The Reality of an Intermediate Type Between Asthma and COPD in Practice

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BACKGROUND: Asthma and COPD are obstructive airway diseases related to chronic airway inflammation. However, it is known that in real practice the 2 diseases overlap. OBJECTIVE: The purpose of this study was to investigate the reality of an intermediate type between asthma and COPD, when diagnosed by physicians in Korea. METHODS: The study involved 633 Korean patients with asthma, 157 with COPD, and 41 with an intermediate type. The latter group consisted of patients with clinically mixed or overlapping characteristics of asthma and COPD. The diagnoses were dependent on physicians' clinical decisions. We analyzed the clinical differences among the 3 groups. RESULTS: There were differences among the 3 groups in age, sex, atopy, and body mass index. Differences in smoking status, including percentages of current smokers, duration of smoking, and number of cigarettes smoked per day, were also observed. Pre-bronchodilator FEV_1 (%), FVC (%), and FEV_1/FVC (%) gradually decreased from the asthma group to the intermediate type group to the COPD group. Positivity of post-bronchodilator response, increase of FEV_1 (%) and post-bronchodilator FEV_1/FVC also showed gradual patterns. For emergency department visits and hospital admissions, frequencies were lowest in the asthma group, higher in the intermediate type group, and highest in the COPD patients. All *P* values were statistically significant (< .001). CONCLUSIONS: We have identified and characterized an intermediate type between asthma and COPD in clinical characteristics. Further investigations are required to determine whether these 3 conditions are part of the chronic obstructive airway diseases spectrum or are rather distinct clinical entities. *Key words: asthma; COPD.* [Respir Care 2012;57(8):1248–1253. © 2012 Daedalus Enterprises]

Introduction

Asthma and COPD are the most common chronic respiratory diseases worldwide. Their diagnostic criteria differ somewhat, in that asthma is a chronic inflammatory disorder of the airways, characterized by variable and reversible air-flow limitation,[1] whereas COPD is a chronic

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airway inflammatory disease characterized by air-flow limitation that is not fully reversible.[2] These 2 diseases also have different pathophysiologies.[3] However, they share many clinical features. It is sometimes difficult to discriminate between the 2 diseases by airway reversibility testings. In fact, a recent study showed that the majority of patients with moderate to very severe COPD demonstrate meaningful increases in lung function following administration of inhaled anticholinergic plus sympathomimetic bronchodilators.[4] A substantial proportion of asthmatic patients have partially reversible air-flow obstruction and even emphysematous changes in the lung.

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In addition, it is often challenging for a physician to accurately discriminate between asthma and COPD in patients who have characteristics of both diseases, especially when they have a history of smoking. Although tobacco smoking is typical of COPD, a considerable number of asthmatic patients smoke. The effects of smoking on asthma patients, however, have not been extensively studied, as smokers and ex-smokers have been excluded from many clinical studies of asthma phenotypes.

These ambiguous findings have suggested that asthma and COPD are distinct diseases, or that they are the same disease with different clinical manifestations. Certainly, some patients may have mixed, concurrent, or overlapping asthma and COPD. The clinical experience of many physicians has suggested that a subtype of "chronic obstructive airway disorders" (COAD) includes features of asthma overlapping with those of COPD.[5] As many patients are suspected of having overlapping asthma/COPD, it is necessary to identify and characterize this disease entity, both to understand the heterogeneity of COAD and to manage these patients more effectively. Most clinical studies of asthma and COPD have enrolled patients with one or other of these conditions, thus not with the overlapping subtype. The aim in this study was to describe overlap syndrome, underlining similarities and differences with both asthma and COPD group in 2 Korean cohorts.

QUICK LOOK

Current knowledge

Asthma and COPD are obstructive airway diseases related to chronic airway inflammation. There is clearly overlap of asthma and COPD in clinical practice.

What this paper contributes to our knowledge

An intermediate type of chronic obstructive airway disease, between asthma and COPD, was found to exist in clinical practice when diagnosed by physicians in Korea. These findings suggest that chronic obstructive airway disease represents different diseases that are each characterized by heterogeneity with differing phenotypes and overlapping features.

Methods

Subjects and Classification of Diagnoses

Patients with COAD were recruited from an adult asthma cohort named as the COREA (Cohort for Reality and Evolution of Adult Asthma in Korea) cohort, attending allergy or pulmonary clinics in 11 university hospitals in Korea,[6] and another COPD cohort named as the KOLD (Korean Obstructive Lung Disease) cohort, treated in the pulmonary clinics of 11 university hospitals in Korea.[7] The former mainly includes adult asthma patients, and the latter mainly includes COPD patients. All enrolled patients had at least one chronic persistent respiratory symptom consisting of dyspnea, cough, sputum production, or wheezing, for more than 3 months, or showed repetition of the symptom(s) for more than 3 months.

