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Use of Serum Periostin as a Marker of Exacerbations of Asthma in Children

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Abstract

The article presents an analysis of the use of periostin, a marker of allergic inflammation in school-age patients with uncontrolled asthma.

Relatively higher serum periostin (SP) values were established in patients with moderate asthma compared with mild asthma. The protein concentration of 5 ng/ml can be used as a cut-off point for patients who had 2 or more seizures per year.

Periostin is the only traditional marker (blood eosinophilia, IgE, FEV1) which has shown a relationship with the severity and number of exacerbations of asthma in children. A high level of periostin increases the risk of frequent exacerbations of asthma (OR 1.15, CI 95% 1.016 - 1.295, p = 0.027).

Introduction

The prevalence of bronchial asthma (BA) in the world according to the WHO is 235 million people. In Europe, this is the most common chronic disease in childhood. Consensus GINA 2018 defines asthma as a heterogeneous disease. The pathogenesis of asthma is based on chronic inflammation of the respiratory tract, manifested by typical respiratory symptoms, variable in time: wheezing, suffocation, chest tightness, coughing. BA in children, beginning with school age, is represented by a BA phenotype, called early onset allergic asthma [1]. At the same time, according to our own data and according to Woodruff (2009), there are significant differences in the level and mechanism of inflammation [2]. Probably, this is associated with failures in the search for predictors of severe BA.

Allergic asthma is associated with IgE-dependent inflammation, but IgE levels do not adequately correlate with the severity and symptoms of the disease. At present, simple and cheap markers of inflammation are being sought, the level of which would allow predicting the course, severity, level of risk of exacerbations. The role of predictors has traditionally been devoted to cells and cytokines playing key roles in inflammation. In assessing future exacerbations as risk factors, GINA 2018 calls eosinophilia, low lung function, and number of severe exacerbations in the previous year ≥1. [3]

Eosinophils play a key role in allergic asthma. Eosinophilia indicates a specific inflammation of the respiratory tract and a good response to corticosteroids in children. One of the most reliable methods of assessing pulmonary eosinophilia is bronchoscopy with bronchial biopsy. For the indirect determination of eosinophilic inflammation, a marker - fractional exhaled nitric oxide (FeNO) has been proposed. The level of FeNO varies with allergic diseases, correlates with the activity of inflammation and can be useful in assessing the risk of exacerbations and correction of therapy. However, the variability of nitric oxide in patients with asthma should be considered. Smoking and infections can affect the content of the marker [3]. The need for additional equipment for FeNO and the invasiveness of the procedure for bronchial biopsy serve as an obstacle to the introduction of these methods into practice.

A serum marker would be optimal in practice that could be performed by a wide range of laboratories, could be affordable and could correlate with the type and activity of the inflammation.

The study is devoted to serum periostin and its significance in clinical practice. The SP is determined at Th_2-dependent BA phenotypes and can probably

be indicative of a specific respiratory inflammation, characteristic of both allergic IgE mediated asthma and non-allergic asthma with eosinophilia.

Periostin was discovered in 1993 as a nonspecific protein, first found in myocardial infarction and osteoma. Later, it was considered in pulmonology as a marker of pulmonary fibrosis and eosinophilic asthma in adults. Periostin is synthesized by fibroblasts under the influence of IL13. In the pathogenesis of bronchial asthma, IL13 is one of the key cytokines of Th2 inflammation. IL13 is a pleiotropic Th2 cytokine, activating T-cells, natural killers, eosinophils, basophils, mast-cells and activated macrophages. The increase in IL13 levels is observed in patients with asthma and is associated with 3 genes: POSTN (periostin), SERPINB2 and chloride - channel accessory protein 1 - CLCA1. Upon contact with IL13, bronchial epithelial cells express mRNA, which is an information carrier, and then fibroblasts produce periostin in the intercellular matrix.

Recent works of Izuhara show the dual role of periostin as a signal cytokine and simultaneously a structural component of the bronchial basal membrane[4]. There are works showing the presence of an αv-receptor to periostin integrated into the membrane on the cell surface, i.e. periostin acts as an information signal carrier protein. Then mechanisms of submucosal fibrosis of bronchial tissue are triggered [5]. An increase in the expression of genes encoding a periostin is observed in patients with asthma and correlates with an increase in IL - 15, IL13 levels.

Our study was focused on the analysis of the possibility of using new and traditional markers of inflammation in children with bronchial asthma to predict moderate/severe asthma and more frequent exacerbations. Isolation of clinical phenotypes of asthma with frequent and rare exacerbations is caused by purely practical reasons. It is noted that according to Dunican E. (2015), 2/3 of patients have more than 1 exacerbation per year, and approximately 20% of patients seek medical help for suffocation more than 6 times. There is an obvious pattern of development of attacks - 3 or more exacerbations per year develop 5% of patients with mild asthma, about 23% - with moderate and 54% - with severe BA. [6,7]. To assess the effect of exacerbations on the quantitative indices of inflammation, serum periostin, blood eosinophilia and FEV1 (forced expiring volume per 1 second) were analyzed.

