Role of periostin in uncontrolled asthma in children. (DADO study)

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ABSTRACT

Introduction and objectives: Asthma is the most common chronic disease in children. Cases of severe asthma (SA) are underdiagnosed. Periostin is a biomarker for SA in adults, but its role in children is poorly understood. The aim of the study was to estimate the percentage of cases of uncontrolled severe asthma (UcSA) in children with poorly controlled asthma and evaluate the role of periostin as a biomarker.

Materials and methods.-Observational study in children aged 5 to 14 years with poorly controlled asthma. Demographic and clinical information were collected in addition to the lung function test, the fraction of exhaled nitric oxide (FeNO), the skin prick test (SPT), total IgE, specific IgE, blood eosinophilia, serum periostin, treatment, asthma control and quality of life (QoL). Variables were compared between the group with UcSA and the other children.

Outcomes.-Fifty children with poorly controlled asthma (72% male) were included. Nineteen children (38%) had UcSA. Most children had limitations in their activities of daily living, emergency visits and 38% required hospitalisation. The mean QoL was low. Only 42% of the children received appropriate treatment. The UcSA group (19 children, 38%) was more likely to have a total IgE >500 kU/ml (52.6% versus 19%, p = 0.02) and less likely to have a serum periostin >1,000 ng/ml (31.2% versus 63%, p = 0.04).

Conclusions: In our setting, 38% of children with poorly controlled asthma have UcSA, which is associated with higher levels of total serum IgE and lower levels of serum periostin.

KEY WORDS: Uncontrolled severe asthma, clinical practice guidelines, children, periostin.

RESUMEN

Introducción y objetivos.- El asma es la enfermedad crónica más frecuente en niños. El asma grave (AG) está infradiagnosticada. La periostina es un biomarcador de asma grave en adultos, pero su papel en niños es pobremente conocido. El objetivo de este estudio ha sido estimar el porcentaje de casos de asma grave no controlada (AGNC) en niños con asma mal controlada y evaluar el papel de la periostina como biomarcador.
Material y métodos.- Estudio observacional en niños de 5 a 14 años de edad con asma mal controlada. Se recogieron datos demográficos y clínicos, pruebas de función pulmonar y, fracción de óxido nítrico exhalado (FENO), prick test, IgE total, IgE específica, eosinófilos en sangre, periostina en suero, tratamiento, control del asma y calidad de vida. Se compararon las variables entre el grupo con AGNC y el resto de niños.
Resultados.- Se incluyeron a 50 niños con asma mal controlada (72% varones). Diecinueve niños (38%) presentaban AGNC. La mayoría de los niños tenían limitaciones en las actividades de la vida diaria, visitas a urgencias y el 38% habían necesitado ingreso hospitalario. La media de calidad de vida fue baja. Solo el 42% de los niños tenían un tratamiento adecuado. El grupo AGNC (19 niños, 38%) tenían más probabilidad de tener una IgE >500 kU/ml (52.6% frente a 19%, p=0.002) y menos probabilidad de tener periostina en suero >1000ng/ml (31.2% frente a 63%, p = 0.04).
Conclusiones.- En nuestra serie, el 38% de niños con asma no controlada tenían AGNC, que está asociado con altos niveles de IgE total y menores niveles de periostina en suero

Palabras clave: asma grave no controlada, guías de práctica clínica, niños, periostina.

At present, asthma is a major public health problem which affects nearly 350 million people worldwide; it is the most common chronic disease in childhood and adolescence. Asthma is more syndrome than disease, exhibiting a great deal of heterogeneity in its presentation and clinical course. [1] Several asthma phenotypes and endotypes have been identified. While 80% of children with asthma have allergies, the differentiation between Th1 and Th2 immune mechanisms in children remains unclear. Some studies show a higher percentage of neutrophils in bronchoalveolar lavage (BAL) or induced sputum in children. [2] Currently the biomarkers whose clinical value is established in adults with asthma are eosinophils and neutrophils in sputum, eosinophilia in bronchial lavage and bronchial biopsies and periostin in peripheral blood. [3] Induced sputum and BAL are not commonly used in children and, as regards periostin, no data are currently definitive on its usefulness in children. [4-8]

