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CLINICAL SIGNIFICANCE OF CALCIUM-SENSING RECEPTORS IN THE DEVELOPMENT AND COURSE OF RECURRENT WHEEZING AND ASTHMA IN YOUNG CHILDREN

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The aim of the study: *to evaluate the role of CaSR in the formation and course of recurrent wheezing and asthma in young children.*
Materials and methods: *a total of 70 patients participated in the study, including 20 children (8 boys and 12 girls) diagnosed with mild asthma, 30 patients (20 boys and 10 girls) with recurrent wheezing, and 20 relatively healthy children. The level of CaSR protein in the peripheral blood was measured twice: in the first 2 days of clinical manifestations and in remission. The levels of blood calcium (Ca), phosphorus (P), vitamin D (25(OH) D3) and indicators of cellular, phagocytic and humoral immunity were also studied. The level of CaSR in the blood serum was analyzed by ELISA using commercial kits (CaSR ELISA Kit Human E-EL-H0621, Elabscience, USA, protocol No. 2301070). Statistical processing was performed using StatSoft STATISTICA version 8.0 (Tulsa, Oklahoma) and MedCalc statistical software version 17.2.*
Results: *the lowest levels of CaSR protein were found in the group of children with asthma both during exacerbation and remission, which is associated with its redistribution from peripheral blood to smooth muscle. The level of CaSR protein in the group with recurrent wheezing did not differ during exacerbation and remission, which may be due to the low severity of the obstructive component of this group and the number of obstructions, which, in turn, does not lead to an obvious redistribution of this indicator to the smooth muscle of the bronchi. The level of CaSR protein is obviously the lowest in young children, which is confirmed by correlations. The available correlations with blood electrolytes and IgE confirm the involvement of CaSR protein in phosphorus-calcium metabolism and the development of the inflammatory process of allergic genesis.*
Conclusions: *level of CaSR protein in the serum of children depends on the number of obstructions, their course and severity of the disease. CaSR protein is directly involved in calcium-phosphorus metabolism*
Keywords: *asthma, recurrent wheezing, calcium-sensing receptors, children*

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1. Introduction

Diseases of the respiratory system remain an urgent and widespread problem in pediatrics. Anatomical and physiological features of the respiratory system in young children, impaired immunoregulatory mechanisms, and the prevalence of allergic diseases among these patients are directly related to the frequency and severity of wheezing. Most young children have manifestations of wheezing during the development of acute bronchitis [1, 2]. It is known that about 30 % of babies in the first year of life have suffered wheezing at least once in their lives, and in 20 % of children it has a recurrent course, which eventually develops into another, rather more complex pathology – asthma [3, 4]. This is a chronic respiratory disease manifested by periodic attacks of shortness of breath and wheezing. This pathology not only significantly affects the patient's quality of life, but can also lead to disability or death. Violation of the aspects of asthma diagnosis can lead to underdiagnosis in 54 % of cases and overdiagnosis in 34 % [5, 6]. The issue of asthma diagnosis among young children remains difficult. It is known that the onset of this disease in almost half of the cases occurs in the first 3 years of life, and its manifestations are often identified with symptoms of other pathologies [7, 8]. There is a rather thin line between the development of recurrent wheezing and asthma. The difficulty of establishing the diagnosis of asthma is mainly due to the limitation of some diagnostic manipulations against the background of age-related indicators. Thus, in children under 6 years of age, the diagnosis of asthma can be established only with the help of diagnostic scales that identify patients at risk of developing this pathology. These models include the Clinical Asthma Prediction Score (CAPS) and the Asthma Predictive Index (API) [7, 9].

Components of the immune system play an important role in the structure of allergic inflammation in asthma. Despite the fact that one of the main indicators of allergic asthma is a persistent increase in IgE and eosinophils in the peripheral blood, a whole cascade of immunological reactions occurs. For example, chronic inflammation in asthma is coordinated by type 2 helper T lymphocytes (Th-2), which produce cytokines IL-4 and IL-5, which play a key role in the development of allergic inflammation [10]. It is known that the reaction of the immune system in young children has its own specificity, which cannot but attract attention.

It is now known that disorders of calcium-phosphorus metabolism are often associated with recurrent bronchial obstructive diseases. Some studies indicate an increased content of total and ionized calcium in the peripheral blood in the setting of recurrent and chronic bronchopulmonary diseases [11].

