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Importance of the Functional Biomarker FEF 25%-75% in the Evaluation of Children and Adolescents with Asthma Sensibilized to House Dust Mites

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Abstract **Original Research Article**

***Introduction*:** The GINA and the ATS do not mention that the forced expiratory flow between 25% and 75% of forced vital capacity (FEF 25%-75%) play importance in evaluation of airflow obstruction in asthma. ***Objectives*:** To investigate whether the evaluation of the FEF25%-75% in children and adolescents with asthma sensibilized to house dust mites (HDM) plays an important hole in airway obstruction from small airways. ***Methods*.** A retrospective study was done in Hospital Municipal Jesus (Rio de Janeiro, Brazil). Thirty-four children and adolescents with asthma were enrolled between January 2016 and December 2019. The FEIA (Immuno CAP®) was used to measure total and specific IgE antibodies to HDM. Standard reference value for small airways diseases with FEF 25%-75% was considered abnormal if below at 65% of predicted with FEV1/FVC ratio above or equal at 80%. ***Results*.** There was a significant difference between the mean ages of the sensitized (n=26; 9.8±2.53) and non-sensitized participants (n=8; 7.75±1.28) to HDM (P=0.0353). Male and female sexes were not significant in both groups (P=0.3698 and P=0.3298, respectively). If the FEF 25%-75% (L/s) was not valued in our study, 62% of sensitized participants (44.27±9.26) and 38% not sensitized (56.62±16.56) to HDM would be considered "according to normal reference values" (t=1.86; P=0.0719). ***Conclusions*.** The asthma in this study presented an obstructive respiratory disorder of small airways, regardless of a sensitization or a non-sensitization to HDM. The obstructive respiratory disorder of small airways was present, even with normal spirometry in the evaluation of large airways.

Keywords: Asthma, children, adolescents, spirometry, small airways, FEF25%-75%.

INTRODUCTION

The asthma is a common chronic disease in children [1-3]. The house dust mites (HDM) are abundantly present in house dust and are considered allergens that trigger allergic asthma. The Dermatophagoides pteronyssinus, Dermatophagoides farinae, Euroglyphus maynei, Pyroglyphus africanus, Tyrophagus putrescentiae, and Blomia tropicalis are HDM prevalent in Brazil [4].

The diagnosis of asthma is confirmed by the history of symptoms and evidence of variable expiratory airflow limitations documented by spirometry with bronchodilatador reversibility and/or other functional respiratory tests [2].

The Global Initiative for Asthma Management and Prevention (GINA, 2021), like the guidelines of the American Thoracic Society (ATS, 2019) do not mention that the forced expiratory flow between 25% and 75% of forced vital capacity (FEF 25%-75%) play importance in evaluation of airflow obstruction in asthma by spirometry [2, 5]. However, there are many studies that concluded that the FEF25%-75% is more

sensitive as an indicator of symptomatic asthma than the FEV1 in children and adults. The FEF25%-75% is less effort-dependent than the FEV1, and it is a functional biomarker of small airway diseases (SAD).

In children, the FEV1/FVC has a correlation with symptoms and medications in large airways while the FEV1 does not [6-9]. The purpose of this study is to investigate whether the evaluation of the FEF25%-75% in children and adolescents with asthma sensibilized to HDM plays an important hole in an airway obstruction from small airways.

METHODS

Subject Characteristics and Study Design

This retrospective cohort study was done in the city of Rio de Janeiro, Brazil. Patients were recruited from the city's public Hospital Municipal Jesus, which offers free attention and treatment. The protocol was approved by the bioethics committee of the Fluminense Federal University under number 31156520.8.3001.5279. Children and adolescents treated at emergency for asthma, defined according to the validated criteria stated by GINA were enrolled between January 2016 and December 2019. A pediatric physician obtained medical history, reviewed home medications, allergies, and review of systems. Written consent was obtained from the child's caregiver.

Inclusion and exclusion criteria

Our participants eligible for spirometry tests had asthma classified as controlled considering the last 4 weeks by GINA, ACQ-6 (Asthma Control Questionnaire without spirometry), and ACT (Asthma Control Test) criteria [10]. Children and adolescents with other chronic conditions and medications were excluded, that were smoking, acute or chronic upper and lower respiratory infections, anatomic nasal disorders, previous or current specific immunotherapy, long-acting beta-2-agonists, antileukotrienes, antihistamines, and patients treated with inhaled corticosteroids and other controller medications to eliminate the interference of anti-inflammatory treatment on results [6, 11].

Atopy test

Atopy was defined by a documented history of sensitization to 1 or more aeroallergens with total and specific serum IgE testing determined by the chemiluminescence immunoassay (CLIA) and FEIA methods, respectively, by commercial kits. The fluorescence enzyme immunoassay (FEIA) with encapsulated cellulose polymer solid-phase (Immuno CAP®) was used to measure specific IgE antibodies to HDM represented by Dermatophagoides pteronyssinus, Dermatophagoides farinae, and Blomia tropicalis according to manufacturer's instructions [12]. ImmunoCAP™ is recognized as the gold standard technology for specific IgE blood tests [13]. The exams were processed in the automated equipment UNICAP 1000 in a commercial laboratory. This equipment performs quantitative measurements of specific IgE in serum with immunoCAP technology. Results were calculated in KU/L. Sensitization by HDM was defined with a specific IgE ≥ 0.35 kU/L [12].

