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The role of immunological biomarkers in the pathogenesis of atopic bronchial asthma

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Keypoints

The aim of this study is to evaluate the role of immunological biomarkers, particularly lymphocyte subpopulations and serum IgE levels, in the pathogenesis and phenotyping of atopic bronchial asthma in children.

Abstract

Introduction

The identification of reliable biomarkers for bronchial asthma, particularly in pediatric patients, is a topic of growing interest. This is primarily due to diagnostic challenges in children, including limited capabilities for pulmonary function testing and heterogeneous clinical manifestations. Traditional assessments such as peripheral eosinophil counts may not fully reflect the underlying inflammatory phenotype. Therefore, alternative cellular and humoral biomarkers are being explored for their diagnostic and prognostic relevance in atopic bronchial asthma.

Materials and Methods

The study included 983 pediatric patients (850 boys, 133 girls) diagnosed with varying severities of bronchial asthma. Flow cytometry was used to assess lymphocyte subpopulation markers (CD3+, CD4+, CD8+, CD16+/CD56+, CD19+), and enzyme-linked immunosorbent assays (ELISA) were performed to quantify total serum IgE levels. Data were analyzed using descriptive statistics, intergroup comparisons, and ROC-curve analysis.

Results

T-cell subpopulations showed tendencies toward decreased CD3+ counts and elevated CD4+, CD8+, and NK cell percentages, though differences did not reach statistical significance. Total serum IgE levels were significantly elevated in 81.3% of asthmatic patients (mean 651.7±66.3 IU/mL), with levels increasing in proportion to asthma severity. In contrast, CD19+ B-cell levels remained within reference ranges. ROC analysis demonstrated that total IgE had strong predictive value for atopic asthma, with an AUC of 0.741 (95% CI: 0.624–0.859, p = 0.002).

Conclusion

Cellular immunity markers, including T-cell subpopulations, did not show significant alterations across asthma severities, suggesting that atopic asthma may not directly impair T-lymphocyte quantitative parameters. In contrast, elevated serum IgE levels were strongly associated with atopic asthma and its severity, confirming its utility as a predictive and diagnostic biomarker in clinical settings.

Keywords

Bronchial asthma, biomarkers, cytokines, T-lymphocytes, immunoglobulin E, children, Th2 inflammation

Introduction

In recent years, there has been a growing interest in identifying reliable biomarkers of bronchial asthma, particularly in pediatric practice. This interest stems from the diagnostic challenges of asthma in children due to

limitations in lung function assessment and the wide spectrum of clinical manifestations. The evaluation of airway inflammation is often based on peripheral blood cell analysis, particularly eosinophil counts. However, eosinophil levels are subject to considerable variability and are influenced by numerous factors, which may limit their diagnostic utility.

Airway inflammation is a central pathogenic mechanism in bronchial asthma, mediated by cytokines and various immunocompetent cells. Bronchial asthma is characterized by eosinophilic inflammation of the respiratory tract, where Th2 cytokines play a pivotal role. The inflammatory response within the bronchial tree is driven by mediators and cytokines produced by different cellular populations. Cytokine-mediated immunity is known to dominate the pathogenesis of many immune-mediated disorders, including asthma.

Accordingly, there is increasing focus on identifying laboratory biomarkers that may enhance the diagnosis of atopic bronchial asthma, support outcome prediction, and enable personalized therapeutic strategies.

The aim of this study is to determine the role of biomarkers in the pathogenesis of atopic bronchial asthma.

Material and Methods

To achieve the stated objective, the study included 983 children with a history of multiple episodes of bronchial obstruction who were subsequently diagnosed with bronchial asthma of varying severity. The study cohort consisted of 850 boys and 133 girls.

The investigation involved the assessment of the expression of surface receptors on major lymphocyte populations and subpopulations in peripheral blood, as well as the evaluation of humoral immune parameters.