Vitamin D plays an important role in this metabolism, especially in children. For example, it is known that repeated episodes of obstruction in the setting of acute respiratory diseases (ARDs) are also associated with a decrease in serum vitamin D levels [12]. Recently, a direct correlation between changes in vitamin D levels and an increased risk of developing asthma has been reported [13–15].

Against the background of significant problems in the diagnosis of asthma among pediatric patients, the task of finding new triggers for the development of this disease arises. One of these factors is considered to be calcium-sensitive receptors (CaSR). CaSR is a G-protein-coupled receptor that plays a fundamental role in the homeostasis of extracellular calcium (Ca2+), and its role is actively associated with diseases of the kidneys, parathyroid glands, cardiovascular and respiratory systems, including the development of asthma. An increase in CaSR expression was found in rat smooth muscle biopsies with compromised asthma of allergic genesis [16]. It is not find any studies on the study of CaSR protein in the peripheral blood of young children and its possible relationship with the course of bronchial obstructive diseases in the available literature, which attracted our attention.

The aim of the study: to assess the role of CaSR on the formation and course of recurrent wheezing and asthma in young children.

2. Materials and methods

The study was conducted on the basis of the pulmonology department at the Municipal Clinical Children's Hospital No.16 in the period from September 2021 to February 2022. A total of 70 patients were studied, including 20 (8 boys and 12 girls) diagnosed with mild asthma, 30 patients (20 boys and 10 girls) diagnosed with recurrent wheezing and 20 conditionally healthy children aged 3 months to 6 years.

Patients participated in the study if they met the inclusion criteria: informed consent signed by the patient's parents; patient's age from 3 months to 6 years; diagnosis of recurrent wheezing and asthma. The diagnoses were made by a pediatric respiratory specialist, a pulmonologist, in accordance with the protocol for the treatment of children with wheezing No. 18 of January 13, 2005, the protocol for the treatment of children with asthma No. 2856 of December 23, 2021, and the GINA 2020 recommendations. Patients were divided into 2 groups depending on the nosological form of the disease. Group 1 included patients with recurrent wheezing who had a history of up to 3 cases of obstruction, Group 2 – patients admitted to the hospital with a diagnosis of mild asthma.

In patients of all groups, the diagnosis was based on the presence of shortness of breath, dry rales, and cough. The number of obstructions in the anamnesis, the presence of allergic diseases and asthma in the patient, his/her relatives of the first degree of kinship, clinical and laboratory typical manifestations of wheezing, response to specific therapy and clinical improvement within 3 months were analyzed in detail. Patients received specific treatment in accordance with the protocols and global recommendations of GINA 2020. All patients underwent a clinical history, physical examination and laboratory evaluation. Serum CaSR levels were measured.

The level of total blood Ca was determined by the method of complexometric titration; inorganic phosphorus (P) – by the molybdenum acid method (A. A. Pokrovsky, 1974). The levels of indicators were determined twice – in the first 2 days of clinical manifestations of the disease and when remission was achieved.

The study of vitamin D 25(OH) and IgE levels in the blood serum was performed once, by enzyme-linked immunosorbent assay (ELISA), according to the instructions for use of reagent kits. Serum vitamin D levels below 10 ng/ml were considered to be deficient, 10 to 29 ng/ml – insufficient, 30–100 ng/ml – normal, according to the World Health Organization (WHO) recommendations.

IgE levels >60.0 IU/mL were considered elevated in children under 4–5 years of age, and >90.0 IU/mL in children over 6 years of age, according to reference values.

The study of CaSR protein levels in the blood serum of patients with OSA and asthma was performed twice: in the first 2 days of clinical manifestations of the disease and when remission was achieved. Blood samples were taken in the morning using the standard venipuncture technique or from a venous catheter. The level of CaSR in the blood serum was determined by ELISA using commercial kits (CaSR ELISA Kit Human E-EL-H0621, Elabscience, USA, protocol No. 2301070).

