Scholars Journal of Medical Case Reports
Abbreviated Key Title: Sch J Med Case Rep
ISSN 2347-9507 (Print) | ISSN 2347-6559 (Online)
Journal homepage: https://saspublishers.com

OPEN ACCESS

Pulmonology

The Diagnostic Performance of the FEF 25%-75% in the Evaluation of 34 Cases of Asthmatic Children and Adolescents Sensitized and Non-Sensitized to House Dust Mites

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DOI: 10.36347/sjmcr.2022.v10i08.007 | **Received:** 13.06.2022 | **Accepted:** 19.07.2022 | **Published:** 06.08.2022

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Abstract **Case Report**

The guidelines for asthma and spirometry do not mention the forced expiratory flow between 25% and 75% of forced vital capacity (FEF 25%-75%) in evaluation of airflow obstruction in asthma. The aim of this study was to assess the diagnostic performance of the FEF 25%-75% of children and adolescents with asthma sensitized to house dust mites (HDM). A retrospective case series was done in the Hospital Municipal Jesus, Rio de Janeiro, Brazil with 34 participants with asthma sensitized (n=26) and non-sensitized (n=8) to HDM. Standard reference value for FEF 25%-75% was considered abnormal if below at 65% of predicted. The percentages of 62% of sensitized participants and 38% of not sensitized to HDM had asthma with small airway obstruction by FEF 25-75% index and normal reference values for large airway flow in the spirometry report according to FEV 1/FVC ratio. The means of FEF 25%-75% for HDM and non-HDM were 44.27±9.96 vs. 56.62±13.56, respectively (t=1.86, P=0.0719). The results calculated were a positive predictive value of 80%, a sensitivity of 65%, and an accuracy of 62% amongst other significant parameters (P<0.05). We concluded that the FEF 25%-75% had a high diagnostic performance in children and adolescents with asthma sensitized to HDM.

Keywords: Asthma, children, adolescents, biomarker, small airway, FEF25%-75%.

INTRODUCTION

The guidelines of the asthma (GINA, 2021) and spirometry (Graham et al., 2019) do not mention that the forced expiratory flow between 25% and 75% of forced vital capacity (FEF 25%-75%) is important in evaluation of airflow obstruction in asthma. The aim of this case series report was to assess the diagnostic performance of the FEF25%-75% of children and adolescents with asthma sensitized to house dust mites (HDM).

METHODS

The 34 participants eligible for spirometry tests had asthma. Children and adolescents with other chronic conditions, current active infection, and active smoking were excluded. The participants were notified about no use of medications before the test and confirmed it at the time of the test (Aggarwal *et al.*, 2019). Atopy was defined by a history of sensitization to one or more allergens with total and specific serum IgE testing determined by the CLIA and FEIA methods,

respectively. Sensitization by HDM was defined with a specific IgE ≥ 0.35 kU/L (Popescu and Vieru, 2021). The spirometry was performed using a Vitalograph Spirotrac®. The diagnostic parameters of the FEF 25%-75% were performed using a 2x2 contingency table. The cases were all participants with standard reference value for FEF 25%-75% considered abnormal if below at 65% of predicted with FEV1/FVC ratio above or equal at 80% (Ciprandi *et al*., 2012). The controls were all participants with FEV1/FVC ratio above or equal at 80% and FEF 25%-75% equal and above 65% of predict. The dataset normality was observed. A two-tailed P value of 0.05 or less and confidence intervals (CI) with 95% probability were considered to indicate statistical and clinical significance, respectively.

CASE SERIES

This retrospective case series (Abu-Zidan, *et al*., 2012) had a protocol approved by the bioethics committee. The participants were recruited from Hospital Municipal Jesus, Rio de Janeiro, Brazil, at emergency, between January 2016 to December 2019. The asthma was defined according to the validated criteria stated by GINA. Before the spirometry test all were classified as controlled considering the last 4 weeks (Pizzichini *et al*., 2020).

Our sample size was according to an inclusion and exclusion criteria. The results reached a post-hoc statistical power of 99% for a P-value of 5% and a critical t-value equal to 2.00958. The value of statistical effect size (d=1.85) was interpreted as very large (d>1.30) according to the Table presented by Sullivan and Feinn (2012), modified from another Table by Ferguson in 2009.

The prevalence obtained of children and adolescents with sensitization was 76% (n=26/34) and 24% for non-sensitization (n=8/34) to the main HDM in Brazil (X2 =6.949; P=0.0084).

There was a statistically significant difference (t=2.19; P=0.0353) between the mean ages of the sensitized (9.8±2.53) and non-sensitized participants (7.75±1.28). The male sex was 66% (n=17/26) for HDM and 38% (n=3/8) for non-HDM. The female sex was 34% and 62%, respectively, with P-values > 0.05).

The median total IgE serum levels in the sensitized group was 782.5 IU/mL and 22.0 IU/mL in the non-sensitized group (U=0.000; P<000.1). The *D. pteronyssinus* had the highest median of IgE in sensitized participants to HDM [100.0 (35.25-100.0)].

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 (X^2=1.39, P=0.2383) and "normal reference values" in the spirometry report according to FEV1/FVC ratio. The means±SD of FEF 25%-75%, respectively, were 44.27±9.96 vs. 56.62±13.56 (t=1.86, P=0.0719).

The Table 1 shows our results.

Table 1: The diagnostic performance of FEF 25%-75% as a biomarker for the diagnosis of small airway obstructive respiratory disorder in 26 children and adolescents with asthma sensitized to HDM in the absence of large airflow obstruction (FEV1/FVC≥80%)

PARAMETERS*	RESULT	CI 95%	P-value**
Sensitivity (%)	65.0	44.33-82.79	<0.05
Specificity (%)	50.0	15.07-84.30	<0.05
Positive predictive value - PPV (%)	80.0	66.23-89.74	<0.05
Negative predictive value- NPV (%)	31.0	16.03-52.16	<0.05
Positive likelihood ratio (PLR)	1.31	0.62-2.76	>0.05
Negative likelihood ratio (NLR)	0.69	0.29-1.65	>0.05
Accuracy (%)	62.0	43.49-77.77	<0.05
Diagnostic Odds Ratio (DOR)	1.89	0.18-4.92	>0.05
Prevalence of sensitization to HDM (%)	76.0	59.87-95.12	<0.05

Abbreviations: HDM, house dust mites; 95% CI, Confidence interval at the 95% probability. *Reference value for FEF25%-75%: less than 65% of predicting. **P<0.05 for the confidence intervals of the percentages because they do not contain the value 1. P>0.05 for the CI of the absolute values because they have a value of zero.

DISCUSSION

According to the Brazilian guidelines, with reduced FEF 25%-75%, clinical data compatible for obstructive disease, and with the FEV1/FCV ratio above 70%, the spirometry report will be of mild obstructive respiratory disorder of small airways. In this document, the standard reference value for FEF 25%-75% also is considered abnormal if below at 65% of predicted for adults, adolescents, and children (Pereira, 2002).

In Table 1 was found in sensitized participants a high diagnostic performance due to the PPV (80%), sensitivity (65%), and accuracy (62%) with P-values minor than 0.05. The reduced FEF 25%-75% values were reported to be significantly associated with the

presence of high fractional FeNO levels in children with allergic asthma (Tosca *et al*., 2016).

CONCLUSION

The asthma in children and adolescents with sensitization to HDM presented a mild obstructive respiratory disorder of small airways with high diagnostic performance in the absence of a normality in the evaluation of large airways.

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