The level of asthma control is the extent to which the manifestations of asthma can be observed in the patient, or have been reduced or removed by treatment. It is determined by the interaction between the patient's genetic background, underlying disease processes, the treatment that they are taking, environment, and psychosocial factors. Asthma control has two domains: symptom control and future risk of adverse outcomes. Both should always be assessed. [9] Asthma severity is assessed retrospectively from the level of treatment required to control symptoms and exacerbations. It can be assessed once the patient has been on controller treatment for several months and, if appropriate, treatment step down has been attempted to find the patient's minimum effective level of treatment. Asthma severity is not a static feature and may change over months or years. According to GINA (Global Initiative of Asthma) guidelines [9], mild asthma is asthma that is well controlled with Step 1 or Step 2 treatment, moderate asthma is asthma that is well controlled with Step 3 treatment and severe asthma (SA) is asthma that requires Step 4 or 5 treatment, e.g. high-dose ICS/LABA, to prevent it from becoming 'uncontrolled', or asthma that remains 'uncontrolled' despite this treatment. The definition of uncontrolled severe asthma (UcSA), for older chlildren and adolescents, according to GEMA

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[10], and the American Thoracic Society Task Force on Severe Asthma [11] is showed in Table 1. This term encompasses other forms such as difficult-to-control asthma, treatment-refractory asthma or difficult-to-treat asthma. Patients with uncontrolled asthma may be difficult to treat due to inadequate or inappropriate treatment, or persistent problems with adherence or comorbidities such as chronic rhinosinusitis or obesity or may be refractory asthma in whom response to treatment of comorbidities is incomplete. [9-12] SA is known to be underdiagnosed, and the concept is not clear among physicians. [1] According to Cowen et al. [13], 47% of children with SA are diagnosed with moderate asthma by clinical. The World Health Organization (WHO) defines SA as "a form of uncontrolled asthma that can increase the risk of frequent severe exacerbations (or death) and/or adverse reactions to medications and/or chronic morbidity, including impaired lung function or reduced lung growth in children". [14]

In recent years, studies have been published on the role of periostin in asthma. Periostin is a cell matrix protein that was first identified in 1993 in mouse periodontal ligament (hence the name). It is secreted by bronchial fibroblasts and epithelial cells, acts as an immunomodulatory, repairs connective tissue, and is involved in fibrogenesis. This protein binds to integrins present on the surface of fibroblasts and epithelial cells. Its main function is to maintain tissue structure by binding to fibronectin, tenascin-C and collagen V. Expression of the periostin (POST) gene is regulated by bronchial epithelial cells, IL-13 and IL-4. [15] Serum periostin levels exhibit very low variability and high reproducibility. [16] According to some authors, this protein is a safe and stable biomarker of chronic inflammation [17] and of the Th2 mechanism underlying severe asthma in adults. [10] A link has been established between periostin and bronchial obstruction, elevated levels of FeNO and eosinophilia in adults. [18-20] One of the effects of periostin is to attract inflammatory cells to the airway; these cells can be neutrophils or eosinophils. In turn, inflammatory cells, macrophages and neutrophils stimulate the expression of periostin and other cell matrix proteins through the induction of TGF-β and cytokine expression. [21] In his study in mice, Masuoka [22] noted that periostin is involved in chronic inflammation of the skin in atopic dermatitis and that it elicits a Th2 and Th1 response similar to airway inflammation.

Very few studies have been published in relation to periostin levels in children, although levels are known to be higher in children than in adults due to the cell turnover that occurs during growth. [15]

The objectives of this study were to estimate the percentage of cases of **UcSA** in a population of children with uncontrolled asthma with different severity, and to analyse associated factors, especially serum periostin.