Immunological parameters: determination of the level of circulating immune complexes (CIC) by the method of V. Haskova et al. in the modification of Yu. Alfyorov (1978); subpopulations of T- and B-lymphocytes (CD3, CD4, CD8, CD16, CD22) in absolute and relative values by determining them using the diagnostic "NVL Granum" (Ukraine); indicators of phagocytosis (phagocytic neutrophils, phagocytic number and neutrophil activity index) based on the principle of the ability of polymorphonuclear leukocytes and monocytes of peripheral blood to bind on their surface, absorb and digest a microbial test culture, NST test according to Stewart (1975) in modification B. S. Nagoyev (1983)), calculation of the average cytochemical coefficient (ACC) of myeloperoxidase (MP)

content in neutrophils by the Graham-Knoll method and the average cytochemical coefficient of lysosomal cationic proteins (LCP) content by the method of M.G. Shubich (D.V. Belokrinitsky, 1987).

Statistical processing was performed using StatSoft STATISTICA version 8.0 (Tulsa, Oklahoma) and MedCalc version 17.2 statistical software. The Shapiro-Wilk test was used, and the histogram and q-q plot were examined to assess the normality of the distribution. If the distribution of the sample was different from normal, the median (Me) and interquartile range (Lq – lower quartile; Uq – upper quartile) were determined. The two dependent groups were compared using the Wilcoxon test (TW). When comparing two samples, the nonparametric Mann-Whitney U test (MW) was used. The difference in parameters compared by two points was considered statistically significant at $p<0.05$. When comparing indicators characterized by a comparison of more than 2 points, the Kruskal-Wallis (KW) test of analysis of variance was used, and differences were considered significant with the Bonferroni correction. The relationship between the series of indicators was assessed using Spearman's rank correlation (r).

The control group consisted of 20 healthy children (of similar age and gender) who had no manifestations of upper respiratory tract disease or other acute pathology in the last month and who visited the clinic for a routine consultation or vaccination. The study was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the Local Ethics Committee (LEC) for all participants. Parents of all patients and children in the control group were informed about the study and voluntary written informed consent was obtained.

3. Results of the study

The distribution of patients by age and sex in the examined groups of children showed that the number of boys prevailed in patients with recurrent wheezing. The age of patients was Me 2.10 (0.80; 3.00) years. In patients with mild asthma, the number of girls prevailed. The age of patients was Me 4.46 (4.00; 5.00) years.

The analysis of anamnestic data in patients with recurrent wheezing showed that in 6/30 children at least one parent had a diagnosis of asthma. 6/30 children had frequent cases of acute respiratory diseases (ARDs) (more than 5 cases per year), and 2/30 children had suffered from sore throat. Food allergies and manifestations of atopic dermatitis (AD) were noted in 10/30 children, and allergic rhinitis (AR) was diagnosed in 3/30 children.

Analyzing the anamnestic data in patients with mild asthma, it was found that in 14/20 children at least one of the parents suffered from asthma or had manifestations of other allergic diseases. 9/20 children had frequent cases of acute respiratory infections (more than 5 cases per year), and 6/20 patients had a history of sore throat. Food allergy and AD manifestations were present in 12 children. AR was diagnosed in 6/20 patients.

Physical examination of all patients revealed general clinical symptoms of exacerbation of asthma in the form of expiratory dyspnea and dry cough. A box sound was determined over the entire surface of the chest by percussion. Auscultation revealed prolonged exhalation and rigid breathing.

When comparing the groups by age, gender, anamnestic and physiological parameters, a statistically significant difference was found.

When comparing the indicators in the groups with recurrent wheezing and asthma, it was found that the highest level of IgE was in patients with asthma. Analysis of these immunological parameters revealed that the levels of CD3 %, CD4 %, CD8abs, CD8 %, CD16 %, CD4/CD8, phagocytic count (PC), lysosomal cationic proteins (LPC, CK) were significantly high in the group with recurrent wheezing and asthma (Table 1).

Table 1

Clinical and laboratory characteristics of patients with recurrent wheezing and mild asthma

