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Original Research

ASTHMA

Increased Risk of Exacerbation and Hospitalization in Subjects With an Overlap Phenotype

COPD-Asthma

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Background: **Several COPD phenotypes have been described; the COPD-asthma overlap is one of the most recognized. The aim of this study was to evaluate the prevalence of three subgroups (asthma, COPD, and COPD-asthma overlap) in the Latin American Project for the Investigation of Obstructive Lung Disease (PLATINO) study population, to describe their main characteristics, and to determine the association of the COPD-asthma overlap group with exacerbations, hospitalizations, limitations due to physical health, and perception of general health status (GHS).**

Methods: **The PLATINO study is a multicenter population-based survey carried out in five Latin American cities. Outcomes were self-reported exacerbations (defined by deterioration of breathing symptoms that affected usual daily activities or caused missed work), hospitalizations due to exacerbations, physical health limitations, and patients' perception of their GHS obtained by questionnaire. Subjects were classified in three specific groups: COPD—a postbronchodilator (post-BD) FEV_1/FVC ratio of < 0.70; asthma—presence of wheezing in the last year and a minimum post-BD increase in FEV_1 or FVC of 12% and 200 mL; and overlap COPD-asthma—the combination of the two.**

Results: **Out of 5,044 subjects, 767 were classified as having COPD (12%), asthma (1.7%), and COPD-asthma overlap (1.8%). Subjects with COPD-asthma overlap had more respiratory symptoms, had worse lung function, used more respiratory medication, had more hospitalization and exacerbations, and had worse GHS. After adjusting for confounders, the COPD-asthma overlap was associated with higher risks for exacerbations (prevalence ratio [PR], 2.11; 95% CI, 1.08-4.12), hospitalizations (PR, 4.11; 95% CI, 1.45-11.67), and worse GHS (PR, 1.47; 95% CI, 1.18-1.85) compared with those with COPD.**

Conclusions: **The coexisting COPD-asthma phenotype is possibly associated with increased disease severity.**

CHEST 2014; 145(2):297–304

Abbreviations: BD = bronchodilator; GHS = general health status; GOLD = Global Initiative for Chronic Obstructive Lung Disease; LLN = lower limit of normal; PLATINO = Latin American Project for the Investigation of Obstructive Lung Disease; PR = prevalence ratio; SF-12 = Short Form 12 questionnaire

COPD and asthma are the most prevalent obstructive airway diseases worldwide. Several surveys have yielded varied global prevalence of COPD because of differences in diagnostic criteria and in study designs.[1-4] The Latin American Project for the Investigation of Obstructive Lung Disease (PLATINO) found an overall prevalence of COPD of 14.3%, according to GOLD (Global Initiative for Chronic Obstructive Lung Disease) stages I to IV, among people > 40 years of age in five Latin American cities.[3]

Few data exist on asthma prevalence in adults. Based on the application of standardized methods, it appears that the global prevalence of asthma ranges from 1% to 18% in different countries.[5]

In the past years, there has been great interest in identifying subgroups of COPD, the so-called COPD

phenotypes. Experts have proposed a definition for COPD phenotype as "a single or combination of disease attributes that describe differences between individuals with COPD as they relate to clinically meaningful outcomes (symptoms, exacerbations, response to therapy, rate of disease progression, or death)."[6] Several COPD phenotypes have been proposed; however, one of the most recognized is the overlap COPD-asthma.