Results and Discussion

Table 1 presents the parameters of cellular immunity in children with bronchial asthma. The values of the studied immunological parameters followed a normal distribution and are presented as M±m. An assessment of T-lymphocyte subpopulation levels revealed the following trend: an increase in the relative levels of $CD4^+$, $CD8^+$, and $CD16^+/CD56^+$ lymphocytes, along with a decrease in $CD3^+$ lymphocytes relative to the lower limit of the reference range.

As shown in Table 1, patients with bronchial asthma exhibited a certain reduction in the proportion of mature T-cells ($CD3^+$) — 50.6±1.6% [95% CI: 47.4–53.8%] (PF = 0.599; Pn = 0.238), and an increase in $CD4^+$ lymphocytes — 38.6±0.7% [95% CI: 37.3–39.9%] (PF = 0.458; Pn = 0.343), $CD8^+$ lymphocytes — 27.8±0.8% [95% CI: 26.1–29.5%] (PF = 0.422; Pn = 0.476), and $CD16^+/CD56^+$ lymphocytes — 11.9±0.8% [95% CI: 10.3–13.6%] (PF = 0.906; Pn = 0.506). These findings indicate a disruption in T-cell balance.

Lymphocyte Subpopulation	Reference Range	Bronchial Asthma (M±m)	95% CI	PF	PH
CD3+ (%)	59.4–84.6	50.6±1.6	47.4–53.8	0.599	0.238
CD4+ (%)	28.5–60.5	38.6±0.7	37.3–39.9	0.458	0.343
CD8+ (%)	11.1–38.3	27.8±0.8	26.1–29.5	0.422	0.476
CD4+/CD8+ (ratio)	0.9–3.6	1.46±0.06	1.34–1.57	0.785	0.461
CD16+/CD56+ (%)	5.6–30.9	11.9±0.8	10.3–13.6	0.906	0.506
NK cells (%)	95.0–105.0	102.0±2.0	98.1–106.0	0.755	0.476

Table 1. Cellular Immunity Parameters in Children with Bronchial Asthma

The immunoregulatory index, calculated as the $CD4^+/CD8^+$ ratio, also exceeded the normal range, with a mean value of 1.46±0.06 [95% CI: 1.34–1.57] (PF = 0.785; Pn = 0.461). The relative number of NK cells was above the reference values, amounting to 102.0±2.0% [95% CI: 98.1–106.0%] (PF = 0.755; Pn = 0.476), indicating a predominance of Th2-type immune activation. The distribution of T-cell lymphocyte subpopulations identified in this study may be associated with the

potential migration of these cells to the site of inflammation, namely, the bronchial mucosa. The observed changes can be interpreted as a reflection of Th2-mediated inflammation in patients with atopic bronchial asthma included in the study. No statistically significant differences in the levels of the studied parameters were found compared to reference values. Only trends toward a lower proportion of $CD3^+$ cells accompanied by increased levels of $CD4^+$ and $CD8^+$ lymphocytes were observed. An assessment of the expression levels of surface receptors on the main populations and subpopulations of lymphocytes in the peripheral blood of children with atopic bronchial asthma of varying severity revealed the following changes (Table 2).

Lymphocyte Subpopulation	Reference Range	Moderate Asthma	Moderate Asthma + Rhinitis	Severe Asthma	PF	Pn
$CD3^+$ (%)	59.4–84.6	49.7±2.3 [33.0–90.0] [45.1–54.3]	49.9±3.0 [34.0–81.0] [43.8–56.1]	54.0±3.5 [34.0–77.0] [47.4–53.8]	0.599	0.238
$CD4^+$ (%)	28.5–60.5	39.3±1.3 [26.0–54.0] [36.6–41.9]	38.9±0.9 [26.0–54.0] [37.3–39.9]	37.3±1.0 [32.0–47.0] [35.2–39.3]	0.458	0.343
$CD8^+$ (%)	11.1–38.3	28.0±1.2 [12.0–40.0] [25.5–30.5]	29.3±1.5 [26.0–54.0] [27.3–39.9]	26.1±1.9 [13.0–37.0] [22.0–39.9]	0.422	0.476
$CD4^+/CD8^+$ (units)	0.9–3.6	1.43±0.09 [0.86–2.50] [1.25–1.60]	1.46±0.10 [0.97–2.50] [1.24–1.67]	1.53±0.12 [0.86–2.54] [1.26–1.79]	0.785	0.461
$CD16^+/CD56^+$ (%)	5.6–30.9	12.3±1.1 [4.0–34.0] [10.0–14.6]	11.8±1.9 [3.0–30.0] [7.7–15.9]	11.4±1.4 [4.0–22.0] [8.4–14.5]	0.906	0.506
NK cells (%)	95.0–105.0	101.0±0.8 [93.0–112.0] [99.3–102.7]	101.3±1.2 [96.0–113.0] [98.8–103.9]	104.5±7.3 [87.0–204.4] [88.9–120.1]	0.757	0.476