Spirometry

The spirometry test was performed using a Vitalograph Spirotrac® diagnostic workstation software. The test interpretation was based on latest ATS/ERS & GINA standards. Standard reference value for small airways diseases with FEF 25%-75% was considered abnormal if below at 65% of predicted with FEV1/FVC ratio above or equal at 80%. Considering a possible variability effort dependent of FEF 25%-75%, a result was considered valid after five repeated measurements with a variability minor than 5% [6].

Statistical Analysis

All quantitative and qualitative data from the participants were analyzed after using Microsoft Excel spreadsheets, version 2010. Both descriptive and inferential statistics were performed using version 6.0 of the GraphPad software and MedCalc Software for version 15.0 for Windows. Post hoc analyzes were performed using a robust computerized tool called GPower 3.1, a software written by Franz Faul, University of Kiel, Germany, Copyright (C), 1992-2014. The collected data were analyzed using univariate statistical tests. The Shapiro-Wilk and Kolmogorov-Smirnov tests were used to assess the normality of the data and the homogeneity of the variances. Non-normal distributions were expressed as medians and interquartile ranges (IQR) of 25%-75% probability. Qualitative or categorical variables were expressed as proportions. The non-parametric Chi-square test was used to compare proportions. The nonparametric Mann-Whitney-Wilcoxon U test was used to compare the medians of data from two independent groups when they were not normally distributed and because logarithmic transformation was not performed. Paired and unpaired t tests for independent samples were used to compare means when the distribution of the studied variables had a normal distribution. Calculations of the diagnostic parameters of the FEF25%-75% were performed using a 2x2 contingency table with a known reference value lower than 65%. A two-tailed P *value* or descriptive level or probability of significance of 0.05 or less and confidence intervals (CI) with 95% probability were considered to indicate statistical and clinical significance. A complete case was used as the primary analysis if the proportions of missing data were insignificant, such as below approximately 10%. However, missing quantitative data were replaced by the mean or median, as appropriate, according to the normality distribution tests.

RESULTS

The demographic, IgE levels, and spirometric characteristics in asthmatic children and adolescents on HDM sensibilisations are shown in Table 1.

A total of 34 children and adolescents were recruited according to an inclusion and exclusion criteria. The results reached a power in post hoc data analysis of 0.99 for a significance level of 5% and a critical value of t=2.00958. The value of an effect size was d=1.85 in our results [14, 15].

The percentages of 62% of sensitized participants and 38% of not sensitized to HDM had asthma with small airways disease by FEF 25-75% index and "normal reference values" in the spirometry report according to FEV1/FVC ratio (Table 1).

Table 1 - Demographic characteristics and other parameters in the sample obtained from 34 participants with asthma who underwent spirometry and biomarkers tests for the diagnosis of sensitization to house dust mites at the Hospital Municipal Jesus, Rio de Janeiro, between the periods from January 2016 to December from 2019

Parameter	**Sensitized participant (case)**	**Non-sensitized participant (control)**	**Test (Two-tailed P value)**
Sample size, n	26	8	X^2=18.117 (P<0.0001)
Prevalence (%)	76.0	24.0	X^2=6.949 (0.0084)
Age (years), median ± SD	9.80±2.53	7,75±1.28	t=2.19 (0.0353)
Male (n, %)	17 (66.0)	3 (38.0)	X^2 =0.805 (P=0.3698)
Female (n, %)	9 (34.0)	5 (62.0)	X^2 =0.950 (P=0.3298)
Total serum IgE (IU/L)*, median, IQR 25%-75%	782.5 (506.5-1660,0)	22.0 (13.25-44.25)	U=0.000 (<0.0001)
Serum IgE** – *D. pteronyssinus* (KU/L), median, IQR 25%-75%	100.0 (35.25-100.0)	0,0	-
Serum IgE** – *D. farinae* (KU/L), median, IQR 25%-75%	64.50 (28.50-100.0)	0,0	-
Serum IgE** – *B. tropicalis* (KU/L), median, IQR 25%-75%	11.0 (6.50-23.75)	0,0	-
FVC pre BD – Liters (% predicted value), mean ± SD	92.54±14.44	95.25±17,31	t=0.4438 (0,6602)
FEV1 pre BD – Liters (% predicted value), mean ± SD	72.96±10.99	78.50±9.94	t=1.272 (0.2124)
FEV1/FVC (%), mean ± SD	86.35±9.376	91.13±6.749	t=1.333 (0.1920)
FEF 25%-75% pre BD - L/s (% predict value), mean± SD	44.27±9.96	56.62±13.56	t=1.86 (P=0.0719)
FEF25%-75% (L/s) pre BD <65% with FEV1/FVC ratio >80% (%)	62.0	38.0	X^2=1.39 (P=0.2383)