All patients were diagnosed by specialists in allergy and pulmonary departments as having asthma, COPD, or asthma plus COPD. We had clinicians classify the diagnosis by clinical decision rather than definite diagnostic criteria. Patients with tuberculous destroyed lungs, bronchiectasis, or lung resection, were excluded. Patients with clinically mixed or overlapping characteristics of asthma and COPD might be diagnosed by clinicians as having asthma plus COPD, or the "intermediate" type, comprehensively based on age, smoking status, pulmonary function, bronchodilator response, and chest radiographs or computed tomography scans. After applying these criteria, 633 subjects were diagnosed with asthma, 157 with COPD, and 41 with the intermediate type. The study was retrospectively analyzed by chart review. Informed written consent was provided by all adult subjects and the study design and protocol were approved by our institutional review board.

Assessments and Measurements

At enrollment, the subjects were in stable state and had a stable specific treatment. Demographic data were collected from each subject. Pulmonary function tests, including FEV_1, FVC, and bronchodilator response assessment, were performed according to standardized methods.[8] Post-bronchodilator spirometry was performed 10–15 min after inhalation of 400 μg of albuterol; an increase in FEV_1 that was both $>$ 200 mL and 12% above the pre-bronchodilator FEV_1 was considered clinically important.[9] The use of bronchodilators was prohibited for at least 4 days before the test. Airway hyper-responsiveness (AHR) was assessed

by methacholine challenge, as described in an earlier report.[10] An AHR-positive response was defined as a PC_{20} (provocational concentration of methacholine that produced a 20% decrease in FEV_1) of < 16 mg/mL. Skin prick tests employing 12 common allergens (Allergopharma, Reinbek, Germany) were employed for detection of atopy.[10] The panel consisted of house dust mites (*Dermatophagoides pteronyssinus, D. farinae*); cat fur; molds (*Aspergillus fumigatus*, *Alternaria tenuis*); various pollens (tree pollen mixture 1 [alder, hazel, popular, elm, and willow tree] and 2 [birch, beech, oak, and plane tree], grass pollen mixture [velvet grass, orchard grass, rye grass, timothy grass, Kentucky blue grass, and meadow grass], mugwort, and ragweed); German cockroach (*Blattella germanica*); and 2-spotted spider mite; plus a negative control and histamine.[11] We also investigated the frequency of emergency department visits and admissions to hospital during the previous year. The smoking history was evaluated; subjects who had a positive lifetime history of cigarette smoking but do not now smoke were considered as ex-smokers, and those who had smoked cigarettes on 5 or more days within the past 30 days were current smokers.

Statistical Analyses

Comparisons of averages were performed using one-way analysis of variance tests, with data presented as mean ± SD. All statistical analyses were performed with statistics software (SPSS 12.0, SPSS, Chicago, Illinois). *P* values < .05 were considered statistically significant.

Results

Demographic Data

We enrolled 633 patients with asthma, 41 with the intermediate type, and 157 with COPD. The mean ± SD (and range) ages of the 3 groups were 48 ± 16 years (15–84 years), 59 ± 10 years (29–77 years), and 65 ± 8 years (35–79 years), respectively ($P < .001$, Fig. 1A). The percentages of males were 49%, 71.4%, and 91.7%, respectively ($P < .001$, see Fig. 1B). Their mean ± SD body mass index values were 23.91 ± 3.27 kg/m^2, 23.24 ± 3.15 kg/m^2, and 22.87 ± 3.80 kg/m^2, respectively ($P = .002$, see Fig. 1C). The atopy/nonatopy ratios of the 3 groups were 0.46 (141/306), 0.35 (7/20), and 0.09 (13/141), respectively ($P < .001$, see Fig. 1D).

Smoking Status

When we assessed smoking status in the asthma, the intermediate type, and COPD groups, we found that 16.6%, 30.0%, and 30.1%, respectively, were current smokers, and that 44.6%, 20%, and 7.1%, respectively, were nonsmokers ($P < .001$, Fig. 2A). The mean duration of smoking by current or ex-smokers in the asthma, the intermediate type, and COPD groups were 21 ± 15 years, 35 ± 13 years, and 39 ± 12 years, respectively ($P < .001$, see Fig. 2B). The mean number of cigarettes smoked per day were 16.52 ± 10.76, 22.35 ± 9.53, and 23.78 ± 13.06, respectively ($P < .001$, see Fig. 2C). The mean pack-years of smoking in the asthma, the intermediate type, and COPD groups were 30 ± 36, 48 ± 26, and 46 ± 28, respectively ($P = .03$).

