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Calcium-sensing receptor protein as a prognostic predictor of asthma formation and exacerbation in young children

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Asthma remains the most common non-communicable disease among children, which often has a chronic course and leads to disability. Particular attention should be paid to the diagnosis of asthma in young children. To date, the calcium-sensing receptor (CaSR) is considered to be one of the specific markers in the development of bronchial obstructive diseases.

Purpose — to assess the level of CaSR protein and its significance in preschool children with asthma.

Materials and methods. The study included 37 patients divided into 3 groups. The Group 1 — children with mild persistent asthma (n=20), the Group 2 — children with moderate persistent asthma (n=17), the Group 3 — almost healthy children (n=20). The study of CaSR protein levels in the blood serum of patients with asthma was performed twice — in the first 2 days of clinical manifestations of the disease and when remission was achieved. The level of CaSR protein in the blood serum was analyzed by enzyme-linked immunosorbent assay (ELISA). All statistical analyses were performed using StatSoft STATISTICA version 8.0 (Tulsa, Oklahoma) and MedCalc version 17.2 statistical software.

Results. There was no significant difference in CaSR protein levels between the Group 1 and the Group 2. The level of CaSR protein was significantly lower in the Group 1 and the Group 2 both in the period of acute and remission than in the control group. The level of the marker in the period of disease flare-up in the Group 1 and the Group 2 was significantly lower than in children of the same groups in the period of remission.

Conclusions. In all patients with asthma, the level of CaSR protein at the acute stage of the disease is lower than at the remission stage, which is obviously associated with its redistribution from the peripheral blood to the smooth muscle of the lungs.

The research was carried out in accordance with the principles of the Helsinki Declaration. The study protocol was approved by the Local Ethics Committee of the participating institution. The informed consent of the patient was obtained for conducting the studies.

No conflict of interests was declared by the authors.

Keywords: asthma, calcium-sensitive receptor protein, calcium metabolism, children.

Білок кальцій-чутливого рецептора як прогностичний предиктор формування та загострення бронхіальної астми в дітей молодшого віку

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Найпоширенішою неінфекційною хворобою серед дитячого населення залишається бронхіальна астма (БА), що досить часто має хронічний перебіг і призводить до інвалідизації. Особливу увагу слід приділяти діагностуванню БА в дітей молодшого віку. На сьогодні серед специфічних маркерів у розвитку бронхообструктивних захворювань розглядають кальцій-чутливі рецептори (CaSR).

Мета — оцінити рівень білка CaSR та його значення в дітей дошкільного віку, хворих на БА.

Матеріали та методи. До дослідження залучено 37 пацієнтів, яких поділено на три групи. Група 1 — діти з БА легкого персистуючого перебігу (n=20), Група 2 — діти з БА середнього персистуючого перебігу (n=17), Група 3 (контрольна) - практично здорові діти (n=20). Дослідження рівня білка CaSR у сироватці крові пацієнтів, хворих на БА, проведено двічі — у перші дві доби клінічних проявів захворювання та після досягнення ремісії. Рівень білка CaSR у сироватці крові проаналізовано методом імуноферментного аналізу. Усі статистичні аналізи виконано за допомогою пакетної програми «StatSoft STATISTICA» версії 8.0 (Талса, Оклахома) і статистичного програмного забезпечення «MedCalc» версії 17.2.

Результати. Вірогідної різниці рівня білка CaSR між Групами 1 і 2 не виявлено. Рівень білка CaSR був вірогідно нижчим у Групах 1 і 2 як у період розпалу, так і в період ремісії, ніж у групі контролю. Рівень показника в період розпалу захворювання в Групах 1 і 2 був достовірно нижчим, ніж у дітей тих самих груп у період ремісії.

Висновки. У всіх пацієнтів із БА рівень білка CaSR на етапі розпалу захворювання нижчий, ніж на етапі ремісії, що очевидно пов'язано з його перерозподілом із периферичної крові до гладенької мускулатури легень.