MATERIALS AND METHODS

An observational, cross-sectional, prospective, single-centre study conducted at the Maternal and Child Hospital of Badajoz, Spain. The study population were children aged 5 to 14 years with uncontrolled asthma according to level of asthma symptom control of GINA and value of FEV1[9] (Table 2) seen in allergy units of the Maternal and Child Hospital of Badajoz and 17 Health Centres of the Healthcare District of Badajoz. In the healthcare area there are about 25,000 children 5 to 14 years. The inclusion criteria detailed in the Table 3. The recruitment period was 9 months (September to June).

All parents or legal representatives and all children over 12 years gave informed consent. The study was approved by the Ethics Committee of Clinical Research of Universitary Hospital of Badajoz and the Spanish Agency for Medicines and Medical Devices (*Agencia Española de Medicamentos y Productos Sanitarios*, AEMPS) classified it as a Post-Authorization Study with Other Designs (*Estudios Post-Autorización con Otros Diseños*, EPA-OD).

The study protocol included a minimum of 2-3 visits for each child over a 6 month period. Expert recommendations for the diagnosis of SA were thus fulfilled. [10,11,23] Diagnosis was reached after the second visits and after proper treatment, in mild, moderate or severe asthma according to GINA [9], and uncontrolled severe asthma (UcSA), for older chlildren and adolescents, according to GEMA [10], and the American Thoracic Society Task Force on Severe Asthma [11]. Parents were given a Questionnaire that recorded demographic and

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psychological factors, home characteristics, exposure to cigarette smoke, and their personal and family medical history. In Case Report Forms (CRFs) recorded:

- Patient´s data: age, sex, BMI (Body Mass Index)
- Clinical characteristics: age of onset of symptoms, seasonality, diurnal and nocturnal symptoms, limitations in the activities of daily living and exercise tolerance, school absenteeism and parental absenteeism from work)
- Comorbidities
- Number of exacerbations, emergency visits, annual hospital admissions
- Treatment taken were
- Diagnostic tests: FeNO, spirometry and post bronchodilator test (Post BD), skin prick testing with aeroallergens and food allergens, total IgE, specific IgE and eosinophils in blood, and serum periostin.

The measurement of FeNO was performed with NIOX Vero, using a cut-off of 20 ppb (sensitivity of 61%, specificity of 59%). [24, **25**] The Post BD test was considered positive with an increase in FEV1 > 9-12% or > 200 cc. [**26**] The skin prick with aeroallergens and food allergens test was considered positive when papules were larger than 3 mm and positive specific IgE > 0.35 kU/l. [**27**] The eosinophilia cut-off was set to > 400 eosinophils/mm^3. Levels of serum periostin were measured using the Enzyme-Linked Immunosorbent Assay (ELISA), specifically the human Periostin DuoSet ELISA (Cat# DY3548) by R&D Systems.

Asthma control was measured using the Asthma Control Test (ACT) in children over the age of 12 years and the Childhood Asthma Control Test (cACT) for children under 12 years. The selected cut-off was <19 (sensitivity of 70%, specificity of 88%). [28] QoL was measured using the self-administered version of the PAQLQ (Paediatric Asthma Quality of Life Questionary). [29]

Diagnosis was made on the medical history and the results of additional tests. Treatment was prescribed according to clinical practice guidelines (CPG), and an action plan was delivered in writing. Finally, two groups were formed: one which met the criteria for UcSA (Table 1) (UcSA

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group), and the other made up of the remaining children with uncontrolled asthma without criteria for UcSA ("No UcSA" group)

Statistical methods

The statistical package SAS® version 9.3 was used. Descriptive analyses of the collected variables were performed. Categorical variables were summarised using frequencies and percentages, and continuous variables using measures of central tendency and dispersion. Contingency tables were used to evaluate the relationship between categorical variables, and the Chi-square test or Fisher's exact test was used to determine a possible statistical association. The T-Test, ANOVA, or the nonparametric Wilcoxon, Mann-Whitney and Kruskal–Wallis tests were used for comparison of numerical variables. The relationship between two numerical variables was measured using the Pearson or Spearman correlation. P values <0.05 were considered statistically significant. A logistic regression model was adapted, and the p values of the adjusted values and their respective odds ratios and 95% confidence intervals were presented in the model. After performing a post hoc analysis and two-by-two comparison of the categories of a given variable, the resulting p-values were adjusted using the False Discovery Rate method.