Materials And Methods

Method: single-center cross-sectional study in patients with uncontrolled asthma vs. control group. All children with asthma were admitted with active complaints and had an uncontrolled course at the time of examination. Patients were examined according to the standard for asthma, additionally, SP was determined by enzyme immunoassay using ELISA-Kit-for-Periostin-(POSTN)-E97339Hu manufactured by Cloud-Clone Corp. USA, Houston.

The statistical data was processed in IBM SPSS 23. The median and quartiles Me [Q1; Q3], Mann-Whitney (U), Kruskal-Wallis (H), ro_s - Spearman correlation and logistic regression analysis were used.

Descriptive sample data are presented in the table (Tab. 1).

Table 1. *Clinical characteristic of patients*

Factor		
	Bronchial asthma	Control group
Number of patients	75	29
Age, year	12,99 ± 2,9	14,07 ± 2,2
duration of the disease, year	5,72 ± 3,6	–
Boys	49	10
Girls	21	5
Mild asthma	51 (49,0 %)	-
Moderate asthma	24 (23,1%)	-
IgE, ME/ml	479,4 (168; 1268)	60,0 (20; 76)
Eosinophils, $\times 10^9$	0,20 (0,0; 0,4)	0,21 (0,10; 0,30)
Periostin, ng/ml	3.93 (1.96; 7.80)	0,63 (0,25; 1.20)
FEV1	89.9 ±17.9	93.0± 9.9
Steroid therapy, patients	23	–
Seasons exacerbation	61 (81,3%)	–
Virus - induced exacerbation	14 (18,7%)	–

Objective

On the basis of assessment of clinical, functional, and immunological indicators, to identify risk factors that worsen the course of bronchial asthma, to prove the significance of periostin as a system biomarker of activity of bronchial Th2 - mediated inflammation and to show the relationship between its concentration and the severity of asthma in school-age children.

Results

Traditional BA markers: blood eosinophils, IgE, FEV1 - did not differ significantly and did not correlate significantly in groups of patients with asthma, divided by the number of exacerbations per year and severity. Regression analysis showed unsatisfactory results for predicting the severity of asthma.

Periostin in our study showed encouraging results. The SP level in patients with bronchial asthma had significant differences in comparison with children without allergic diseases: with BA, the concentration of periostin was 0.17-22.26 ng/ml, with Me = 3.93 (1.94, 7.87) ng/ml; in the control group - 0.1-4.44, Me = 0.63 (0.25, 1.20) ng/ml (U = 205.5, Z = -5.23, p = 0.001).

In groups divided by severity, a clear trend is observed for an increase in blood SP: in mild asthma - 3.14 (1.80, 5.42) ng/ml, in moderate to severe BA - 5.71 (3.52; 10,53) ng/ml (significant differences, p = 0.03).

In order to objectify complaints during the in-depth interview, the number of exacerbations in children for a year was analyzed. The correlation analysis according to Spearman showed a low level of correlation between the number of exacerbations per year with the level of serum periostin, ro_s = 0.3, p = 0.011). In patients exclusively with pollen sensitization, the correlation increased sharply and amounted to r_s = 0.581, p = 0.014 (n = 17). This phenomenon may be associated with an increase in the proportion of patients with a high allergic Th2 response, with the predominance of immediate-type reactions when exposed to the pollen trigger. As a result, a cluster of patients with pollen sensitization seems to be the most promising for further research.

The number of exacerbations in the observed group of patients ranged from 0 to 10 per year: Me (Q1; Q3) = 2 (1; 4) per year. The number of patients with exacerbations ≤1 per year was 32 (42.7%); patients with exacerbations ≥2 per year - 43 (57.3%). Serum periostin was significantly higher in group II: Me (Q1; Q3) 2.82 (1.41, 5.53) and 4.96 (2.90, 8.31) ng/ml, p = 0.019). Fig.1

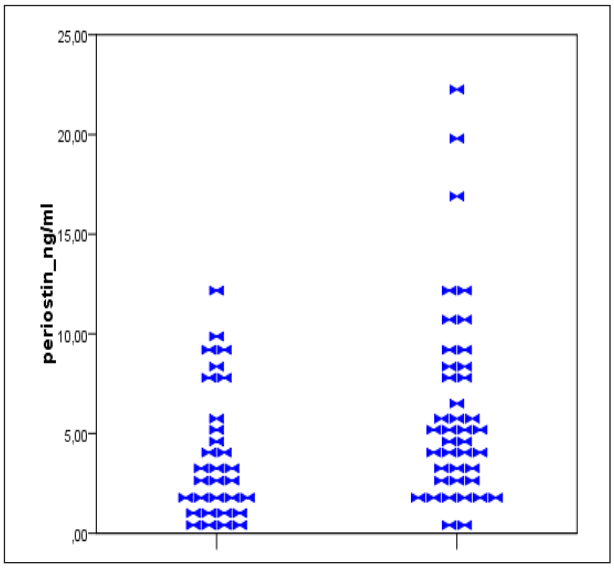

Figure 1. *Concentrations serum periostin for patients with execrations ≤ 1 per year (left) and ≥ 2 per year (right)/*