Дослідження виконано відповідно до принципів Гельсінської декларації. Протокол дослідження ухвалено Локальним етичним комітетом зазначеної в роботі установи. На проведення досліджень отримано інформовану згоду пацієнтів.

Автори заявляють про відсутність конфлікту інтересів.

Ключові слова: бронхіальна астма, білок кальцій-чутливих рецепторів, кальцієвий обмін, діти.

Introduction

Asthma remains one of the most common non-communicable diseases among children worldwide, which often leads to disability, significantly affects the quality of life of a sick child and the moral and psychological state of they family [6,15]. According to epidemiologic studies, the prevalence of this disease in the world ranges from 1% to 18%, and among children — from 5% to 10%. The proportion of asthma in all respiratory pathology ranges from 0.6% to 2%. According to the Center for Medical Statistics of the Ministry of Health of Ukraine, in recent years, the incidence of asthma in children has been ranging from 0.6–0.5%, which, in particular, indicates the problem of underdiagnosis of the disease [2]. In Ukraine, this disease ranks 4th in the structure of total disability among children aged 10–14 years [10,17].

Asthma is a heterogeneous disease with different mechanisms of development, but the main component is the inflammatory process. Depending on this, four ways of developing this disease can be distinguished: eosinophilic, neutrophilic, mixed granulocytic, and eosinophilic-granulocytic [11]. Particular attention should be paid to the diagnosis of asthma in young children, which is quite a challenge. To date, researchers propose to consider asthma in terms of vitamin D and calcium metabolism disorders, which is of great importance in the mineral metabolism of young children. Recent experiments have shown a link between vitamin D deficiency and an increased risk of developing asthma [4,7]. It has been reported that a decrease in serum 25-hydroxyvitamin D (25(OH)D) levels correlates with an increase in the prevalence of the disease, hospitalization, and the number of emergency room visits, as well as worsening lung function and increased airway hypersensitivity in children with asthma [1].

Currently, research is ongoing to identify specific markers of obstructive respiratory disease, with the calcium-sensing receptor (CaSR) playing an important role. The CaSR is a unique G-protein-coupled receptor (GPCR) that is activated by extracellular Ca^{2+} and other physiological cations, including Mg^{2+}, amino acids, and polyamines. Being the main controller of the extracellular Ca^{2+} homeostatic system, it is expressed at high levels in the parathyroid gland, kidneys, intestines and bones, regulates the secretion of parathyroid hormone (PTH), vitamin D synthesis, secretion of digestive hormones, airway constriction, cardiovascular effects, cell differentiation and proliferation, as well as Ca^{2+} uptake and resorption, respectively [5,8,13]. According to a study, CaSR expression in human bronchial biopsies and in mouse interlobular bronchi is increased during asthma [19]. To date, there are no data on the study of this indicator in the peripheral blood of children with asthma, which drew our attention to this study.

The ***purpose*** of the study — to evaluate the level of CaSR protein and its value in preschool children with asthma.

Materials and methods of the study

A cohort prospective study was conducted at the Municipal Clinical Children's Hospital No. 16 Kharkiv City Council based on the pulmonology department in the period from September 2021 to February 2022, which included children with persistent asthma of mild to moderate severity who were treated and examined in the clinic.

Inclusion criteria: informed consent signed by the patient's parents; patient's age from 1 to 6 years; diagnosis of asthma. Exclusion criteria: acute and chronic nonspecific upper respiratory tract disease; bronchopulmonary dysplasia; congenital malformations of the lungs and bronchial tree; secondary lung damage in the setting of diffuse connective tissue diseases, neoplasms of any localization.

The study included 37 patients aged 4 to 6 years, including 15 boys and 22 girls who met the inclusion criteria and had no exclusion criteria. The diagnosis of asthma was made by a pediatric respiratory specialist-pulmonologist, according to the GINA 2020 guidelines. All patients were diagnosed with persistent asthma of mild to moderate degree, with a mild to moderate attack. Depending on the age of the patients and the clinical course of asthma, they were divided into 2 groups (the Group 1 — children under 5 years of age with persistent mild asthma, the Group 2 — over 5 years of age with moderate asthma).