RESULTS

Fifty eight children fulfilling criteria for uncontrolled asthma were deemed eligible, of whom 50 were included in the study. Of these 50 children, 19 (38%) met the criteria for UcSA, 22 (44%) for uncontrolled moderate asthma, 8 (16%) for uncontrolled mild asthma and one patient (2%) for controlled mild asthma.

Clinical and sociodemographic characteristics are shown in Table 4. The median age was 8 years [interquartile range (IQR) 6-13]. Psychological disturbances were present in half of the families, the most frequent anxiety and depression in the mother. The median BMI was 18 kg/m^2 (IQR 16-21). In 64% of the children, symptoms had first appeared in the first year of life. 85% had a family history of atopy, and over 90% had nocturnal and daytime symptoms and

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limitations in exercise tolerance. Most of the children had comorbidities (96% rhinitis, 62% atopic dermatitis and 32% food allergies). Comparison of the UcSA and "No UcSA" groups revealed significant differences in exposure to cigarette smoke (higher percentage exposure in children in the "No UcSA" group), hospital admissions rates (63.2% for the UcSA group and 22% for the "No UcSA" group), limitations in the activities of daily living (100% of children with UcSA and 54.8% of those in the "No UcSA" group) and in recorded rates of school absenteeism (higher for the group with UcSA).

Allergy test results and the comparison between biomarkers are shown in Table 5. Note that total IgE values were elevated, averaging 535 IU/ml, with a higher rate of IgE >500 kU/l in the UcSA group (52.6% vs. 19%, p = 0.02). Periostin values (ng/ml) were generally very high, averaging 972 (median 1000, interquartile index 554 -1275). Dilution of some of the serums to 1/10 and 1/100 was necessary for the ELISA determination of periostin values. The difference values compared to other studies [4,6,7] could be due to the ELISA technique used. A trend to an increase in mean levels of periostin (ng/ml) was observed with increasing patient age (838 for children aged 5-7 years, 961 for children aged 8-12, and 1,242 in those >12 years); levels of periostin were also higher in boys than in girls (1,081 ± 705 ng/ml vs. 690 ± 528 ng/ml, p=0.09). No correlation was found between serum periostin and total IgE levels, eosinophils levels and FEV1 or FeNO values.

Based on CPGs, only 42% of the children had proper treatment, with no significant differences between the two groups. 72% were treated with high-dose ICs. 80% required more than 2 OC treatment cycles in the past year and 13 children were receiving or had received specific allergen immunotherapy. Only 15% of children were treated with Long-Acting Beta-Agonists (LABAs) in combination with ICs.

A logistic regression model was used that showed **UcSA** to have relation, with an odds ratio (OR) of 5.02 (95% confidence interval [CI] 1.02-24.7), for non-exposure to cigarette smoke, 8.48 (95% CI 1.86-38.63) for hospital admissions for asthma, and 7.16 (95% CI 1.11-46.14) for FEV1<80%.

DISCUSSION

This is a real-life study of uncontrolled asthma in children in a healthcare district in the South-west of Spain. Patients were referred by paediatricians following hospital and primary care consultations, so that the sample is representative of children with asthma in the area. Thirty-eight percent of the children with uncontrolled asthma met the clinical criteria for UcSA. At present, it is estimated that people with severe forms of asthma account for less than 15% of the total asthma population. [30] According to the ISAAC study, there is a general trend in Europe to an increased prevalence of SA. [31] The results of the Spanish multi-centre study on difficult-to-control asthma in children showed a prevalence of SA of 8.8%, and 24.2% of this population had difficult-to-control asthma. [32] Although we studied only children with poorly controlled asthma, the percentage of UcSA seems high. There may have been a selection bias, and the children referred may have been patients with a very poor clinical course; this percentage could also be due to poor management of the disease. As in other epidemiological studies, frequency was higher in males. [30] The percentage of children exposed to cigarette smoke was lower in the UcSA group; their parents may have had better awareness of the disease and taken appropriate action.

