**	NS
	Moderate	22	55.0%	30	75.0%		
	Strong	8	20.0%	2	5.0%		
Combined blood vessel score		2.60	2.10	2.30	1.60	0.289**	NS
Combined blood vessel score	Negative	10	25.0%	8	20.0%	0.834*	NS
	Moderate	16	40.0%	21	52.5%		
	Strong	14	35.0%	11	27.5%		
Overall expression		2.80	2.00	1.90	1.30	0.0001**	HS
Overall expression	Negative	6	15.0%	7	17.5%	0.0001**	HS
	Mild	8	20.0%	15	37.5%		
	Moderate	12	30.0%	13	32.5%		
	Strong	14	35.0%	5	12.5%		

* McNemar test

** Wilcoxon signed ranks test

Conclusion

Patients with nasal polyposis and chronic rhinosinusitis have highly expressed serotonin receptors in both the turbinate and polypoidal tissues, indicating a significant influence of serotonin on the development and proliferation of nasal polypi and allergic reactions. Consequently, serotonin-modulating medications may be investigated as a novel treatment for nasal polyposis and chronic rhinosinusitis.

Acknowledgements
Not applicable.

Authors' contributions
S Sabry has made design of the work and approved the submitted version and have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work. F Samia has made substantial contributions to the conception, revised the manuscript and analysed data and approved the submitted version and has agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work. S Manal has made a histopathological interpretation of collected samples and approved the submitted version and has agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work. K Ahmed reviewed literature and collected the samples and did the statistical analyses and ensured that all listed authors had approved the manuscript before submission, including the names and order of authors, and that all authors received the submission and all substantive correspondence with editors, as well as the full reviews, verified that all data, figures, materials (including reagents), and code, even those developed or provided by other authors, comply with the transparency and reproducibility standards of both the field and journal. A Heba has aided in the collection of samples and drafted the work or substantively revised it and approved the submitted version and has agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work.

Funding
Not applicable.

Availability of data and materials
All data generated or analyzed during this study are included in this published article [and its supplementary information files].

Declarations

Ethics approval and consent to participate
Informed consent from participants was obtained to participate in the study at the Otorhinolaryngology Department, Faculty of Medicine Ain Shams University. This work was approved by an ethical committee of the Faculty of Medicine Ain Shams University before the start of the recruitment (FMASU M D 406/2019).

Consent for publication
Written informed consent was obtained from all participants for publication.

Competing interests
Dr. Samia Fawaz is a co-author of this study and an Editorial Board member of the journal. She was not involved in handling this manuscript during the submission and review processes. The rest of the authors have no conflict of interest to declare.

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Received: 19 January 2024 Accepted: 8 March 2024
Published online: 11 April 2024

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