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ORIGINAL ARTICLE

Assessment of the effect of inflammatory changes and allergic reaction on TAS2R38 receptor expression in patients with chronic sinusitis (CRS)

Authors' Contribution:
A – Study Design
B – Data Collection
C – Statistical Analysis
D – Manuscript Preparation
E – Literature Search
F – Funds Collection

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ABSTRACT:

Background: Chronic rhinosinusitis (CRS) is one of the most common health complaints affecting 15% of the world's population. Recent reports confirm the participation of sensory organs in the defense process against pathogenic microorganisms. The bitter taste receptor TAS2R38 is described to play a role in the upper airway defense system.

Purpose: The purpose of this study was to assess the function of the bitter taste receptor in correlation with the severity of CRS, sensory organ disorders and allergic reaction.

Material and method: The study contained 100 patients undergoing nasal surgery, divided into two groups: CRS with and without nasal polyps. The control group consisted of patients undergoing septoplasty after excluding rhinosinusitis. Sinus mucosa samples obtained during surgery were used to assess TAS2R38 expression using immunohistochemistry. The IgE level was indicated from blood samples collected from patients. The Sniffin' Sticks Test was performed.

Results: CRS patients had higher expression of TAS2R38 receptor compared to controls (p = 0.0175). A statistically significantly higher TAS2R38 H-score in nasal mucosa was found among patients with a higher inflammation process in CT scan (p = 0.001), higher IgE level (p = 0,04) and an abnormal result of the Sniffin' Sticks Test.

Conclusions: Patients with CRS had significant TAS2R38 receptor overexpression correlating with the severity of inflammatory changes in CT scans, abnormal perception of smells and higher IgE level. A cumulative impact was found between the inflammatory changes, smell disfunction and the severity of subjective symptoms of CRS (according to EPOS) and the intensity of cell staining (index H-score).

KEYWORDS: bitter taste receptor, chronic rhinosinusitis, TAS2R38 gene, TAS2R38 receptor

ABBREVIATIONS

CRS – chronic rhinosinusitis
CRSsNP – chronic rhinosinusitis without nasal polyps
CRSwNP – chronic rhinosinusitis with nasal polyps
CT – computed tomography
EPOS – European Position Paper on Rhinosinusitis and Nasal Polyps
GCRP – G protein-coupled receptor
HLA – human leukocyte antigen
HRP-DAP – horseradish peroxidase-3,3'-Diaminobenzidine
HSEC – Human Nasal Epithelial Cells
IgE – immunoglobulin E
IHC – immunohistochemistry
SNP – Single Nucleotide Polymorphism
T2R – bitter taste receptors

INTRODUCTION

Chronic rhinosinusitis (CRS) is at the forefront of health and economic problems in highly developed societies [1]. Results of epidemiological studies suggest that it concerns about 15% of the population and ranks second among all chronic diseases [2]. The pathogenesis of CRS covers a number of dependent environmental and pathophysiological factors, but the underlying cause and mechanism of CRS formation are largely unknown. It is now thought that the development of CRS is associated with an incorrect immune response of the body to the antigen, which leads to dysregulation and overactivity of the body's defense system [3]. Risk factors which negatively impact on the intensity of CRS include, inter alia, atopy [4]. It has been argued that in these patients swelling of tissues and vasodilation lead to impaired patency of the ostiomeatal complexes [5, 6], and numerous studies report

a positive correlation between the level of immunoglobulin E (IgE) in the blood and the severity of inflammatory changes in the paranasal sinuses [7, 8]. It is also assumed that genetic factors may participate in the formation of CRS [9].

Bitter taste receptors (T2R) are a newly discovered family of genes that are likely to contribute to the development of CRS. Interestingly, bitter taste receptors are not only located in the mouth [10]. They can also be found in distal parts of the upper respiratory tract, including the nasal cavity, where they play a role other than the reception of taste stimuli [11–13]. T2R belong to the group of G-protein coupled receptors (GCPR) [14] whose activation is associated with innate mechanisms of antimicrobial defense [15]. They generate calcium ion dependence of nitric oxide synthase, which leads to an increase in mucociliary clearance [16]. Recent reports suggest that the genetic variability of the TAS2R38 bitter taste receptor, which is expressed within the cilia of epithelial cells of the nasal/sinus mucosa (HSEC), is associated with susceptibility to upper respiratory tract infections and the development of CRS.