*Chemiluminescence method (CLIA) with reference value for 3-9 years: ≤ 52 IU/mL. **Fluorescence enzyme immunoassay (FEIA); sensitization by HDM was defined with a specific serum IgE ≥ 0.35 kU/L. Abbreviations: Total serum IgE, total immunoglobulin E in serum; FVC, Forced vital capacity; FEV1, Forced expiratory volume in the first second; FEV1/FVC ratio; BD, bronchodilator test; SD, standard deviation; t, unpaired t test; X^2, Chi-square test; IQR, interquartile range; U, Mann-Whitney test; HDM, house dust mites

DISCUSSION

The mean age (years) in our study was 9.8 for patients with asthma and sensitized to HDM. In the paper by Roncada et al. (2020) carried out in Porto Alegre (Brazil), also among children and adolescents was 11.0; 10.8 and 9.7 years, with no statistically significant difference among the GINA mild, moderate and severe asthma groups. In our series, there was a statistically significant difference between the mean ages of the sensitized (9.8±2.53) and non-sensitized participants to HDM (7.75±1.28, P = 0.0353), as shown in Table 1.

The median total IgE serum levels in the sensitized group were 782.5 IU/mL and 22.0 IU/mL in the non-sensitized group, as summarized in Table 1 (U=0.000; P<000.1). In Brazilian paper by Cabral *et al*., (2017), the "mean" with high standard deviation was total IgE equal to 721.0±682.3 in cluster 1 of asthmatic patients with phenotypes defined by normal spirometry, in addition to other parameters [17].

As shown in Table 1, the *D. pteronyssinus* had the highest median of IgE in sensibilized participants to HDM [100.0 (35.25-100.0)]. Brazilian paper published by Binotti et al.(2005) with 92 samples of mites from rugs analysed by light microscopy demonstrated a total of 483 mites bodies. The most prevalent families were *Pyroglyphidade* (81%), mainly *D. pteronyssinus* [18].

Analyzing Table 1, it can be concluded that only the assessment of the small airways by the FEF 25%-75% in spirometry was a good parameter to determine the functional ventilatory diagnosis of asthma in children and adolescents in our series, considering a reference value below 65% of the predicted value [6]. Cabral et al. (2017) concluded that "many children and adolescents with severe asthma have normal lung function during symptom-free days, as FEV 1 does not correlate well with symptoms; in addition, FEV 1 values of less than 80% are predicted to have low sensitivity for distinguishing different levels of asthma severity in children" [17]. Thus, the ATS guidelines for interpreting and classifying obstructive respiratory disorders should be used with caution in children and adolescents [5]. If the FEF 25%-75% were not valued in our study, 62% of sensitized participants and 38% not sensitized would be considered "normal" in the spirometry report. Considering the literature and Table 1, this study demonstrates the importance of the FEF 25-75% for the assessment of peripheral airways in children and adolescents with asthma. It was proposed that the maximum mean expiratory flow rate (MMEF or FEF 25-25%) derived from spirometry could be used in the evaluation, especially in the presence of a normal flow in relation to the forced expiratory volume in 1 s (FEV1) and forced vital capacity (FVC) ratio (FEV1/FVC). Recent and past research advocates that diagnostic criteria used to define obstructive respiratory disorder of small airways are repeated measurements of FEF 25-75%, FEF50% and FEF75% less than 65% of predicted [6-9].

Hansen *et al*., (1993) reports that sometimes small changes in a percentage or absolute values of a bronchodilation may be statistically non-significant but clinically important. They conclude that their studies demonstrate that it is preferable to use a patient as their own control rather than a significant response to inhaled beta-2-agonist based on variability in other subjects [19].

Finally, some considerations in this study should be mentioned. First, as a future perspective for the diagnosis of asthma in childhood and adolescence, attention was drawn to the importance of evaluating the small airways through FEF 25%-75% by spirometry. Second, the limitations of this study were the failure to use the forced oscillometry technique to assess the small airways of asthmatic participants, in addition to the absolute eosinophil count in peripheral blood and the failure to perform the exhaled fraction of nitric oxide for assessment of bronchial inflammation [20-22].

CONCLUSIONS

The asthma in children and adolescents in this study presented an obstructive respiratory disorder of small airways, regardless of a sensitization or a non-sensitization to house dust mites. The obstructive respiratory disorder of small airways was present, even with normal spirometry in the evaluation of large airways. In this group, FEF 25%-75% was the better index for diagnosing an airway obstruction than the FEV1/FVC ratio.

Additional information

Human subjects: A consent was obtained by all participants. Conflicts of the interest: According to the ICMJE uniform disclosure form, all authors declare the following: Payment/services: All authors have declared that no financial support was received from any organization for the submitted paper. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted paper.

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