Nonasthmatic Eosinophilic Bronchitis and Asthma Development: analysis of biomarkers

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In 1989, Gibson et al. described a condition that manifests as a corticosteroid-responsive chronic cough in non-smokers, with no variable airway obstruction or airway hyperresponsiveness (AH), though with airway eosinophilia [1]. This condition was termed nonasthmatic eosinophilic bronchitis (NAEB). The prevalence of NAEB is uncertain, but NAEB accounts for 10%-30% of specialist referrals among patients with chronic cough [2,3]. The etiology of NAEB is not well known, although it has been associated with exposure to common inhaled allergens and occupational sensitizers [4]. These conditions share immunopathological features with asthma, including airway eosinophilia and a similar degree of basal membrane thickening. However, NAEB seems to differ mainly in terms of fewer mast cells in the bundles of airway smooth muscle [5], and in prostaglandin E2 production [6]. Both findings likely offer a partial explanation of why NAEB manifests as bronchitis and cough without AH.

The natural history of NAEB has not been thoroughly studied. Larger series of patients with NAEB reported that is rarely self-limiting, and some patients progress to asthma [7-9]. Aiming to assess potential predictive markers of

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asthma and the natural history of NAEB, we retrospectively included consecutive subjects over 18 years of age who presented to our hospital with a diagnosis of NAEB between 2003 and 2019.

The Ethics Committee of University Hospital Fundacion Jimenez Diaz approved this study. All patients had prolonged cough lasting > 3 weeks which was not related to exposure to allergen/s detected by skin prick tests. Included patients had a normal chest radiograph, negative methacholine test (>16 mg/mL), and 3% sputum eosinophils. In some patients, adenosine challenge was performed. Induced sputum, bronchial challenges and FeNO methods have been described in detail previously (10). All the patients were treated with medium-high doses of inhaled steroids.

Quantitative variables were checked for normality and described by mean and standard deviation, and qualitative variables by absolute and relative frequencies. Paired data was analysed by paired-t test, inter-group comparisons were performed using Student's t test or U Mann-Whitney for quantitative variables, and chi-square test or Fisher's exact test for qualitative variables. Associations between quantitative variables were studied with Pearson's correlation coefficient. Logistic regression models were used to identify factors potentially associated with asthma development. P values <0.05 were considered significant.

Data collected included demographic characteristics, presence of atopy (1 or more positive skin test response or specific IgE to common allergens), allergic

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rhinitis and clinical course based on recovery from disease, number of disease relapses and development of asthma, Other characteristics included were pulmonary function tests, sputum eosinophil and peripheral blood eosinophil (PBE) count, exhaled nitric oxide (FeNO), and bronchial hyperreactivity to methacholine at least on first and last visit. A major limitation of this study is the retrospective design.

Forty-one NAEB patients fulfilled the diagnosis criteria and were followed for a mean of 5.8 years (range, 1-15 years). Results are summarized in Table E1: supplementary material. Three patient's groups were made depending on their clinical course during follow-up: relapse group (>1 clinical EB exacerbation-cough recurrency), non-relapsing (suitable clinical control), and asthma development (asthma symptoms during follow-up with postbronchodilator FEV1>12% on spirometry and/or methacholine PC20 <16 mg/ml). 41.46% of patients experienced relapse (cough) during follow-up with a mean of 2 relapses/patient. Retreatment with inhaled steroids controlled the recurrent cough in all patients.

In 16 patients, sputum was repeated during follow up (8 in non-relapsing group, 5 in relapsing and in 3 with asthma progression). There was a significant decrease in sputum eosinophilia percentage from the initial to the last visit (8%(5.9) vs 2.42%(2.4), p<0.05. 43.9% of patients had >300cells/μL and 17% >500cells/ μL of PBE at baseline visit, stable during follow-up (p=0.59). There is no significant difference in FeNO between baseline and last visit (46.59(57.11) vs 34.56(33.8) ppb p=0.95). At baseline, 29.1% of patients had FeNO<20 ppb, 44.5% between 20-50 ppb and 26.3% >50 ppb.

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We examined the relationship of sputum eosinophils with PBE count, finding no correlation (r=-0.17 p=0.65). Therefore, PBE was not a potential biomarker for airway eosinophilia in NAEB. The correlation of eosinophils in sputum and FeNO was 0.21 (p=0.23). We also studied correlations of PBE, FeNO, or sputum eosinophils at baseline and number of relapses, though none had significant results (r=-0.37, r=-0.14 and r=0.55, respectively, p> 0.05).

The median length of time to asthma development was 2 years. Baseline FeNO in patients who developed asthma was significantly higher compared with total studied group (95.2(124) vs 46.59(57.11), ppb p <0.05). Lung function was stable between baseline and last visit in all patients, including asthma development group (FEV1 110.8%(18.2) vs 108.63%(15.06), p= 0.95; FEV1/FVC 80.90 (5.9) vs 80.40(5.85), p=0.95). Atopy and allergic rhinitis were present in all patients who developed asthma; in contrast with the other groups, in which atopy and allergic rhinitis were present in 53.8% and 38.4% respectively in relapse group and 50% both in non-relapse group. Univariate logistic regression analysis (sex, age and FeNO) shows that only FeNO levels was significantly associated with asthma development (OR1.016 (1.002-1.041) p=0.028). Due to low number of patients was not possible to apply multivariate analysis. However, when compared asthma development with sex, atopy, and rhinitis (Fisher exact test) and age and FeNO (U-Mann-Witney) only the presence of atopy and rhinitis were significant (p=0.023 and 0.009, respectively).

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In other NAEB series, development of asthma varied from 9% described by Berry et al., 3% [7] by Park et al. [8], and 5.7% in the study by Lai et al. [9]; in our study, 15% developed asthma. NAEB patients with high FeNO at baseline, atopy, and allergic rhinitis, are more prone to develop asthma (12%) These clinical features may suggest that OEB is an early “preclinical” stage of asthma. NAEB recurrence was frequent in all series reviewed [7-9] despite substantial variation (15%-90%, with 38% found for our patients), confirming that recurrence is a common outcome. FEV1 remains stable during follow-up in all groups studied. This finding agrees with the study by Lai K, et al [9], but not with other studies [7,8]. Park et al. [8] suggested that a recurrent episode of EB is associated with progressive deterioration of the airflow rate.

Few studies had evaluated the FeNO as diagnostic tool in this entity. Mi-Jung et al. depicted that a FeNO value < 31.7 ppb has a helpful negative likelihood ratio (0.19) for determining the absence of NAEB. However, Wiszniewska et al. in patients with occupational NAEB (4) Feno showed a moderate diagnostic accuracy with an estimated sensitivity of 72% and a specificity of 83%. In our study we found a wide variation of FeNO among our patients. Applying the cut-off of Mi- Jung et al. we missed 40% of our patients. On the contrary, to the former authors we did not find a correlation between FeNO and eosinophils in sputum.

Though uncommon, NAEB is neither entirely benign nor self-limiting, since half of the patients experience numerous relapses. The non-invasive markers PBE

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and FeNO were not sufficiently good to substitute induced sputum analysis for diagnosis and follow-up. Further studies are necessary to confirm these results.

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Conflict of interest

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