The TAS2R38 receptor is unique due to its genetic variants [17]. Variable receptor activity affects different individual sensitivity to the bitter taste of phenylthiocarbamide [18] and depends on three single nucleotide polymorphisms (SNPs) in the TAS2R38 gene [19]. Leading to changes, SNP generates two popular haplotypes: (1) functional "defensive" and (2) non-functional allele. People who are homozygous for the taste allele feel intense bitter taste already at low concentrations of phenylthiocarbamide, while people with a non-functional allele do not feel bitterness. Furthermore, SNP in this gene has recently been shown to correlate with Gram-negative sinusitis [20]. Previous studies have confirmed the increase of TAS2R38 receptor expression in tissues in patients with CRS. However, there is no data on the effect of allergic reaction on the intensity of TAS2R38 receptor expression. To date, there has been no comparative assessment of the severity of inflammatory changes in patients with CRS with the level of TAS2R38 receptor expression in the tissues of the nasal mucosa. An interesting and unresearched aspect is also the relationship between the functioning of the sense of smell and changes in the expression of the TAS2R38 taste receptor. We have known for a long time that the sense of taste and smell are mutually dependent, and anosmia is often accompanied by an incorrect sensation of taste [21].

In view of the abovementioned findings, the aim of this study was to determine the impact of allergic reaction and the severity of sinus inflammation on TAS2R38 receptor expression in patients with CRS. The study also analyzed the correlation between the presence of the bitter taste receptor in the nasal mucosa and the functioning of the sense of smell. Before the commencement of trials, the consent of the Bioethical Committee of the Medical University of Warsaw for the abovementioned research was obtained and registered under no. KB/130/2015.

MATERIAL

The study covered 100 randomly selected patients of the Otolaryngology Department of the Międzyleski Specialist Hospital in Warsaw with CRS or a deviated septum, qualified for endoscopic surgery on the nose or paranasal sinuses. The age of the patients was from 19 to 68 (average age 38 years). Women constituted 39 people (39%) and men 61 (61%). In each of the examined groups, the proportion of both genders was comparable.

On the basis of physical examination, medical history, nasal endoscopy and sinus computed tomography (Lund-Mackay CT staging), patients were divided into 2 study groups: I – patients with chronic rhinosinusitis without nasal polyps (CRSsNP) – n = 39, II – patients with chronic rhinosinusitis with nasal polyps (CRSwNP) – n = 30. The control group (K) were other patients (n = 31) who underwent plastic surgery of deviated nasal septum without sinus symptoms in physical examination, medical history and computed tomography of the sinuses.

The research material included fragments of the mucosa taken during surgery around the olfactory area and patients' blood serum.

METHOD

Assessment of TAS2R38 receptor expression

The expression of TAS2R38 receptor was analyzed using methods of immunohistochemical staining (IHC). Fragments of the mucosa taken during endoscopic surgery were fixed by paraffinization. The paraffin blocks were then cut with a microtome, dewaxed and incubated with specific primary anti-TAS2R38 antibodies. The level of protein expression was determined by the intensity and amount of brown colored horseradish peroxidase – 3,3'-diaminobenzidine (HRP-DAB). The semi-quantitative analysis of IHC results was based on the calculation of the H-score (Histoscore). Both the percentage of stained cells and the degree of their staining were used.

Olfactometry testing

Each patient underwent a full olfactory testing using Sniffin' Sticks, consisting of three subtests: T – threshold test, D – discrimination and I – identification of smells, on the basis of which olfactometric diagnosis was made.

Assessment for allergy

Allergic origins of chronic sinusitis were assessed based on: medical history, cytological examination of the nasal mucosa and level of IgE immunoglobulin in blood serum.

RESULTS

The conducted immunohistochemical analyses assessing the H-score for each tested sample allowed the reconciliation of TAS2R38 receptor expression in nasal epithelial cells in individual groups. The results assessing the relationship between the occurrence of the tested receptor and: the severity of inflammation, the presence of IgE antibodies and the result of olfactometry testing are set out below.

Tab. I. Multiple regression model for the H-score factor.