Table 2. Expression Levels of Surface Receptors in the Main Populations and Subpopulations of Peripheral Blood Lymphocytes in Children with Atopic Bronchial Asthma of Varying Severity (M±m; min–max; 95% CI). Note: PF — Fisher's exact test; Pn — Kruskal–Wallis test.

In 62.7±5.9% of cases with moderate asthma and 48.0±10.0% of cases with severe asthma, the level of mature T-cells ($CD3^+$) was reduced. Accordingly, in the group of patients with moderate asthma, the mean $CD3^+$ lymphocyte level was 49.7±2.3% [95% CI: 45.1–54.3%]; in those with moderate asthma accompanied by allergic rhinitis — 49.9±3.0% [95% CI: 43.8–56.1%]; and in those with severe asthma — 54.0±3.5% [95% CI: 47.4–53.8%] (PF = 0.599; Pn = 0.238). In the group of patients with moderate bronchial asthma, the mean $CD4^+$ lymphocyte level was 39.3±1.3% [95% CI: 36.6–41.9%]; in those with moderate asthma and concomitant allergic rhinitis — 38.9±0.9% [95% CI: 37.3–39.9%]; and in those with severe asthma — 37.3±1.0% [95% CI: 35.2–39.3%] (PF = 0.458; Pn = 0.343). In the group of patients with moderate bronchial asthma, the mean $CD4^+$ lymphocyte level was 39.3±1.3% [95% CI: 36.6–41.9%]; in those with moderate asthma and concomitant allergic rhinitis — 38.9±0.9% [95% CI: 37.3–39.9%]; and in those with severe asthma — 37.3±1.0% [95% CI: 35.2–39.3%] (PF = 0.458; Pn = 0.343). In the group of patients with moderate bronchial asthma, the mean $CD8^+$ lymphocyte level was 28.0±1.2% [95% CI: 25.5–30.5%]; in those with moderate asthma and concomitant allergic rhinitis — 29.3±1.5% [95% CI: 27.3–39.9%]; and in those with severe asthma — 26.1±1.9% [95% CI: 22.0–39.9%] (PF = 0.422; Pn = 0.476). The $CD4^+/CD8^+$ cell ratio in children with bronchial asthma remained within normal reference values, with a mean of 1.46±0.06 units. In patients with moderate asthma, the mean $CD4^+/CD8^+$ index was 1.43±0.09 units [95% CI: 1.25–1.60]; in those with moderate asthma and concomitant allergic rhinitis — 1.46±0.10 units [95% CI: 1.24–1.67]; and in those with severe asthma — 1.53±0.12 units [95% CI: 1.26–1.79] (PF = 0.785; Pn = 0.461). In the group of patients with moderate bronchial asthma, the mean level of $CD16^+/CD56^+$ lymphocytes was 12.3±1.1% [95% CI: 10.0–14.6%]; in those with moderate asthma and concomitant allergic rhinitis — 11.8±1.9% [95% CI: 7.7–15.9%]; and in those with severe asthma — 11.4±1.4%

