Nonasthmatic Eosinophilic Bronchitis and Asthma: Analysis of Biomarkers

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In 1989, Gibson et al [1] described a condition known as nonasthmatic eosinophilic bronchitis (NAEB), which manifests as corticosteroid-responsive chronic cough in nonsmokers and in which eosinophilia is recorded in the airway, albeit with no variable airway obstruction or airway hyperresponsiveness. This condition was termed nonasthmatic eosinophilic bronchitis (NAEB). The prevalence of NAEB is uncertain, although it accounts for 10%-30% of specialist referrals among patients with chronic cough [2,3]. While its etiology is not well known, NAEB 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 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 airway hyperresponsiveness.

The natural history of NAEB has not been thoroughly studied. Larger series of patients with NAEB reported that it is rarely self-limiting, with some patients progressing to asthma [7-9]. In order to assess potential predictive markers of asthma and the natural history of NAEB, we retrospectively included consecutive individuals aged ≥18 years who came to our hospital with a diagnosis of NAEB between 2003 and 2019.

The Ethics Committee of University Hospital Fundación Jimenez Diaz approved this study. All patients had prolonged cough lasting >3 weeks that was not related to exposure to allergen(s) detected by skin prick tests. The patients included had normal chest radiograph findings, a negative methacholine test result (>16 mg/mL), and 3% sputum eosinophils. Some patients underwent adenosine challenge. Induced sputum, bronchial challenge, and fractional exhaled nitric oxide (FeNO) have been described in detail previously [10]. All patients were treated with medium-high doses of inhaled corticosteroids.

Quantitative variables were checked for normality and expressed as mean (SD); qualitative variables were expressed as absolute and relative frequencies. Paired data were analyzed using a paired *t* test. Intergroup comparisons were performed using the *t* test or Mann-Whitney test for quantitative variables and the χ^2 test or Fisher exact test for qualitative variables. Associations between quantitative variables were studied using the Pearson correlation coefficient. Logistic regression models were used to identify factors potentially associated with asthma. *P* values <.05 were considered significant.

We recorded demographic characteristics, presence of atopy (1 or more positive skin test responses or specific IgE to common allergens), allergic rhinitis, and clinical course based on recovery from disease, number of relapses, and development of asthma. We also recorded pulmonary function test results, sputum eosinophil and peripheral blood eosinophil (PBE) counts, FeNO, and bronchial hyperreactivity to methacholine at least at the first and last visits. A major limitation of this study is its retrospective design.

Forty-one NAEB patients fulfilled the diagnostic criteria and were followed for a mean of 5.8 years (range, 1-15 years). The results are summarized in Table E1: supplementary material. Patients were divided into 3 groups depending on their clinical course during follow-up: relapse (>1 clinical exacerbation of eosinophilic bronchitis, recurrence of cough), nonrelapsing (suitable clinical control), and asthma (asthma symptoms during follow-up with postbronchodilator FEV_1 >12% in spirometry and/or methacholine PC_{20} <16 mg/mL). During follow-up, 41.46% of patients experienced relapse (cough), with a mean of 2 relapses per patient. Retreatment with inhaled corticosteroids controlled recurrent cough in all cases.

In 16 patients, sputum was reassessed during follow up (8 in the nonrelapsing group, 5 in the relapsing group, and 3 in the group with progression of asthma). The sputum eosinophil count decreased significantly from the initial to the last visit (8% [5.9] vs 2.42% [2.4]; *P*<.05). At the baseline visit, 43.9% of patients had PBE >300/μL and 17% >500/μL; these values remained stable during follow-up (*P*=.59). No significant differences in FeNO were detected between the baseline and the last visit (46.59 [57.11] vs 34.56 [33.8] ppb; *P*=.95). At baseline, 29.1% of patients had FeNO <20 ppb, 44.5% had 20-50 ppb, and 26.3% had >50 ppb.

Analysis of the association between sputum eosinophils and PBE count revealed no correlation (r=–0.17 *P*=.65). Therefore, PBE was not a potential biomarker for airway eosinophilia in NAEB. The correlation between eosinophils in sputum and FeNO was 0.21 (*P*=.23). We also studied correlations for PBE, FeNO, and sputum eosinophils at baseline and the number of relapses, although significant results were not detected (r=–0.37, r=–0.14, and r=0.55, respectively; *P*>.05).

The median time to onset of asthma was 2 years. Baseline FeNO in patients who developed asthma was significantly higher than for the total group (95.2 [124] vs 46.59 [57.11] ppb; *P*<.05). Lung function was stable between the baseline and last

visits in all patients, even in the asthma group (FEV_1, 110.8% [18.2] vs 108.63% [15.06], *P*=.95; FEV_1/FVC, 80.90 [5.9] vs 80.40 [5.85], *P*=.95). Atopy and allergic rhinitis were present in all patients who developed asthma, in contrast with the other groups, where atopy and allergic rhinitis were present, respectively, in 53.8% and 38.4% of the relapse group and in 50% and 50.0% of the nonrelapse group. Univariate logistic regression analysis (sex, age, and FeNO) showed that only FeNO level was significantly associated with onset of asthma (OR, 1.016 [1.002-1.041]; *P*=.028). Given the low number of patients, it was not possible to apply multivariate analysis. However, when onset of asthma was compared with sex, atopy, and rhinitis (Fisher exact test) and with age and FeNO (Mann-Whitney test), the only significant findings were for atopy and rhinitis (*P*=.023 and .009, respectively).

In other NAEB series, onset of asthma was reported in 9% by Berry et al [7], 3% by Park et al [8], and 5.7% 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 occupational eosinophilic bronchitis is an early, "preclinical" stage of asthma.

Recurrence of NAEB was frequent in all the series reviewed [7-9], despite substantial variation (15%-90%, with 38% in our study), thus confirming that recurrence is a common outcome. FEV_1 remained stable during follow-up in all the groups studied. This finding agrees with the study by Lai et al [9], but not with other studies [7,8]. Park et al [8] suggested that a recurrent episode of eosinophilic bronchitis is associated with progressive deterioration of the airflow rate.

Few studies have evaluated FeNO as diagnostic tool in this entity. Oh et al [11] reported 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 [4] reported that in patients with occupational NAEB, FeNO showed moderate diagnostic accuracy, with an estimated sensitivity of 72% and a specificity of 83%. We found wide variation in FeNO among the study patients. Applying the cut-off of Oh et al, we missed 40% of the study patients. In contrast, we did not find a correlation between FeNO and eosinophils in sputum.

While uncommon, NAEB is neither entirely benign nor self-limiting, since half of affected patients experience numerous relapses. The noninvasive markers PBE and FeNO were not sufficiently good to replace induced sputum analysis for diagnosis and follow-up. Further studies are necessary to confirm these results.

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Conflicts of Interest

JS reports having served as a consultant to ThermoFisher, MEDA, Novartis, Sanofi, Leti, Faes Farma, Mundipharma, and GSK and having been paid lecture fees by Novartis, GSK, Stallergenes, Leti, and Faes Farma, as well as having received grant support for research from ThermoFisher, Sanofi, and ALK. DB is supported by a Rio Hortega research contract. The remaining authors declare that they have no conflicts of interest.

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