ESTIMATED PARAMETERS VARIABLE	PARAMETER ESTIMATION	STANDARD ERROR	VALUE T	PR > |T| P VALUE CALCULATED USING T DISTRIBUTION
Polyps	-11,12490	4,17355	-2,67	0,0128
Discharge	-46,03690	9,83870	-4,68	<,0001
Sniffin' Sticks Test	34,72170	5,97161	5,81	<,0001
Subjective symptoms of CRS (according to EPOS)	-14,07447	3,17647	-4,43	0,0001

Dependence of TAS2R38 expression in the nasal mucosa from the severity of sinusitis

The use of anti-TAS2R38 antibodies manifested an increase in the intensity of brown color (DAB) in patients suffering from CRS as compared to control (Fig. 1.), and statistical analysis confirmed that the higher expression of the TAS2R38 receptor (H-score) in patients with CRS relative to control patients is statistically significant ($p = 0.0175$).

Statistically significantly higher TAS2R38 expression was found in subjects with high Lund-Mackay scoring in CT of the sinuses ($p = 0.001$). By contrast, there were no significant differences in the expression of the tested bitter taste receptor between the first and second study group (Fig. 2.).

Multiple regression analysis found a statistically significant cumulative effect of the severity of the inflammatory changes observed in ENT examination, deviations in the Sniffin' Sticks Test, and the severity of the subjective symptoms of CRS (according to EPOS; European Position Paper on Rhinosinusitis and Nasal Polyps) on the intensity of cell staining (index H-score), indicating an increase in the density of the TAS2R38 receptor in the nasal mucosa (Tab. I.).

Dependence of TAS2R38 expression in the nasal mucosa from the serum IgE levels

A statistically significant relationship was found between cell staining (H-score) and IgE immunoglobulin concentration ($p = 0.04$). The highest serum IgE was confirmed in patients with the highest TAS2R38 receptor expression in mucosa cells (Fig. 3.).

Dependence of TAS2R38 expression in the nasal mucosa from the olfactometric testing result

The correlation between the odor perception threshold in olfactometric testing and the amount of bitter taste receptor in the nasal mucosa was found in all three groups included in the study. People who could smell n-butanol only at high concentrations of the solution had a higher amount of TAS2R38 receptor in the IHC study. Although the control group did not report any olfactory impairment and the odor threshold in the Sniffin' Stick Test was within normal limits, its result correlated with the H-score of TAS2R38 expression in immunohistochemistry ($p = 0.0466$). By contrast, there was no significant relationship between the threshold of discrimination and odor identification and the expression of the bitter taste receptor in the nasal mucosa. For individuals with CRSwNP, the H-score also demonstrated a correlation with subjective olfactory impairment reported by patients ($p = 0.024$).

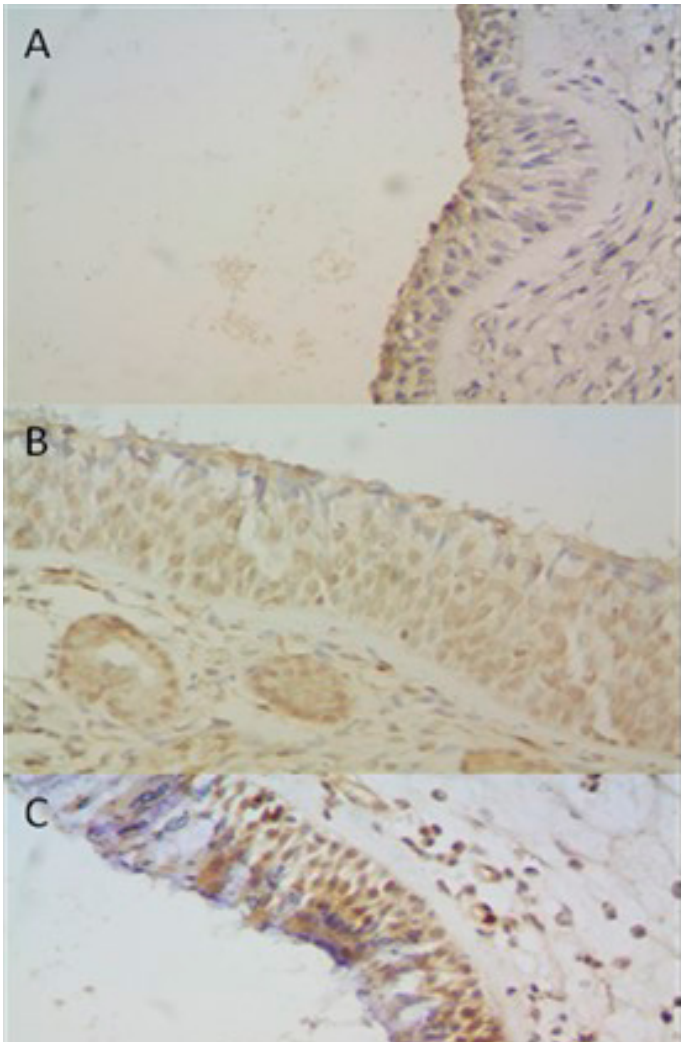

Fig. 1. Immunohistochemical staining of mucosal tissues with anti-TAS2R38 antibodies. Individual photos demonstrate tissue of: A – control patients, B – patients with CRS without polyps, C – patients with CRS with polyps. An increase in the intensity of brown color (DAB) was seen in affected patients.

