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ORIGINAL ARTICLE

Comorbid diseases in aspirin-exacerbated respiratory disease, and asthma

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Abstract
Background: Asthma, persistent rhinosinusitis, and/or nasal polyposis accompanying non-steroidal anti-inflammatory drug (NSAID) intolerance is defined as aspirin-exacerbated respiratory disease (AERD). Although the literature includes considerable data on comorbidities in asthma, data on comorbidities in AERD have not been previously published.
Objective: This study aimed to determine the prevalence of comorbidities in AERD and compare the findings to those in asthmatic patients.
Materials and methods: The records for 330 AERD patients that presented to our allergy clinic were reviewed. Patients with urticaria/angio-oedema type reactions to NSAIDs were included in the pseudo Samter's group ($n = 83$) and 338 randomly selected NSAID-tolerant asthma patients constituted the control group.
Results: Gender, age at presentation, age at onset of asthma, and follow-up periods were similar in all groups. Hypertension ($P = 0.035$), diabetes mellitus ($P = 0.323$), gastro-oesophageal reflux ($P < 0.001$), psychological disorders ($P = 0.099$), obesity ($P = 0.003$), and hyperlipidaemia ($P = 0.002$) were significantly more prevalent in the asthma group. Interestingly, coronary artery disease (CAD) and congestive heart failure (CHF) were more common in the AERD group ($P = 0.178$); CAD/CHF was associated with AERD (OR: 4.5; 95% CI: 1.206–16.93).
Conclusion: AERD and asthma are associated with several comorbidities. Even though systemic steroid dependency and severe asthma were significantly more common in the AERD group, comorbidities occurred more frequently in the asthma group. Additional longitudinal studies are needed to more clearly discern if the risk of CAD/CHF is increased in AERD.

Introduction

Aspirin-exacerbated respiratory disease (AERD) is characterised by asthma, persistent rhinitis/sinusitis, and/or nasal

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polyposis accompanying non-steroidal anti-inflammatory drug (NSAID) intolerance. AERD affects 0.3–0.9% of the general population, but its prevalence rises to 10–20% in asthma patients and up to 30–40% in those asthmatics with nasal polyposis.[1] In AERD patients, localised inflammation in the upper respiratory tract is more prevalent and aggressive; therefore, relapse and treatment failure is common in patients with nasal polyposis and rhinosinusitis.[2] Asthma is often associated with various comorbidities, but the prevalence of comorbidity varies between studies.

Comorbidity is an important factor in asthma patients, as it can negatively affect disease management and control. Rhinitis, sinusitis, gastro-oesophageal reflux disease (GERD), obstructive sleep apnoea (OSA), hormonal disorders, and psychopathologies are frequently observed in asthmatic patients.[3] Analysis of large databases has shown a high prevalence of various conditions in asthma patients that do and do not affect asthma treatment outcomes.[4,22] The majority of asthma patients also have allergic rhinitis, which is often undiagnosed and untreated. Patients with allergic rhinitis have a high risk of developing asthma, but allergic rhinitis also impairs asthma control, and increases symptoms and disease severity. In Soriano et al.'s data-based study the most prevalent condition in adult asthmatic patients was time-limited minor infections, whereas other conditions that were highly prevalent included depression, hypertension, diabetes mellitus (DM), ischaemic heart disease, degenerative joint disease, cardiac arrhythmia, cancer, congestive heart failure, cerebrovascular disease, and chronic obstructive pulmonary disease (COPD).[5] Asthma with comorbidity results in elevated healthcare system usage and costs, and decreased quality of life and poor asthma control.

An earlier study conducted at our centre that investigated the relationship between NSAID hypersensitivity, and chronic urticaria, rhinitis/rhinosinusitis, and asthma, and identified the NSAID reaction patterns in asthmatics[6] reported that AERD patients are a heterogeneous group, and proposed a new classification system (Kalyoncu classification). According to Kalyoncu classification, NSAID-induced urticaria/angio-oedema in asthma patients is defined as pseudo Samter's syndrome. The clinical characteristics of this group are unique and additional research is required to delineate the behaviour and natural course of pseudo Samter's syndrome.