In children under 5 years of age, the diagnosis was based on the presence of shortness of breath, dry wheezing and cough, allergic diseases in history, allergen sensitization, asthma in history in first-degree relatives, response to bronchodilators and clinical improvement within 3 months while receiving specific therapy. In patients over 5 years of age, the diagnosis of asthma was based

on typical respiratory symptoms and pulmonary function tests. Patients received specific treatment according to the global GINA 2020 guidelines. All patients underwent a clinical history, physical examination, and laboratory evaluation.

The study of serum 25(OH)D and IgE levels was performed once, by enzyme-linked immunosorbent assay (ELISA), according to the instructions for use of reagent kits. 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 serum 25(OH)D level below 10 ng/ml was considered a deficiency, 10 to 29 ng/ml — insufficiency, 30–100 ng/ml — normal, according to the World Health Organization (WHO) recommendations.

The study of CaSR protein levels in the blood serum of patients with 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 analyzed by ELISA using commercial kits (CaSR ELISA Kit Human E-EL-H0621, Elabscience, USA, protocol No. 2301070).

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. Parents of all patients and children in the control group were educated about the study and voluntary written informed consent was obtained.

All statistical analyses were performed using StatSoft STATISTICA version 8.0 (Tulsa, Oklahoma) and MedCalc version 17.2 statistical software. Nonparametric methods were used. The median (Me) and interquartile range (Lq — lower quartile; Uq — upper quartile) were determined. The Mann–Whitney U test (MW) was used to compare two samples. The difference in parameters was considered statistically significant at $p<0.05$. The H criterion of the Kruskal–Wallis analysis of variance (KW) was used. For the comparison of indices of dependent samples, the Wilcoxon non-parametric criterion (t test) was used. Receiver operating characteristic (ROC) curves were drawn for the variables to determine the optimal cutoff values for endpoint prediction. For ROC analysis, an area under the curve (AUC) of 1.0 indicates perfect discrimination, while an area of 0.5 indicates that the test discriminates no better than by chance.

Results and discussion

The distribution of patients by age and gender in the examined groups of children did not show a statistically significant difference.

Physical examination of patients in both groups revealed general clinical symptoms of asthma exacerbation in the form of mild expiratory dyspnea and dry cough. The percussion was determined over the entire surface of the chest. Auscultation revealed prolonged exhalation and rigid breathing. The anamnestic data did not have a statistically significant difference in the groups. No significant difference was found in the comparison of laboratory parameters in the groups (Table 1).

Levels of Ca and 25(OH)D in blood serum

The analysis of calcium metabolism revealed that the level of Ca in the Group 1 during the acute phase of the disease and in remission was almost the same and amounted to Me 2.20 (2.00; 2.36) mmol/l, 2.20 (2.10; 2.35) mmol/l, respectively. The level of Ca in the Group 2 during the period of disease and in remission was Me 2.10 (2.00; 2.22) mmol/L, 2.20 (2.00; 2.22) mmol/L and did not differ significantly. In the control group, this figure was 2.40 (2.27; 2.53) mmol/L. Statistical processing using the Kruskal–Wallis test revealed that the H criterion for Ca was significantly high in children during the clinical manifestations ($H=16.805$; $p<0.01$) and in remission ($H=16.909$; $p<0.01$), and the level of this parameter depended on the patient's belonging to one group or another.

The level of 25(OH)D in the Group 1 and the Group 2 was Me 27.35 (24.75; 29.20) IU/mL, 27.50 (26.40; 29.00) IU/mL, respectively, and was lower than in the control group Me 30.00 (31.50; 27.50) IU/mL. Statistical analysis using the Kruskal–Wallis test revealed that the H criterion for 25(OH)D in the Group 1 and the Group 2 ($H=7.88$; $p>0.05$) was statistically insignificant. When comparing the values of Ca and 25(OH)D in pairs, no significant difference was found between the Group 1 and the Group 2 ($p<0.05$). The level of these parameters was significantly lower in the Group 1 and the Group 2, both during the acute and remission periods, than in the control group ($p<0.05$). The level of Ca and 25(OH)D in the period of disease in the Group 1 and the Group 2, and in the same groups in the period