[95% CI: 8.4–14.5%] (PF = 0.906; Pn = 0.506). In 21.4±5.5% of patients with atopic asthma, a marked increase in the number of NK cells in the blood was observed relative to the reference values (Pn = 0.476). Specifically, elevated NK cell levels were detected in 19.2±7.7% of children with moderate bronchial asthma, in 20.0±10.3% of those with moderate asthma and concomitant allergic rhinitis, and in 26.7±11.4% of those with severe asthma (PF = 0.757; Pn = 0.476). In the group of patients with moderate bronchial asthma, the mean NK cell level in the blood was 101.0±0.8% [95% CI: 99.3–102.7%]; in those with moderate asthma and concomitant allergic rhinitis — 101.3±1.2% [95% CI: 98.8–103.9%]; and in those with severe asthma — 104.5±7.3% [95% CI: 88.9–120.1%] (PF = 0.757; Pn = 0.476). No statistically significant intergroup differences were found for any individual cellular immunity parameter (p > 0.05). It is well established that the development of atopic bronchial asthma is based on an immediate-type hypersensitivity reaction. This type of reaction, in turn, is associated with specific features of humoral immune responsiveness. In our study, the activity of humoral immunity was assessed by measuring the levels of immunoglobulin E (IgE) and the number of B-lymphocytes ($CD19^+$) in peripheral blood. No significant alterations were observed in B-cells expressing the CD19 molecule on their surface. The mean percentage of $CD19^+$ lymphocytes in the peripheral blood of patients with bronchial asthma was 14.8±0.3% [95% CI: 14.2–15.3%], which falls within the reference range (Table 3). A reduction in the relative number of $CD19^+$ lymphocytes was noted in only 5.4±1.9% of children with bronchial asthma (PF = 0.669; Pn = 0.238). The pathogenesis of allergic diseases is primarily associated with a Th2-type immune response phenotype, which leads to increased synthesis of total immunoglobulin E (IgE). IgE plays a central role in conditions mediated by immediate-type hypersensitivity reactions. Therefore, the determination of total IgE levels holds significant diagnostic value in atopic disorders. In accordance with the study objectives, total IgE levels were analyzed. Frequency analysis revealed elevated total IgE levels in 81.3±4.5% of patients with bronchial asthma. The mean total IgE concentration was 651.7±66.3 IU/mL [95% CI: 497.1–778.2 IU/mL], which was approximately 3.0 times higher than the corresponding values in children with acute obstructive bronchitis — 215.2±48.4 IU/mL [95% CI: 117.4–313.0 IU/mL] (PF < 0.001; Pn < 0.001), supporting the atopic nature of the immune response in allergic patients (Table 3).

Parameter	Reference Range	Bronchial Asthma (M±m)	95% CI	Obstructive Bronchitis (M±m)	95% CI (Bronchitis)	PF	PH
CD19+ (%)	6.4 – 22.6	14.8±0.3	14.2 – 15.3	-	-	0.669	0.238
IgE (IU/mL)	60.0 – 90.0	651.7±66.3	497.1 – 778.2	215.2±48.4	117.4 – 313.0	<0.001	<0.001

Table 3. Humoral Immunity Indicators in Examined Children

In the group of patients with moderate bronchial asthma, the mean percentage of $CD19^+$ lymphocytes in peripheral blood was 14.7±0.4% [95% CI: 13.9–15.5%]; in those with moderate asthma and concomitant allergic rhinitis — 14.5±0.5% [95% CI: 13.6–15.4%]; and in those with severe asthma — 15.2±0.8% [95% CI: 13.6–16.9%]. No statistically significant intergroup differences were identified for any individual parameter of the cellular immune response (Table 4). Alterations in $CD19^+$ levels were observed in only 5.8±2.8% of patients with moderate asthma, 4.2±2.9% of those with moderate asthma and concomitant allergic rhinitis, and 6.7±4.6% of children with severe asthma, and these changes were not statistically significant (PF = 0.669; Pn = 0.238). The observed trend toward increased B-lymphocyte levels in severe bronchial asthma reflects a pro-inflammatory immune response and indicates ongoing allergic inflammation in the body. An analysis of total serum IgE levels in patients

with atopic bronchial asthma revealed that, in cases of moderate disease, the IgE level was 489.9±113.3 IU/mL [95% CI: 246.8–732.9 IU/mL]; in moderate asthma with concomitant allergic rhinitis — 555.3±101.9 IU/mL [95% CI: 347.2–763.3 IU/mL]; and in severe asthma — 1000.4±141.4 IU/mL [95% CI: 704.5–1296.4 IU/mL] (PF < 0.001; Pn < 0.001) (Table 4).