Sign	Group 1 (recurrent wheezing) (n=30)	Group 2 (mild asthma) (n=20)	p
1	2	3	4
Gender, M/F	66.7 % (20/10)	40 % (8/12)	p<0.05
Age (years), Me (Lq; Uq)	2.10 (0.80; 3.00)	4.46 (4.00; 5.00)	p<0.05
Weight (kg), Me (Lq; Uq)	12.750 (8.60; 14.50)	17.00 (16.40;17.85)	p<0.05
Height (cm), Me (Lq; Uq)	87.00 (70.00; 96.00)	107.50 (103.00; 110.00)	p<0.05
Heart rate (per min.), Me (Lq; Uq)	108.00 (96.00; 120.00)	102.00 (99.00; 106.00)	p>0.05
Breathing rate (per min.), Me (Lq; Uq)	26.00 (24.00; 32.00)	24.00 (22.00; 24.00)	p<0.05
Body temperature (°C), Me (Lq; Uq)	37.00 (36.60;37.50)	36.60 (36.50; 36.70)	p<0.05
Positive family allergic history and asthma in relatives	20 % (6/30)	70 % (14/20)	p<0.05
Frequent acute respiratory diseases	20 % (6/30)	35 % (7/20)	p<0.05
History of sore throat in the past	6.7 % (2/30)	5 % (1/20)	p<0.05
Presence of atopic dermatitis and food allergy in children	33.3 % (10/30)	60 % (12/20)	p<0.05
Localized form of atopic dermatitis (among children with atopic dermatitis)	7/10	9/12	p<0.05

Continuation of Table 1

1	2	3	4
Generalized form of atopic dermatitis (among children with atopic dermatitis)	3/10	3/12	p<0.05
Positive allergic rhinitis in children	10 % (3/30)	30 % (6/20)	p<0.05
Seasonal course of allergic rhinitis (among children with positive allergic rhinitis)	1/3	4/6	p<0.05
Year-round allergic rhinitis (among children with positive allergic rhinitis)	2/3	2/6	p<0.05
Ig E increase, IU/ml Me (Lq; Uq)	41.75 (27.00;66.00)	700.00 (320.00; 877.00)	p<0.05
CD3,(%)	64.00 (47.00; 68.00)	69.00 (64.00: 71.00)	
KW: H=8.424. (p=0.014). MW: p_{1-2}=0.004. $p_{к-1}$=0.414. $p_{к-2}$=0.047			
CD4.(%)	45.50 (37.00; 55.00)	39.00 (37.50; 40.00)	
KW: H=25.393 (p<0.01). MW: p_{1-2}=0.024. $p_{к-1}$=0.000. $p_{к-2}$=0.000			
CD8. abs.	0.80 (0.70; 1.00)	1.15 (0.90;)	
KW: H=25.629 (p<0.01). MW: p_{1-2}=0.000. $p_{к-1}$=0.414. $p_{к-2}$=0.244			
CD8. (%)	26.00 (0.70; 1.00)	41.00 (31.00; 44.00)	
KW: H=29.267 (p<0.01). MW: p_{1-2}=0.000. $p_{к-1}$=0.010. $p_{к-2}$=0.000			
CD16. (%)	40.00 (19.00; 46.00)	25.50 (17.50; 33.00)	
KW: H=29.267 (p<0.01). MW: p_{1-2}=0.020. $p_{к-1}$=0.010. $p_{к-2}$=0.000			
CD4/ CD8 (IRI)	1.80 (1.30; 2.50)	1.10 (1.00: 1.35)	
KW: H=19.526 (p<0.01). MW: p_{1-2}=0.000. $p_{к-1}$=0.004. $p_{к-2}$=0.015			
Phagocyte count (PC)	3.50 (3.20; 4.20)	3.00 (2.80; 3.85)	
KW: H=31.114 (p<0.01). MW: p_{1-2}=0.025. $p_{к-1}$=0.000. $p_{к-2}$=0.000			
Lysosomal cationic proteins	1.16 (0.89; 1.23)	1.28 (1.21;1.39)	
KW: H=50.719 (p<0.01). MW: p_{1-2}=0.000. $p_{к-1}$=0.000. $p_{к-2}$=0.000			

Note: the table includes indicators of cellular, humoral and phagocytic immunity, which had a statistically significant difference when compared between groups

3. 1. Statistical analysis of phosphorus-calcium metabolism and CaSR protein

In the statistical analysis, no differences were found between the levels of Ca in the peripheral blood in the groups of children with recurrent wheezing and asthma both during the period of clinical manifestations and in remission. In the pairwise comparison, no significant difference was found in the groups. The serum Ca level was significantly lower in the groups of patients with recurrent wheezing and asthma both during the acute phase of the disease and in remission than in the control group.