Table 1

The main group clinical and laboratory data

Sign	The Group 1 (<5 years old) (n=20)	The Group 2 (>5 years old) (n=17)	Control (n=20)	p
Gender, M/F	8/12	7/10	9/11	p>0.05
Age, years at recruitment Me (Lq; Uq)	4.46 (4.00; 5.00)	5.88 (5.80; 6.00)	4,00 (3.25; 4.75)	p>0.05
Presence of atopic dermatitis and food allergy in children	12/20	11/17	–	p=0.3321 p>0.05
Localized form of atopic dermatitis (among children with atopic dermatitis)	9/12	8/11	–	–
Generalized form of atopic dermatitis (among children with atopic dermatitis)	3/12	3/11	–	–
Positive family allergic history and asthma in relatives	14/20	12/17	15% (3/20)	p>0.05
Positive allergic rhinitis in children	6/20	6/17	–	p>0.05
Seasonal course of allergic rhinitis (among children with positive allergic rhinitis)	4/6	4/7	–	–
Year-round allergic rhinitis (among children with positive allergic rhinitis)	2/6	3/7	–	–
Body temperature (degrees Celsius)	36.75 (36.60; 37.00)	36.70 (36.60; 36.80)	36.60 (36.50; 36.60)	–
Heart rate (beats per minute)	102.00 (99.00; 107.00)	102.00 (100.00; 106.00)	99.00 (98.00; 105.00)	–
Breathing rate (per minute)	24.00 (22.00; 26.00)	24.00 (22/00; 26.00)	22.00 (20.00; 24.00)	–
Peripheral oxygen saturation (SpO_2), (%)	97.00 (96.00; 98.00)	97.00 (96.00; 98.00)	99.00 (99.00; 100.00)	–
High eosinophil blood parameters, (more than 5%)	50% (10/20)	53% (9/17)	–	–
IgE increase, IU/ml Me (Lq; Uq)	700.00 (320.00; 877.00)	690.00 (280.00; 816.00)	–	–

Table 2

Serum CaSR protein level (ng/ml) in children with asthma during the period of clinical manifestations and in remission, (Me (Lq; Uq)

Groups	CaSR in clinical manifestations	CaSR in remission	TW
The Group 1 (<5 years) n=20	2.89 (2.28; 3.51)	5.04 (4.47; 5.48)	p<0.001
The Group 2 (>5 years) n=17	3.00 (2.41; 3.21)	5.50 (5.11; 5.81)	p<0.001
Control n=20	13.31 (12.34; 13.90)	13.31 (12.34; 13.90)	–
	KW: H=38.308; p<0.001 MW: p_{1-2}>0.05 $p_{1\text{-control}}$<0.001 $p_{2\text{-control}}$<0.001	KW: H=38.759; p<0.001 MW: p_{1-2}>0.05 $p_{1\text{-control}}$<0.001 $p_{2\text{-control}}$<0.001	–

Notes: KW — the Kruskal–Wallis analysis of variance; MW — the Mann–Whitney U test; H — is an indicator of the result of statistical calculation by the Kruskal–Wallis method; TW — Wilcoxon non-parametric criterion (pairs test).

of remission did not have a significant difference (p<0.05).

CaSR level in blood serum

Statistical analysis using the Kruskal–Wallis test revealed that the H criterion for CaSR protein was significantly high in children during the clinical manifestations (H=38.308; p<0.001) and in remission (H=38.759; p<0.001), and the level of this parameter depends on the patient's belonging to one group or another.

The level of CaSR protein was significantly lower in the Group 1 and the Group 2 both during the acute and remission periods than in the control group. The level of CaSR protein in the period of disease in the Group 1 and the Group 2 was significantly lower than in children of the same groups in the period of remission (Table 2).