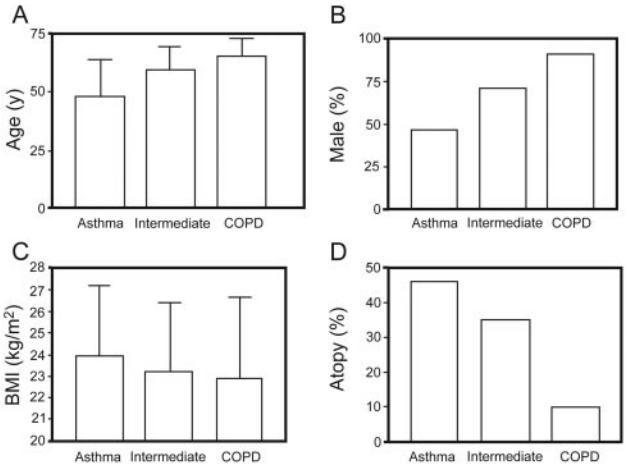

Fig. 1. Demographic distribution of the asthma, intermediate type, and COPD groups. A: Age. B: Sex. C: Body mass index. D: Frequency of atopy. All the differences were significant by one-way analysis of variance.

Pulmonary Functions

We observed a decrease in mean ± SD predicted FEV_1 (%) from the asthma (82.50 ± 21.63%) to the intermediate type (66.79 ± 21.63%) to the COPD (53.39 ± 19.16) group ($P < .001$, Fig. 3A). The mean ± SD of absolute value of FEV_1 was 2.36 ± 0.91 L in asthma, 1.79 ± 0.79 L in the intermediate type, and 1.40 ± 0.55 L in COPD. Similarly, mean ± SD predicted FVC (%) was significantly higher in the asthma (89.89 ± 16.66%) than in the intermediate type (83.88 ± 17.94%) and COPD (84.40 ± 20.29%) groups ($P = .001$, see Fig. 3B). Prebronchodilator FEV_1/FVC was < 75% in each group, decreasing from the asthma (73.49 ± 13.16%) to the intermediate type (61.07 ± 11.86%) to the COPD (46.12 ± 13.08%) group ($P < .001$, see Fig. 3C).

Bronchodilator Response and Airway Hyper-responsiveness

Positivity of bronchodilator response was 16.8% (62/369) in the asthma, 25.0% (8/32) in the intermediate type, and 38.6% (56/145) in the COPD group ($P < .001$, Fig. 4A). The mean percentage increases in FEV_1 after bronchodilator, compared with baseline, were 7.85% in the asthma, 10.67% in the intermediate type, and 12.64% in the COPD

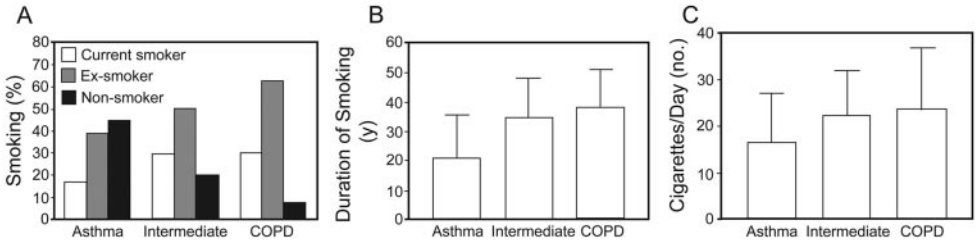

Fig. 2. Smoking data of the asthma, intermediate type, and COPD groups. A: Percentage of smokers. B: Duration of smoking. C: Cigarettes per day. All the differences were significant by one-way analysis of variance.

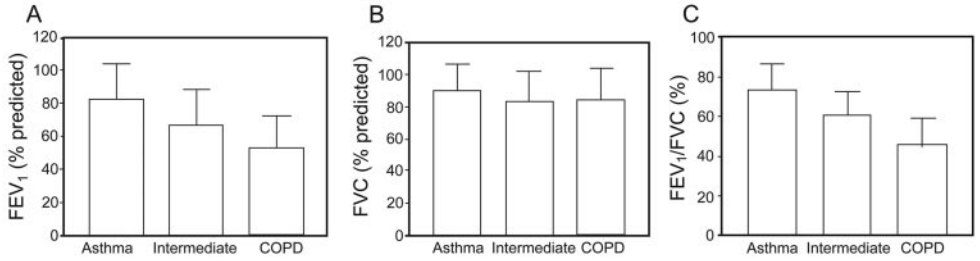

Fig. 3. Pulmonary functions of the asthma, intermediate type, and COPD groups. A: Percent of predicted FEV_1. B: Percent of predicted FVC. C: FEV_1/FVC. All the differences were significant by one-way analysis of variance.