Statistical analysis of P levels in the peripheral blood of children with asthma and recurrent wheezing showed a significant difference both in the acute and remission periods. The level of the index is significantly higher in patients with recurrent wheezing both in the period of acute and remission than in children of the control group. The level of this indicator is significantly higher in patients with asthma in the acute period than in the remission period.

Statistical analysis using the Kruskal-Wallis test revealed that the H criterion for CaSR protein was significantly high both during the period of disease manifestation (H=55.806; p<0.01) and during remission (H=43.185; p<0.01), and the level of this parameter depends on the patient's belonging to one or another group. The level of CaSR protein in the blood serum was significantly lower in children with recurrent wheezing and asthma than in control both during the disease flare and in remission. Its lowest value was observed in patients with asthma both during the disease's acute phase and in remission. No significant difference was found in patients with recurrent wheezing and asthma in remission. A pairwise comparison of the index revealed that the level of CaSR protein in the blood serum of patients with asthma is significantly lower at the stage of disease manifestation, while in patients with recurrent wheezing no significant difference was found.

Statistical analysis of vitamin D (25(OH)D3) levels in the blood serum in the group with recurrent wheezing and asthma showed no significant difference between the groups. The level of vitamin D was not significantly different in the group with recurrent wheezing compared to the control group. The level of 25(OH)D3 was significantly lower in patients with asthma than in control (Table 2).

Table 2

Statistical data of phosphorus-calcium metabolism and CaSR protein levels in groups during the disease and in remission, Me (Lq; Uq)

Groups	In clinical manifestations	In remission	TW
	Ca blood serum (mmol/l)		-
Group 1 (recurrent wheezing) n=(30)	2,10 (1,90; 2,30)	2,13 (1,90; 2,30)	p>0,05
Group 2 (mild asthma) n=(20)	2,20 (2,00; 2,36)	2,20 (2,10; 2,35)	p>0,05
Control n=(20)	2,40 (2,27;2,53)		
	KW: H=17,014, (p<0,01) MW: p_{1-2}=0,550, $p_{к-1}$=0,002, $p_{к-2}$=0,002	KW: H=15,789, (p<0,01) MW: p_{1-2}=0,287, $p_{к-1}$=0,000, $p_{к-2}$=0,002	
	P blood serum (mmol/l)		
Group 1 (recurrent wheezing) n=(30)	1,40 (1,10; 1,70)	1,60 (1,40;1,80)	p>0,05
Group 2 (mild asthma) n=(20)	1,39 (1,20; 1,47)	1,25 (1,15:1,40)	p<0,05
Control n=(20)	1,26 (1,13; 1,38)		-
	KW: H=4,425, (p=0,109) MW: p_{1-2}=0,014, $p_{к-1}$=0,053 $p_{к-2}$=0,142	KW: H=20,175, (p=0<0,01) MW: p_{1-2}=0,000, $p_{к-1}$=0,000 $p_{к-2}$=0,827	-
	CaSR protein blood serum (ng/ml)		
Group 1 (recurrent wheezing) n=(30)	5,98 (4,31;6,55)	5,95 (4,28; 6,67)	p>0,05
Group 2 (mild asthma) n=(20)	2,89 (2,28; 3,51)	5,04 (4,47; 5,48)	p<0,05
Control n=(20)	13,31 (12,34; 13,90)		-
	KW: H=55,806 (p<0,01), MW: p_{1-2}=0,000, $p_{к-1}$=0,000, $p_{к-2}$=0,000	KW: H=43,185 (p<0,01), MW: p_{1-2}=0,178, $p_{к-1}$=0,000, $p_{к-2}$=0,000	
	25(OH) D3 blood serum (ng/ml)		
Group 1 (recurrent wheezing) n=(30)	28,00 (26,62; 30,00)		-
Group 2 (mild asthma) n=(20)	27,35 (24,75; 29,20)		-
Control n=(20)	30,00 (27,50; 31,50)		-
	KW: H=5,829, (p<0,01) MW: p_{1-2}=0,376, $p_{к-1}$=0,143, $p_{к-2}$=0,013		-

3. 2. Correlation relationships

Significant correlations were found in patients with recurrent wheezing (n=30) between CaSR protein and patients' age (r=0.77), body weight (r=0.71), height (r=0.73), heart rate (r=-0.68), breath rate (r=-0.71), (p<0.05). In patients with asthma, correlations were found between serum CaSR protein and serum IgE (r=0.70), phagocytic number (r=-0.64), (p<0.05). In the control

group, there were significant correlations of serum CaSR protein with the level of total serum Ca (r=-0.70).