Predictive range

In predicting the risk of developing asthma, it was found that CaSR protein levels below 6.508 ng/ml in the serum of patients may indicate the probable formation of asthma (Fig. 1). If the level of this indicator is less than 4.008 ng/ml, there is a risk of developing an exacerbation of asthma (Fig. 2).

CaSR as an integral membrane protein in the development of asthma has been studied recently.

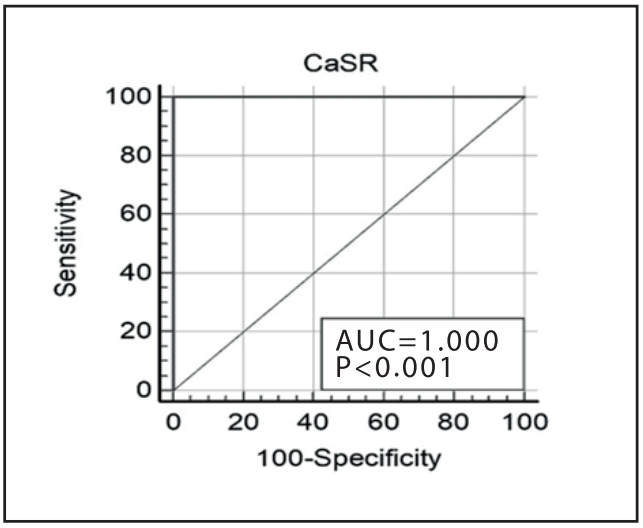

Fig. 1. Prognostic criteria for the formation of asthma in children

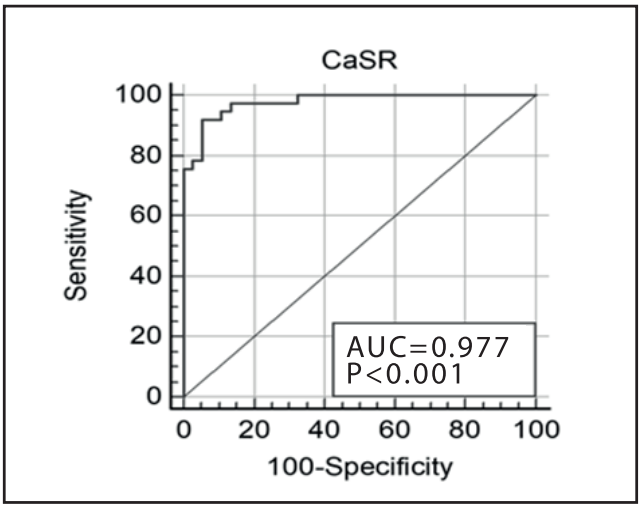

Fig. 2. Predictive criteria for the risk of asthma exacerbation in children

It is known to be involved in the development of human embryonic lung tissue [3]. Currently, there are studies confirming an increase in the expression of this indicator in smooth muscle biopsy in a mouse model of albumin-induced asthma and in humans. It has been proven that the level of CaSR increases in the asthmatic state in airway smooth muscle cells and targets locally produced polycations to cause hypersensitivity and inflammation [15,16]. Researchers have also shown that CaSR promotes the proliferation of airway smooth muscle cells to further trigger their contractility, thus participating in the development of asthma in adulthood [17].

In our study, the level of CaSR protein was significantly reduced during the disease's peak. It can be assumed that this is due to a certain redistribution of CaSR protein in the peripheral blood and, thus, its possible increase in bronchial smooth muscle cells [16], since CaSR is known to be actively involved in the inflammatory process [9].

The high levels of CaSR protein in the serum of the control group of patients may indicate a decrease in its expression in the smooth muscle bronchi in children without a history of obstruction and its redistribution to the peripheral blood. This result was confirmed in a study that showed that in adult patients with asthma and mice sensitized to allergens, more CaSR was detected in the smooth muscle bronchial epithelium than in healthy subjects [18].