Indicator	Reference Range	Moderate Asthma	Moderate Asthma + Rhinitis	Severe Asthma	PF	Pn
CD19⁺ (%)	6.4–22.6	14.7±0.4 [8.0–25.0] [13.9–15.5]	14.5±0.5 [8.0–29.0] [13.6–15.4]	15.2±0.8 [7.0–27.0] [13.6–16.9]	0.669	0.238
IgE (IU/mL)	60.0 – 90.0	489.9±113.3 [7.46–1450.0] [246.8–732.9]	555.3±101.9 [17.5–2141.0] [347.2–763.3]	1000.4±141.4 [300.0–2494.0] [704.5–1296.4]	<0.001	<0.001

Table 4. Indicators of Humoral Immunity in Children with Atopic Bronchial Asthma of Varying Severity (M±m; min–max; 95% CI). Note: PF — Fisher's exact test; Pn — Kruskal–Wallis test.

The elevated levels of total IgE reflect the involvement of allergic mechanisms in the pathogenesis of this asthma phenotype and show a direct correlation with the severity of bronchial asthma. According to the findings, the risk of developing atopic bronchial asthma in the presence of hyperimmunoglobulinemia E is significantly increased, with an odds ratio (OR) of 53.0 [95% CI: 2.8–988.3; $p < 0.05$].

The diagnostic value of total serum IgE as a biomarker for atopic bronchial asthma was assessed using ROC (Receiver Operating Characteristic) analysis. A high diagnostic accuracy of serum IgE as a biomarker for atopic bronchial asthma in children was established. The ROC curve for IgE lies above the reference diagonal line and demonstrates a sensitivity of 74.1±0.060% ($p = 0.002$) within a 95% confidence interval (95% CI: 0.624–0.859), indicating a well-performing logistic model.

As shown in Figure 1, the ROC curve along with the calculated area under the curve (AUC) confirms the high predictive power of total serum IgE in identifying bronchial asthma in the examined patients with bronchial obstructive syndrome.

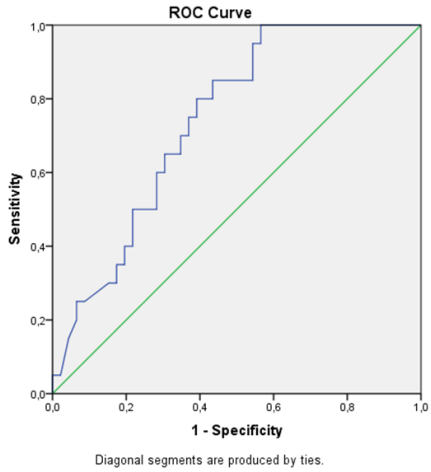

Figure 1. ROC Curve for Total Serum IgE as a Biomarker. ROC curve evaluating the diagnostic performance of total serum IgE as a biomarker for atopic bronchial asthma. The area under the curve (AUC) was 0.741 (95% CI: 0.624–0.859), indicating strong predictive value.

Conclusion

Analysis of the obtained data indicates that atopic bronchial asthma does not lead to significant alterations in the parameters of cellular immunity. This suggests that asthma may not directly affect the functional activity or baseline quantitative balance of the studied T-lymphocyte subpopulations. In contrast, elevated levels of total serum IgE reflect the involvement of allergic reactions in the pathogenesis of atopic bronchial asthma, underscoring its role as a key immunological marker in this condition.

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