Although the literature contains a great deal of data on comorbidities in asthma, comorbidities in AERD have yet to be evaluated. As such, the present study aimed to determine the prevalence of comorbidities in AERD patients and compare them with those in asthma patients, and to investigate their associations in pseudo Samter's patients.

Materials and methods

The study included 414 consecutive AERD patients that presented to the allergy clinic between January 1991 and December 2011. Among the 414 patients, we were able to obtain detailed records concerning comorbidities for 330 (79.7%). The patients were divided into two groups: AERD and pseudo Samter's. The pseudo Samter's group included asthma patients with NSAID-induced urticaria/angio-oedema ($n = 83$, 25.1%) and the AERD group included asthma patients with NSAID-induced anaphylaxis, rhinitis/asthma, or a combination of reactions.[6] The control group included 338 randomly selected NSAID-tolerant asthma patients that presented during the same time period. Demographic and clinical data were obtained from patient files. History of rhinitis, smoking status, age at onset of asthma, NSAID intolerance, nasal polyps, polypectomies, oral corticosteroid dependency, aspirin desensitisation, asthma severity, additional atopic diseases, atopy, and skin prick test results at presentation were recorded. Physician-diagnosed comorbidities during the follow-up period were also recorded. Depression and panic attacks were recorded as psychological disorder. Although obesity was defined as a body mass index >30 kg m^{-2}, data were not recorded in the patient files, but obesity as a diagnosis was recorded by the examining physicians. Atopy was defined as being positive ($\geq$3 mm diameter) for one or more allergens in skin prick test. Skin prick testing included aeroallergens of *Dermatophagoides pteronyssinus*, *Acarus siro*, *Lepidoglyphus destructor*, *Tyrophagus putrescentiae*, pollens (*Phleum pratense*, *Artemisia vulgaris*, *Parietaria officinalis*, *Corylus avellana*, *Olea europeae*, and *Betula verrucosa*), moulds (*Aspergillus fumigatus*, *Cladosporium herbarum*, and *Alternaria alternata*), animal dander (dog and cat), latex, and *Blatella germanica*.

Diagnoses of rhinitis and asthma were made by allergists in the allergy clinic based on international and national asthma/rhinitis guidelines (GINA, ARIA, and national guidelines), and diagnosis and surgical treatment of nasal polyps were performed by otorhinolaryngologists at our centre. Patients who were oral steroid dependent or had taken high dose inhaler steroids together with two or more controller medications for the previous year were defined as having severe asthma. A reliable clinical history of or a positive oral challenge with the tested NSAIDs was required for the diagnosis of NSAID intolerance. Asthma/rhinitis, urticaria/angio-oedema, or urticaria, and angio-oedema and/or anaphylaxis induced by a single NSAID or a group of closely chemically related compounds within 24 h were defined as positive reaction history.[7] The challenge response was considered positive if it fulfilled $\geq$1 of the following criteria: (1) a FEV1 decrease $\geq$20%; (2) sneezing, rhinorrhoea, nasal blockage, and oropharyngeal itching; (3) pruritic and erythematous areas over normal skin; (4) macular and/or popular areas in any localisation; (5) swelling of the skin and/or external mucosa; (6) systemic anaphylaxis.[8] The study protocol was approved by the Hacettepe University School of Medicine Ethics Committee. Informed consent was provided by all the participants.

Statistical analysis

Statistical analysis was performed using SPSS v.15.0 for Windows. Categorical variables are expressed as frequencies, versus mean $\pm$ standard deviation for continuous variables. Chi-square analysis was used to test differences for nominal variables. The association between comorbidities, and AERD and pseudo Samter's syndrome groups was adjusted for age, gender, smoking status, and follow-up period in the logistic regression analysis models. The association between comorbid cardiovascular diseases, and metabolic conditions and