A large number of studies have been conducted on CaSR gene mutation and its functions associated with calcitropic organs, such as the parathyroid gland [8]. Abnormal expression and function of CaSR is associated not only with calcitropic disorders, such as hyper- and hypoparathyroidism, but also with diseases related to non-calcitropic systems, such as the nervous, reproductive, and respiratory systems, and even with diseases such as chronic inflammation and cancer [12]. It is possible that some genetic mutations or the immaturity of CaSR itself can lead to a decrease or increase in its serum levels in children.

The relationship of CaSR not only with extracellular Ca but also with vitamin D remains important [5]. In our study, there was a slight decrease in the level of Ca in the blood of children with asthma compared to the control group. Vitamin D deficiency was observed to a greater extent in children with asthma. These findings can be attributed to the age of patients, when there is an increased metabolism at the stage of active growth. On the other hand, an active inflammatory process in asthma exacerbation is accompanied by Ca accumulation in bronchial smooth muscle along with CaSR activation, which can also lead to a decrease in peripheral blood Ca in a growing body.

Currently, there are no available literature data on the role of CaSR protein in the development and course of asthma in children.

The performed ROC analysis allowed us to determine which levels of CaSR protein in the blood serum can predict exacerbation of asthma or its development, and had prognostic significance.

Conclusions

In all patients with asthma, the serum CaSR protein level at the acute stage of the disease is lower than at the remission stage, which is obviously due

to its redistribution from the peripheral blood to the smooth muscle of the lungs.

The lowest levels of CaSR protein in the blood serum of patients with asthma at the acute stage of the disease compared to the remission period and the control group. The decrease in inflammation and bronchial obstruction is accompanied by a slight increase in CaSR protein in the peripheral blood. The highest levels of CaSR protein in peripheral blood may confirm the absence of an inflammatory and bronchial obstructive component in bronchial smooth muscle.

In our opinion, the concentration of the index in the blood serum of children with asthma below CaSR protein <6.508 ng/ml can be considered as an additional marker of asthma formation, and CaSR protein <4.008 ng/ml as a marker of the risk of developing the disease.

Prospects for further research

Our study has shown that the level of CaSR protein in the blood serum of children significantly decreases during exacerbations of asthma. This, in turn, may be important in predicting the exacerbation and formation of asthma. These observations are important for further examination and treatment of patients.

No conflict of interests was declared by the authors.