In most patients, the onset of bronchial symptoms occurred in the first year of life, and this phenotype was associated with poor asthma control and a worse prognosis. [33] Most patients exhibited significant limitations in activities of daily living and exercise tolerance, which negatively affected the children and their families on an emotional and social level. Our group exhibited a high percentage of A&E visits and hospital admissions for asthma exacerbations, which entails a risk of impaired lung function in adult life. These data are alarming both from a health and economic standpoint.

The BMI was lower than expected; children with severe forms of asthma tend to have a low body weight and height. Lung function measurements showed normal FEV1 values in 80% of children, which was consistent with the findings of the TENOR study (The Epidemiology and Natural history of asthma: Outcomes and Treatment Regimens). [30] Lung function in

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children is not directly related to the severity of asthma, since many children with moderate or severe asthma have normal lung function. However, the use of pulmonary function tests is essential for disease management. According to the TRAP study [34], only a third of Spanish paediatricians use spirometry for the diagnosis of asthma, and about half of these paediatricians use it to monitor the disease. There is urgent need to increase use of the lung function, which seems to be crucial for improving management of childhood asthma. [35] In children in the UcSA group with a FEV1 <80%, irreversible obstruction or remodelling may well have already occurred.

Levels of total serum IgE were found to be higher in the UcSA group, which has been linked to greater asthma severity, [36] and most were sensitised to aeroallergens. According to various studies, [37, 38] unlike adults, [39] children tend to be atopic with high levels of total IgE and FeNO and with peripheral eosinophilia and aeroallergen sensitisation.

There is evidence that ACT is a useful tool in the management of asthma, and that it is a better predictor of poor asthma control than FeNO measurements. Our results are very similar to those found in the SA group of the recent European U-BIOPRED study, [38] where 70% had an ACT score <19. More than half of the children in the UcSA group had an ACT score <14 due to poorly controlled asthma and a high risk of serious exacerbations. [28] The mean PQLQ score was 4.3, slightly lower than the SA group of the European study (mean 4.7 for school aged group), [38] and the TENOR study (5.4 in the children group), [30] suggesting poor quality of life among the patients in our study. Subjective measures of asthma control and QoL are both known to be useful for identifying children with problematic asthma, [40] these tests have clinical value and provide a subjective perception of the disease.

Only 42% of patients were found to have been prescribed the right treatment in line with the CPGs. [9, 10] Inappropriate treatment of asthma in children is known to be associated with a risk of exacerbations and worse disease prognosis. It has also been shown that proper follow-up of severe asthma involves control of the disease in over 80% of cases, and that the

implementation of an asthma management program improves QoL while being cost effective. [9]

Serum and sputum periostin are linked with eosinophilic asthma and airway remodelling in some studies in adults. This protein is considered as a biomarker of asthma, and serum levels exhibit very low variability and high reproducibility. [16] Other studies have found no differences between eosinophilic and noneosinophilic airway inflammation in terms of serum levels of periostin. [41] Some published studies have also concluded that adult patients with high levels of periostin show a better response to treatment with inhaled corticosteroids, [42] omalizumab, [44] or lebrikizumab (anti-IL-13). [44] All this suggests that periostin is linked to increased inflammatory or immunological activity.