Hardin et al[7] compared subjects with COPD and asthma to subjects with COPD alone in the COPDGene Study, and they found that 13% of subjects with COPD reported physician-diagnosed asthma. These subjects had worse health-related quality of life and experienced more frequent and severe respiratory exacerbations, despite younger age and reduced lifetime smoking history. In PLATINO, we found that 23% of the subjects with COPD have self-reported medically diagnosed asthma.[8] Marsh et al[9] estimated the prevalence of asthma in a COPD cohort to be 55.2% using a composite definition of asthma (post-bronchodilator [post-BD] increase in $FEV_1 > 15\%$, or peak flow variability > 20% during 1 week of testing, or physician diagnosis of asthma in conjunction with current symptoms). The comparison of different estimates is problematic because of different definitions of asthma.[9]

The aims of the present study are: (1) to evaluate the prevalence of three subgroups: asthma, COPD, and COPD-asthma overlap in the PLATINO population; (2) to explore the main characteristics among the three subgroups; and (3) to determine the association between COPD-asthma overlap with the outcomes: exacerbation, hospitalization, limitation due do physical health, and perception of general health status (GHS).

Manuscript received May 1, 2013; revision accepted August 20, 2013.

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*A complete list of PLATINO team participants is located in e-Appendix 1.

Funding/Support: The PLATINO study was funded by Boehringer Ingelheim GmbH; GlaxoSmithKline supported the analysis presented in this paper.

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DOI: 10.1378/chest.13-0622

Materials and Methods

The PLATINO study was a population-based survey carried out in Latin America; subjects performed spirometry with a portable spirometer (EasyOne spirometer; ndd Medical Technologies, Inc) at baseline and 15 min after the administration of 200 μg of salbutamol, according to the American Thoracic Society criteria of acceptability and reproducibility.[10] Complete details of the methodology have been published elsewhere.[11]

The outcomes of this paper were self-reported exacerbations in the last year defined as deterioration of breathing symptoms that affected usual daily activities or caused missed work (yes/no), number of self-reported exacerbations in the last year, hospitalizations in the last year due to the exacerbations (yes/no), number of hospitalizations in the last year, limitations due to physical health, and patients' perception of their GHS (in general you would say that your health is excellent, very good, good, fair, or poor, assessed by the Short Form-12 questionnaire (SF-12) Quality of Life Questionnaire; the last two options were joined for the multivariate analysis).

The independent variables were the three phenotypes: (1) COPD—based on the ratio of the post-BD $FEV_1/FVC < 0.70$[12]; (2) asthma—those who had answered positively for the question of wheezing in the last 12 months plus post-BD increase in FEV_1 or FVC of 200 mL and 12%; (3) overlap—the combination of the two previous diseases. "Medical diagnosis of asthma" (a self-reported prior diagnosis of asthma) was also applied as another definition for asthma, and the lower limit of normal (LLN) (defined as the lower fifth percentile for predicted post-BD FEV_1/FEV_6 and FEV_1/FVC using equations derived from our own population)[13] as another criterion for COPD (e-Appendix 2). Other variables were included as potential confounders (e-Appendix 2). The ethical committee of each site approved the study protocol, and the participants gave signed informed consent (listed in e-Appendix 2).

Statistical Analysis

Descriptive analysis was performed to obtain mean and SD for numerical variables and absolute and relative frequencies for categorical variables. Pearson χ^2 test was used for categorical variables and *t* test and analysis of variance for numerical ones. Poisson regression models were fit to assess the association of the outcomes and the exposures including estimates of the prevalence ratios (PRs) for dichotomous variables and the relative risk for count variables with 95% CI. In the multivariate analyses, the COPD group, as the largest group, was considered as the reference category.

Results

Out of the population of 5,044 subjects, 767 were classified as having one phenotype; 594 (11.7%) belonged to the COPD group, 84 (1.7%) to the asthmatic group, and 89 (1.8%) to the overlap group (Fig 1). The prevalence of these phenotypes using "medical diagnosis of asthma" is shown as e-Figure 1. e-Figure 2 shows the prevalence of these phenotypes calculated with a denominator of 767 (only those affected with asthma and COPD) rather than 5,044, as shown in Figure 1. The prevalence for overlap among only the affected population was 11.6% (95% CI, 9.2-14.0). Table 1 describes the characteristics of the groups; the asthmatic group showed younger age, fewer men, highest