Gratitude

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REFERENCES/ЛІТЕРАТУРА

1. Ali NS, Nanji K. (2017, May 29). A Review on the Role of Vitamin D in Asthma. Cureus. 9 (5): e1288. doi: 10.7759/cureus.1288.
2. Antypkin YuH, Chumachenko NH, Umanets TR, Lapshyn VF. (2016). Analiz zakhvoriuvanosti ta poshyrenosti bronkhialnoi astmy v ditei riznykh vikovykh hrup po rehionakh Ukrainy. Perynatolohyia y pedyatryia. 1 (65): 95–99. [Антипкін ЮГ, Чумаченко НГ, Уманец ТР, Лапшин ВФ. (2016). Аналіз захворюваності та поширеності бронхіальної астми в дітей різних вікових груп по регіонах України. Перинатология и педиатрия. 1 (65): 95–99].
3. Brennan SC, Wilkinson WJ, Tseng HE, Finney B, Monk B, Dibble H, Quilliam S, Warburton D, Galietta LJ, Kemp PJ, Riccardi D. (2016, Feb 25). The extracellular calcium-sensing receptor regulates human fetal lung development via CFTR. Sci Rep. 6: 21975. doi: 10.1038/srep21975.
4. Carroll KN, Gebretsadik T, Larkin EK, Dupont WD, Liu Z, Van Driest S, Hartert TV. (2011, Sep). Relationship of maternal vitamin D level with maternal and infant respiratory disease. Am J Obstet Gynecol. 205 (3): 215.e1–7. doi: 10.1016/j.ajog.2011.04.002. Epub 2011 Apr 13.
5. Díaz–Soto G, Rocher A, García–Rodríguez C, Núñez L, Villalobos C. (2016). The Calcium–Sensing Receptor in Health and Disease. Int Rev Cell Mol Biol. 327: 321–369. doi: 10.1016/bs.ircmb.2016.05.004. Epub 2016 Jun 25.
6. Global Initiative for Asthma (GINA). (2020). The Global Strategy for Asthma Management and Prevention. URL: https://www.ginasthma.org. [Last accessed at: 01.06.2020].
7. Hall SC, Fischer KD, Agrawal DK. (2016, Feb). The impact of vitamin D on asthmatic human airway smooth muscle. Expert Rev Respir Med. 10 (2): 127–135. doi: 10.1586/17476348.2016.1128326. Epub 2015 Dec 28.
8. Hannan FM, Kallay E, Chang W, Brandi ML, Thakker RV. (2018, Dec). The calcium-sensing receptor in physiology and in calcitropic and noncalcitropic diseases. Nat Rev Endocrinol. 15 (1): 33–51. doi: 10.1038/s41574-018-0115-0.
9. Hendy GN, Canaff L. (2016, Jan). Calcium-sensing receptor, proinflammatory cytokines and calcium homeostasis. Semin Cell Dev Biol. 49: 37–43. doi: 10.1016/j.semcdb.2015.11.006.
10. Iaroshchuk LB. (2015). Predictability and risk factors of severe bronchial asthma in children. Asthma and Allergy. 2: 47–52.
11. Israel E, Reddel HK. (2017, Sep 7). Severe and Difficult-to-Treat Asthma in Adults. N Engl J Med. 377 (10): 965–976. doi: 10.1056/NEJMra1608969.
12. Kallay E. (2018, May 8). Editorial: Physiology and Pathophysiology of the Extracellular Calcium-Sensing Receptor. Front Physiol. 9: 413. doi: 10.3389/fphys.2018.00413.
13. Leach K, Hannan FM, Josephs TM, Keller AN, Møller TC, Ward DT et al. (2020, Jul). International Union of Basic and Clinical Pharmacology. CVIII. Calcium-Sensing Receptor Nomenclature, Pharmacology, and Function. Pharmacol Rev. 72 (3): 558–604. doi: 10.1124/pr.119.018531.
14. Papi A, Brightling C, Pedersen SE, Reddel HK. (2018, Feb 24). Asthma. Lancet. 391 (10122): 783–800. doi: 10.1016/S0140-6736(17)33311-1. Epub 2017 Dec 19.
15. Ramratnam SK, Bacharier LB, Guilbert TW. (2017, Jul-Aug). Severe Asthma in Children. J Allergy Clin Immunol Pract. 5 (4): 889–898. doi: 10.1016/j.jaip.2017.04.031. PMID: 28689839.
16. Roesler AM, Wicher SA, Ravix J, Britt RD Jr, Manlove L, Teske JJ, Cummings K, Thompson MA, Farver C, MacFarlane P, Pabelick CM, Prakash YS. (2019, Aug). Calcium sensing receptor in developing human airway smooth muscle. J Cell Physiol. 234 (8): 14187–14197. doi: 10.1002/jcp.28115.
17. Umanets TR. (2015). Bronchial asthma and allergic rhinitis: way to optimize the compliance and effectiveness of treatment. Asthma and Allergy. 1: 61–64. [Уманець ТР. (2015). Сучасні аспекти лікування бронхіальної астми та алергічного риніту. Астма та алергологія. 2: 47–52].
18. Xiang ZY, Tao DD. (2022, Dec). The role of calcium-sensitive receptor in ovalbumin-induced airway inflammation and hyperresponsiveness in juvenile mice with asthma. Kaohsiung J Med Sci. 38 (12): 1203–1212. doi: 10.1002/kjm2.12601.
19. Yarova PL, Stewart AL, Sathish V, Britt RD Jr, Thompson MA, P Lowe AP. (2015, Apr 22). Calcium-sensing receptor antagonists abrogate airway hyperresponsiveness and inflammation in allergic asthma. Sci Transl Med. 7 (284): 284ra60. doi: 10.1126/scitranslmed.aaa0282. Epub 2015 Apr 22.

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