4. Discussion of the study results

The study of CaSR and its role in the development of certain pathologies remains an urgent issue today. In particular, its role in the development of broncho-obstructive diseases. In the study of bronchial smooth muscle biopsies, it was found that the level of CaSR increases in the asthmatic state and promotes the proliferation of airway smooth muscle cells to further trigger their contractility, playing a significant role in the development of asthma in adulthood [16–18].

The question of CaSR expression in children with bronchial obstructive diseases arises. Our study examined the protein component of CaSR in the serum of children. It was found that the level of CaSR protein in asthma at the stage of the disease's acute onset was the lowest, which, in our opinion, may be due to its redistribution to the smooth muscle of the bronchi. When patients achieved remission, its level increased slightly and approached the level of patients with recurrent wheezing. Moreover, there was no difference between CaSR protein in recurrent wheezing during the disease's acute phase and in remission. This fact, in our opinion, is associated with the frequency of obstructions, chronicity of the process, and the possible effect of inhalation therapy. It seems possible that children with frequent episodes of asthma during its exacerbation have a kind of abnormal expression or function of CaSR, as indicated by other studies [19].

Our study showed a direct dependence of serum CaSR protein levels on age parameters and physical development data (body weight, height) in patients with recurrent wheezing, which was confirmed by direct correlations. Such results, in our opinion, are related to the existing relationship between the growing child's body and the possible expression of CaSR, i.e., in children, the level of receptor expression is most likely lower than in adults at the stage of maturation.

When studying the level of CaSR protein in the blood serum of children in the acute period of recurrent wheezing, a significant negative correlation with serum P was found, which may indicate the effect of P on CaSR as an antagonist [20]. Based on the above, it is obviously fair to consider the disruption of calcium-phosphorus metabolism in patients with the formation of a negative correlation between P and CaSR, since the level of calcium in the blood serum during the acute period of recurrent wheezing is probably lower than normal with an increased value of serum P.

The presence of a significant correlation between serum CaSR protein levels and serum IgE immunoglobulin in children in the acute period of asthma is noteworthy. In our opinion, this is due to the complete direct interaction of these indicators. According to our data, in patients with asthma during the exacerbation period, the level of CaSR protein in the blood was recorded significantly lower than its level, and serum IgE levels were quite high relative to the norm, both in the acute and in the period of improvement of the disease. These results have been confirmed by other scientific data.

Practical significance: our study showed that the level of CaSR in children's serum significantly decreases during asthma exacerbations and increases during remission to levels similar to those of patients with recurrent wheezing. This, in turn, may be important for predicting asthma exacerbations and the formation of asthma. These observations are important for further examination and treatment of patients.

Limitations of the study: the small sample size is another limitation of this study, as it may make it difficult to determine the accuracy of the study findings.

The impact of martial law conditions: military actions prevented the involvement of more patients in the study.

Prospects for further research: our study showed the possible involvement of the CaSR protein in the onset and development of obstruction, and its interaction with other indicators points to new possible pathogenetic mechanisms of asthma.

5. Conclusions

The lowest levels of CaSR protein in the blood serum were found in patients with asthma both during exacerbation and remission, which is obviously associated with its redistribution from the peripheral blood to the bronchial smooth muscle.

The level of CaSR protein in patients with recurrent wheezing did not differ during exacerbation and remission, which may be due to the low severity of the obstructive component of this group and the number of obstructions, which, in turn, does not lead to an obvious redistribution of this indicator to the smooth muscle of the bronchi.

The level of CaSR protein in the blood serum is obviously the lowest in young children, which is confirmed by the existing significant correlation with age and body weight. The existing correlations with blood electrolytes and IgE indicate the involvement of CaSR protein in phosphorus-calcium metabolism and the development of the inflammatory process of allergic genesis.

Conflict of interest

The authors declare that they have no conflict of interest in relation to this research, whether financial, personal, authorship or otherwise, that could affect the research and its results presented in this article.

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Data availability

Data will be provided upon reasonable request

Using artificial intelligence tools

The authors confirm that they did not use artificial intelligence technologies in the creation of the presented work.

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