To date, there are only few published studies on this biomarker in children. Levels of periostin have been shown to be higher in children than in adults [4]. Lopez-Guinsa et al. [5] detected a greater expression of periostin in the nasal and bronchial mucosa of children with asthma. Song et al. [6] found significantly higher periostin values in children with asthma compared with healthy children or atopic children without asthma. Moreover, Konradsen and his working group [7] analysed biomarkers of Th2-inflammation in 96 children with persistent asthma, finding levels of eosinophils and FeNO to have a high predictive value for identifying SA, and found no relationship between periostin and SA. Recently Inoue et al. [8] suggest that measuring levels of serum periostin combined with the measurement of FENO, eosinophilia and lung function could improve the diagnosis of asthma in children. In our study, we found serum periostin levels much higher than in studies published. We must take into account that in these studies all patients had mild or moderate controlled asthma with a correct treatment, and the children in our study were uncontrolled patients and without correct treatment. We found lower mean serum periostin values and a lower proportion of patients with levels >1000 ng/ml in the group with UcSA. We found no correlation between the presence of this protein in serum and total IgE, eosinophil counts and FEV1 or FeNO values, unlike the results in adults. Possible confounding factors such as atopic dermatitis, rhinitis or age were similar in both groups. In our

series, high levels of serum total IgE, eosinophilia and FeNO >20ppb were observed in the group with UcSA, which is consistent with the data published in other studies; however, there was no relationship between these biomarkers and periostin.

The limitations of this study included not having a healthy control group to compare variables, wide variability in levels of asthma control and severity over time, and the sample size, which may have influenced some statistical findings. Nevertheless, it is the first study on periostin in children with poorly controlled asthma, and that suggesting that there may be differences in levels of periostin to be related to the severity of asthma in children. We continue with this line of research, we are currently measuring serum periostin of healthy children without allergies and allergic without asthma, as a control group; and are also studying the levels of serum periostin once a prospective follow-up one year.

Periostin appears to be related to the inflammatory process in asthma, although the mechanisms remain to be fully understood. The inflammatory mechanism is not a unique and isolated characteristic of each type of asthma patient, especially in children. This disease is subject to a complex interaction of many molecular and cellular factors, as well as genetic predisposition and environmental factors.

In our sample of uncrontrolled asthmatics children, serum periostin levels do not discriminate between severe and not serious asthma. Further studies are needed with controlled and uncontrolled asthma, to establish clinical relevance. This opens up an interesting research to improve the future management of asthma in children.

Ethical principles

Data confidentiality: The main author states that the study protocol was observed and that the Data Protection Act relating to the publication of patient data was complied with. In addition, all patients and their legal guardians received sufficient information and were given informed consent forms.

The main author obtained the informed consent of the patients and/or their legal guardians, and is in possession of the forms.

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The main author states that no experimental studies have been carried out for their research.

This study had been present at as the "30 SEAIC National Congress", (October 20, 2016) with the title "Periostin as asthma biomarker ".

Conflicts of interest

The authors declare that they have no conflicts of interest in relation to this article

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Table 1. Definition of uncontrolled severe asthma[10, 11]

- OC used for six months or more in the last year or - High-dose IC used in combination with other drug
At least one of the following
- Air flow limitation: FEV1 <80% (after bronchodilatador) - Two or more OC burst in the previous year - Hospital admission in the previous year - Previous life-threatening episode - ACT <20

OC: oral corticosteroid, IC: inhaled corticosteroids

Table 2. Criteria for uncontrolled asthma according to Level of asthma symptom control of GINA 2016 [9] and value of FEV1.

UNCONTROLLED ASTHMA three or more of the following criteria:
Daytime symptoms >twice/week
Limitation of activity diary life
Night-time symptoms or awakenings
Need for rescue medication >2x/week
FEV1 <80%

Table 3. Inclusion and exclusion criteria

INCLUSION CRITERIA	EXCLUSION CRITERIA
- Diagnosis of uncontrolled asthma - Age: 5-14 years (inclusive) - Signed informed consent form - Able to read and understand Castilian	- Serious cardiopulmonary disease - Cancer (excluding cancer in remission for >5 years) - Serious psychiatric disorders