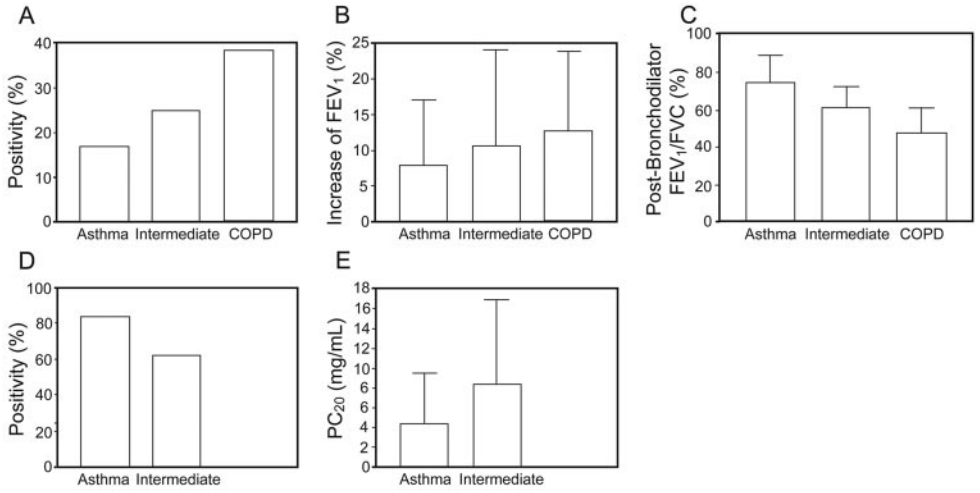

Fig. 4. Bronchodilator response and airway hyper-responsiveness in the asthma, intermediate type, and COPD groups. A: Percent with positive bronchodilator response (15% increase in FEV_1). B: Post-bronchodilator response (increase in FEV_1). C: Post-bronchodilator FEV_1/FVC. D: Positivity on the methacholine provocation test. E: PC_{20} (provocational concentration of methacholine that produced a 20% decrease in FEV_1). All the differences were significant by one-way analysis of variance.

group ($P < .001$, see Fig. 4B). Mean ± post-bronchodilator FEV_1/FVC (%) showed a similar pattern, being 74.88 ± 13.83%, 60.74 ± 11.29%, and 47.66 ± 13.37%, respectively ($P < .001$, see Fig. 4C). A positive response on the methacholine provocation test was observed in 83.4% (257/308) of subjects in the asthma group and in 62.5% (5/8) of subjects in the intermediate type group ($P < .001$, see Fig. 4D), with mean PC_{20} values of 4.32 mg/mL and 8.25 mg/mL, respectively (difference not significant, see Fig. 4E).

Frequency of Emergency Department Visits and Hospital Admission

When we checked the frequencies of emergency department visits during the previous year, we found that the mean ± SD number of visits was highest for COPD subjects (2.20 ± 3.34), lower for the intermediate type subjects (0.52 ± 1.18), and lowest for asthma subjects (0.14 ± 0.78) ($P < .001$, Fig. 5A). Mean ± SD numbers of hospital admissions during the previous year showed a

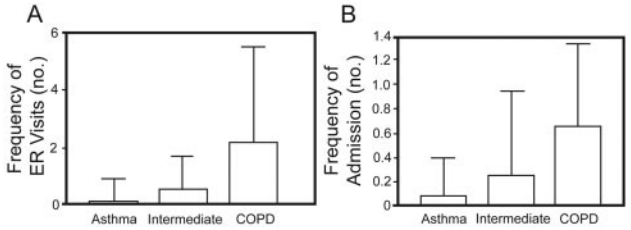

Fig. 5. Frequency of emergency department visits (A) and admission rates (B) in the asthma, intermediate type, and COPD groups. All the differences were significant by one-way analysis of variance.

similar pattern, being 0.65 ± 0.68, 0.25 ± 0.69, and 0.08 ± 0.32, respectively ($P < .001$, see Fig. 5B).