DISCUSSION

The pathogenesis of CRS covers a range of pathophysiological factors [22]. Despite the lack of research clearly indicating the

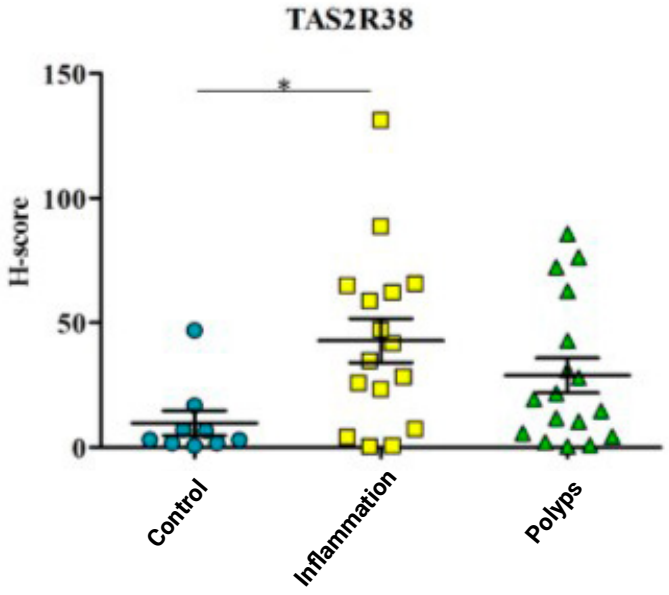

Fig. 2. The H-score of the control group and the study group, including the division into CRS with and without nasal polyps. A relationship was observed between the intensity of the brown color and the incidence of CRS (p = 0.0175).

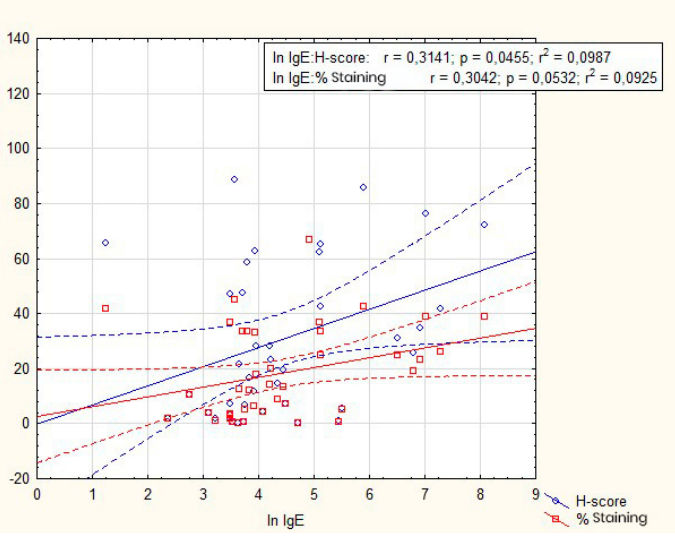

Fig. 3. Logarithmic transformation of data on the relationship of IgE levels to H-score.

heredity of the disease, genetic background in the development of CRS has long been suspected. Some believe that the heredity of inflammatory changes in the sinuses reaches even 14–42% of cases [23, 24]. Genetic material disorders may include: (1) disorders in mucociliary transport [25], (2) gene disorders associated with the mechanism of innate and mixed HLA immunity [26], (3) single nucleotide polymorphisms, including disturbances within newly explored bitter taste receptors – TAS2R38, which also demonstrates expression in the upper respiratory tract mucosa [27].

Our IHC analyses demonstrated statistically significantly elevated TAS2R38 receptor expression in patients with chronic rhinosinusitis and its close correlation with the severity of lesions in CT of the sinuses (high Lund-Mackay score). This result suggests that TAS2R38 is associated with CRS. The explanation for this phenomenon may be one of the functions of the already known TAS2R38 receptors, i.e. mediation in the initiation of mucociliary clearance after pathogens (bacterial fragments) are combined with it. Similar observations were made by Lee and Cohen [12].