Table 4. Clinical and sociodemographic characteristics

Variables	Total (n = 50)	UcSA group (n = 19)	"NO UcSA" group (n = 31)	P value
Sociodemographic Characteristics				
Age	9.3±3.5	9.3±3.6	9.3±3.4	0.9947
Male sex	36 (72%)	12 (63.2%)	24 (77.4%)	0.2756
Female	14 (28%)	7 (36.8)	7 (22.6%)	0.2756
Exposure to cigarette smoke	18 (36%)	3 (15.8%)	15 (48.4%)	**0.0198***
Clinical data				
BMI (kg/m^2)	19.4±4.2	19.6±4.2	19.4±4.3	0.8563
Onset of symptoms				0.1243
1st year of life	32 (64%)	15/19 (78.9%)	17 (54.8%)	
Preschool	13 (26%)	4/19 (21.1%	9 (29%)	
School	5 (10%)		5 (16.1%)	
Exacerbations				**0.0544**
1-12/year	16 (32%)	3/19 (15.8%)	13 (41.9%)	
>12/year	34 (68%)	16/19 (84.2%)	18 (58.1%)	
Hospital admissions	19 (38%)	12 (63.2%)	7 (22.6%)	**0.0041***
Limitations in the activities of daily living	36 (72%)	19 (100%)	17 (54%)	**<0.001***
Limitations in exercise tolerance	46 (92%)	19 (100%)	27 (87.1%)	0.2839
School absenteeism	38 (76%)	18 (94.7%)	20 (64.5%)	**0.0182***
Parental absenteeism	25/49 (51%)	13 (68.4%)	12 (40%)	**0.0525**
Rhinitis	48 (96%)	18 (94.7%)	30 (96.8%)	1.00
Overweight	9 (18%)	4 (21%)	5 (16.1%)	0.7152
Food allergies	16 (32%)	6 (31.6%)	10 (32.3%)	0.9601
Atopic dermatitis	31 (62%)	13 (68.4%)	18 (58.1%)	0.4640

*Statistically significant differences. UcSA: uncontrolled severe asthma. BMI: Body Mass Index. Quantitative variables expressed as mean ± standard deviation.

Table 5. Biomarkers and measuring tools

Variables	Total (n = 50)	UcSA group (n = 19)	"No UcSA" group (n = 31)	P value
Biomarkers				
Total IgE (IU/ml)	536±682	608.9±612.3	490.7±727.5	0.2946
IgE >500 IU/ml	16 (32%)	10 (52.6%)	6 (19%)	**0.02***
FeNO >20 ppb	29/42 (69%)	12 (85.7%)	17 (60.7%)	0.1587
Eosinophils >400/c	31 (62%)	10 (52.6%)	21 (67.7%)	0.2853
Periostin >1,000 ng/ml	22/43 (51,2%)	5/16 (31.2%)	17/27 (63%)	**0.04***
Periostin (ng/ml)	972±678	727±499	1,117±735	**0.05**
Sensitisation to aeroallergens aeroallergens	42 (84%)	16 (84.2%)	26 (83.9%)	1.00
Pollen	35 (70%)	13 (68.4%)	22 (71.0%)	
Mites	25 (50%)	11 (57.9%)	14 (45.2%)	
Fungi	20/49 (40.8%)	6 (31.6%)	14 (46.7%)	
FEV1 (pre-BD%)				**0.0233***
>80%	40 (80%)	12 (63.2%)	28 (90.3%)	
80-70%	7 (14%)	4 (21.1%)	3 (9.7%)	
<70%	3 (6%)	3 (15.8%)	0	
Measuring tools				
ACT (score)				0.1173
>19	15/49 (30.6%)	3 (15.8%)	12/30 (40%)	
14-19	18/49 (36.7%)	7 (36.8%)	11/30 (36.7%)	
<14	16 (32.7%)	9 (47.4%)	7/30 (23.3%)	
PAQLQ	**4.3±1.3**	**3.9±1.5**	**4.6±1.2**	**0.0729**

**Significant differences. UcSA: Uncontrolled severe asthma. FeNO: Fractional exhaled nitric oxide. cACT: childhood Asthma Control Test. PAQLQ: Paediatric Asthma Quality of Life Questionnaire. Quantitative variables expressed as mean ± standard deviation.*