For patients with exacerbations ≤ 2 per year (n = 49), median SP was 3.26 (1.79, 5.53) ng/ml, in the group with more than 3 exacerbations per year (n = 26), significantly higher values were observed 5.55 (3.31, 8.74) ng/ml (p = 0.016). In both cases, the cut-off point for a high level of periostin was ≈ 5 ng/ml.

With the help of ROC-analysis, the sensitivity-specificity curves were constructed to assess the applicability of the SP in practice. For patients with exacerbations ≤1 per year, a cut-off point of 5 ng/ml corresponds to 72% of sensitivity and 51% of specificity of the indicator (AUC = 0.66, p = 0.019). For patients who have 2 or more attacks - sensitivity / specificity - is 71/38% (AUC = 0.68, p = 0.019).

Remember that for traditional markers (eosinophils, IgE and FEV1), no significant results were obtained.

When analyzing groups of patients who have more than 4 exacerbations a year the differences cease to be detected. It is obvious that moderate asthma with frequent exacerbations is combined with an increase in the level of SP. The degree of severity of the disease, determined on the basis of an integrated assessment of complaints, volume of therapy, function of external respiration, remains an important indicator correlating with the concentration of inflammatory mediators.

The association between the lung function and markers of inflammation with asthma is interesting but difficult to verify, given the high spirographic indices in children. Even in the period of exacerbation, FEV_1 values <80% were detected only in 25% of children in the observed group. In groups divided by median SP (3.96 ng/ml) and by the conditional high level of 5 ng/ml, no significant differences were found in FEV1 ($p > 0.05$). We assume that the level of inflammation is associated with changes in the function of external respiration, but FEV1 is not sensitive enough. The SP did not correlate with any indicator of the function of external respiration.

The prognostic ability of serum periostin is verified by the method of logistic regression. The models with the number of exacerbations > 2 per year were checked. The definition of the SP is able to predict up to 66.7% of the results of the model of "periostin - frequent exacerbations" with the odds ratio (OR) (OR 1.15, CI 95% 1.016 - 1.295), $p = 0.027$, i.e. with an increase in the SP value of 1 ng/ml, the probability of getting into the group with frequent exacerbations of asthma increased by ≈15%. And for a group with rare exacerbations, the accuracy of the forecast reaches 91.7%.

Realizing that the concentration of the SP is a continuous series of numbers, it is possible to single out groups of low to moderate and high and very high risk by the cut-off points of the SP concentration:

1. Low risk, SP = 0 -1.85 ng/ml. Moderate to severe asthma with 3 or more exacerbations per year is practically not found in patients with ≤ 1.85 ng/ml, these patients have a low risk of exacerbations, mild asthma, or require a revision of the diagnosis of allergic disease.
2. Moderate risk, SP = 1.85-3.5 ng/m. 17% of patients with moderate to severe disease, the others have mild degree disease. Dynamic control of patient symptoms is required.
3. High risk, SP ≥ 3.5 -10 ng/ml. 75% of cases, patients with moderate BA have a content of periostin above this value, 40% of mild asthma also fall in the group, but given the need to identify adverse course in childhood, it is advisable to focus on lower concentrations of the marker. An increase in the threshold value of up to 5 ng/ml excludes 72% of patients with mild asthma and, correspondingly, SP > 5 ng/ml have 68% of children with moderate asthma.
4. Group of very high risk, SP ≥ 10 ng/ml, mild asthma course does not occur. Recommendation - when high SP values are obtained, the risk of frequent exacerbations is very high, frequent monitoring and examination are necessary.

Conclusion

The appearance of the serum marker of allergic inflammation - serum periostin, opens new prospects for the objectification of information and personalization of the approach to therapy. The study of the molecular level of the pathogenesis of asthma allows a deeper understanding of the mechanisms of chronic inflammation in children and proves a common pathogenesis with allergic asthma in adults. The common bronchial inflammation makes potentially effective the use of monoclonal antibodies developed for adult patients with allergic bronchial asthma in children. The definition of risk groups based on SP can be useful in choosing asthma therapy. Identifying the pool of patients with IL13-dependent phenotype (based on the definition of serum periostin) makes it possible to use it as a predictor of exacerbations and moderate/severe asthma.

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