In this study, a statistically significant relationship between the expression of TAS2R38 protein in the nasal mucosa and elevated levels of IgE antibodies in the patient's blood serum were also observed (p = 0.04). No studies have been found in the literature regarding such relationships.

In the general population, in patients with CRS the incidence of olfactory disorders is between 30 and 60% [28] and increases up to 95% in patients with CRSwNP [29, 30]. Unfortunately, despite the availability of many olfactometric methods [31], in practice assessment of the sense of smell is time-consuming and cost-intensive, which is why it is performed by ENT specialists occasionally [32]. In the present paper, the Sniffin' Sticks olfactory test was used, which was introduced for diagnosis by Kobal and Hummel in 1997. For the first time in the literature, the conducted analyses also concerned the assessment of the correlation between the presence of the bitter taste receptor in the nasal mucosa and the functioning of the sense of smell. Abnormal smell is one of the symptoms of CRS, which is given increasing attention [34]. The current EPOS consensus [35] mentions it as the main symptom of the disease, along with pain in sinus projection. The relationship between the sense of taste and smell has been known for a long time and it is believed that smell disorders accompany most cases of dysgeusia[36]. In the presented studies it was found that the threshold of perception of smells correlates with the expression of the TAS2R38 receptor and thus – the perception of bitter taste. This relationship was observed in each of the three examined groups. Even in the control group, despite the normal olfactometric outcomes in the Sniffin' Sticks Test, the odor threshold correlated with the expression of TAS2R38 in immunohistochemistry (p = 0.0466). The results of the other two Sniffin' Sticks subtests did not have a significant effect on the expression of the bitter taste receptor in the nasal mucosa. Individual parts of the test – subtests, affect the differentiation of etiology of impaired smell. In 2010, Hedner et al. demonstrated that a worse result of the test of discrimination and odor identification correlates with cognitive impairment [37]. This observation would explain why the two thresholds did not have a substantial relationship with the change in the count of TAS2R38 receptor in patients. Furthermore, the research of Chen et al. conducted in 2019 [38] showed that in the nasal cavity the TAS2R38 receptor is located in the largest number within the rush – near the olfactory area, which might contribute to their interdependence.

Furthermore, considering the joint impact of the severity of inflammatory changes, deviations in the Sniffin' Sticks Test and the severity of the subjective symptoms of CRS (according to EPOS) on the intensity of cell staining (index H-score), a statistically significant increase in the density of the TAS2R38 receptor in the nasal mucosa was found in individuals in whom these factors coexisted.

The research of Lee et al. proved that the TAS2R38 protein is a receptor for bacteria, e.g. Pseudomonas aeruginosa, which activates mucociliary transport after attachment of bacterial cell wall fragments. The same authors report that SNP in this gene correlates with sinusitis caused by Gram-negative bacteria [39]. In our studies we confirmed overexpression of this receptor in patients with CRS.

A debatable issue, which requires further study, is whether the overexpression of TAS2R38 in CRS is a cause or an effect of inflammation. Given its beneficial effect of improving local defense mechanisms against the pathogen, an excess of the receptor may result from the body's response to inflammation. On the other hand, the high presence of the receptor should protect or accelerate the control of inflammation. In order to improve this knowledge, the authors of the presented research began the analysis of the receptor genotype and assessment of single nucleotide polymorphisms (SNP) in the TAS2R38 gene in excess, to determine whether it has a functional – "defensive" or non-functional form. A more detailed analysis of this aspect will further broaden our knowledge of the role of TAS2R38 in the pathophysiology of CRS.

CONCLUSION

1. Patients with CRS have significant TAS2R38 overexpression that correlates with the severity of inflammatory changes in CT of the sinuses;

2. A statistically significant relationship was observed between the expression of TAS2R38 protein in the nasal mucosa and elevated levels of IgE antibodies in the patients' blood serum;

3. Immunohistochemical analysis confirmed the correlation of the high index H-score for TAS2R38 and abnormal perception of smells in the Sniffin' Sticks Test;

4. A statistically significant joint effect of the severity of inflammatory changes, deviations in the Sniffin' Sticks Test and the severity of the subjective symptoms of CRS (according to EPOS) on the intensity of cell staining (index H-score) was found, indicating an increase in the density of the TAS2R38 receptor in the nasal mucosa.

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