Discussion

We have shown here that a group of patients diagnosed with "asthma plus COPD" had clinical features intermediate between those of asthma and COPD. This finding is clinically important in that it showed the existence of an intermediate type of COAD, statistically distinguished from both asthma and COPD. We also suggest the adoption of "COAD" as a clinical spectrum that includes asthma, an intermediate type, and COPD.

Asthma and COPD are major chronic inflammatory diseases of the respiratory tract; both are characterized primarily by airway obstruction. In general, the conditions can be distinguished by the reversibility of airway obstruction. Patients with proven reversibility have been diagnosed with asthma, whereas patients with irreversible or partially reversible airway obstruction have been diagnosed with COPD. This distinction, however, is somewhat arbitrary and incomplete, as, in many patients it is difficult to draw a distinction between these 2 conditions. Although these diseases have distinctive physiologic features at the time of diagnosis, an observational study showed that subjects with active asthma at the age of 20 years were at markedly increased risk of developing COPD during a subsequent 20-year follow-up period.[12] Likewise, Lange et al demonstrated a significantly greater annual rate of decline in FEV_1 in both men and women with asthma, independent of smoking, compared to non-asthmatic controls.[13] These findings could explain why some patients with asthma are diagnosed with COPD later in life.

Interestingly, we found that patients with COPD showed greater airway reversibility than did patients with asthma and the intermediate type. The bronchodilator response of patients with severe asthma, defined by the Global Initiatives for Asthma (GINA) guidelines,[1] was similar to that of those with COPD, with 37.3% of the former patients having a positive bronchodilator response and an increased FEV_1 of 13.37 ± 12.31% (data not shown). The reason of the higher bronchodilator response in COPD patients may be that they have plenty of room for more increase of FEV_1 after inhalation of short-acting bronchodilator, due to their low baseline FEV_1. Poorer pulmonary function may be associated with a greater bronchodilator response, according to the definition used in the present survey.[14] There is a study showing that a good bronchodilator response occurred in COPD, with pre-bronchodilator FEV_1 values < 55% of predicted, like those of our COPD patients.[15] A couple of reports showed that substantial acute bronchodilator reversibility has been observed in patients with COPD who had no other features of asthma, regardless of the method used to define reversibility.[4,16] Another large study, using a threshold bronchodilator FEV_1 change of 15%, found that this test showed only a 44% sensitivity for detecting asthma and a 72% specificity in distinguishing asthma from COPD.[17] Moreover, 30% of individuals with fixed air-flow obstruction had a history of asthma.[18] This may explain, at least in part, the confusion between asthma and COPD based on airway reversibility.

Several recent studies have included patients with concomitant asthma and COPD. One report, based on information in the database of the International Classification of Diseases, suggested that patients with COPD and co-occurring COPD/asthma were sicker and used more medical services than did asthma patients.[5] A second study, which included patients > 40 years of age, with a smoking history > 10 pack-years, an acute bronchodilator response of 200 mL, and a 12% pre-bronchodilator FEV_1 during the previous 5 years, defined the concomitant type of asthma/COPD as a disease associated with a post-bronchodilator FEV_1 < 80% and a post-bronchodilator FEV_1/FVC < 70%.[19] In contrast, we did not precisely define the criteria of the intermediate type, because we wished to select patients clinically diagnosed with this disease by physicians in real practice. We believe that this type of clinical diagnosis may be more accurate, because experts who have treated large numbers of patients with COAD for a long period of time can diagnose patients based on a comprehensive consideration of various clinical situations and phenotypes. As a result, we have deduced the reality of an intermediate type using an inductive method.

Our findings may have an impact on the management of patients with COAD. For example, the treatment goals and steroid requirements may be different for patients with the intermediate type than for patients with pure asthma or COPD. We intend to monitor any changes in diagnosis over time, to determine if the patients with the intermediate type are still being diagnosed with the same disease by physicians through the follow-up.

One limitation of our study was our inability to evaluate differences in inflammatory markers, such as sputum eosinophil counts or exhaled nitric oxide, among the 3 groups. This comparison may have provided clues to the pathogenic progress of the disease entities. Another limitation

was the small number of patients with the intermediate type. This may reflect the fact that the actual proportion of such patients relative to patients with other types of COAD is low. In addition, the proportion of the intermediate type in asthma or COPD was not even, since the number of patients in each group was dependent on the number of enrollment by physicians.

Conclusions

In conclusion, we found that an intermediate type of COAD, between asthma and COPD, evidently exists in real practice when diagnosed by physicians. These findings suggest that COAD represents different diseases that are each characterized by heterogeneity with differing phenotypes and overlapping features. Additional studies are needed to determine whether asthma progresses to COPD via the intermediate type, and, if so, under what conditions it develops.

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