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Original article

Phenotypic analysis of asthma in Japanese athletes

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Abbreviations:
EIB, exercise-induced bronchoconstriction; FEV_1, forced expiratory volume in 1 s; FeNO, fraction of exhaled nitric oxide; FVC, forced vital capacity; GETE, Global Evaluation of Treatment Effectiveness; ICS, inhaled corticosteroid; IgE, immunoglobulin E; LABA, long-acting β-adrenergic receptor agonist; LTRA, leukotriene receptor antagonist; PC_{20}, provocative concentration causing a 20% drop in FEV_1; RAST, radioallergosorbent test

ABSTRACT

Background: Asthma in athlete populations such as Olympic athletes has various pathogeneses. However, few reports are available on the features of asthma in the athlete population in clinical practice. In this study, we focused on classifying asthma in Japanese athlete population.
Methods: We performed a cluster analysis of data from pulmonary function tests and clinical biomarkers before administering inhaled corticosteroids (ICS) therapy in athlete population of individuals diagnosed with asthma (n = 104; male, 76.9%; median age, 16.0 years), based on respiratory symptoms and positive data on methacholine provocation tests. We also compared backgrounds, sports types, and treatments between clusters.
Results: Three clusters were identified. Cluster 1 (32%) comprised athletes with a less atopic phenotype and normal pulmonary function. Cluster 2 (44%) comprised athletes with a less atopic phenotype and lower percent predicted forced expiratory volume in 1 s (%FEV_1) values, despite less symptomatic state. Cluster 3 (24%) comprised athletes with a strong atopic phenotype such as high eosinophil count in the blood and total serum immunoglobulin E level. After treatment with ICS or ICS plus long-acting β-adrenergic receptor agonist for 6–12 months, %FEV_1 values were significantly improved in Cluster 2 athletes, whereas Cluster 3 athletes had a significant decrease in the fraction of exhaled nitric oxide compared to pretreatment values.
Conclusions: These data suggest three clusters exist in Japanese athlete population with asthma. Between the clusters, the characteristics differed with regard to symptoms, atopic features, and lower %FEV_1 values. The pathogeneses between clusters may vary depending on the inflammation type and airway hyperresponsiveness.

Introduction

Exercise is a well-established factor that is associated with asthma exacerbation.[1] Approximately 70%–80% of asthma patients experience exercise-induced bronchoconstriction (EIB).[2] A higher prevalence of asthma has been reported in athletes than in the general population.[3,4] Athletes participating in sports such as cross-country skiing, skating, swimming, cycling, and marathon running have an increased risk of developing airway hyperresponsiveness (AHR). These sports are characterized by cold air exposure or a high amount of ventilation.[5,6]

Inhaled corticosteroids (ICS) are recommended for managing asthma in the athlete population and in the general population.[7] We previously reported that monotherapy with ciclesonide (CIC), a new ICS administered once daily as a prodrug, is more effective for symptom control and reducing the fraction of exhaled nitric oxide (FeNO) compared with montelukast, a leukotriene modifier administered once daily.[8] Another study[9] of cross-country skiers showed that ICSs have a minimal effect in ameliorating respiratory symptoms and AHR to methacholine. Based on these reports, the pathogeneses of athlete asthma are likely diverse. We previously

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reported differences between ICS-responders and ICS–non-responders in an athlete population.[10] Another study reported that the features of asthma in an athlete population were characterized by two distinct phenotypes: (1) atopic asthma and (2) sports asthma.[11] However, detailed investigations of a less atopic phenotype that is less responsive to ICS and presumably induced by hard training has been insufficiently described.

Cluster analysis has recently been used for the classification of populations with asthma, especially in difficult-to-treat asthma.[12–14] This technique is helpful for classifying phenotypes and for determining treatment or warning of exacerbation. To date, cluster analyses of asthma were conducted on individuals with severe asthma,[12,13] adult asthma,[14,15] and pediatric asthma,[16,17] whereas a cluster analysis of asthma in an athlete population has not been reported. Moreover, most studies associated with asthma analyzed the data after the induction of therapy because the aim of the analysis was to elucidate the classification of difficult-to-treat asthma[13] or asthma with rapidly declining forced expiratory volume in 1 s (FEV_1).[15]

In this study, we classified asthma in an athlete population by using the data from pretreatment with a controller such as an ICS. We separated asthma patients in an athlete population into three clusters based on data from lung function and biomarkers before the induction of therapy.

Methods

Athletes

Between January 2010 and December 2013, we screened regional athletes, primarily high school students, at Niigata Institute for Health and Sports Medicine (Niigata City, Japan). Athletes with respiratory symptoms and positive findings on the methacholine provocation test were diagnosed as having asthma. Some athletes with relatively low FEV_1/forced vital capacity (FEV_1/FVC) levels (i.e., FEV_1/FVC <80%) and AHR to methacholine were diagnosed with asthma, despite having few symptoms. One hundred fifty-four athletes were diagnosed with asthma. Eighteen athletes had already undergone maintenance therapy such as with an ICS or an ICS plus a long-acting β-adrenergic receptor agonist (LABA) combination (e.g., budesonide/formoterol or fluticasone/salmeterol). For 24 athletes, we did not have important pretreatment data such as FeNO values, the provocative methacholine concentration causing a 20% drop in FEV_1 (PC_{20}), immunoglobulin E (IgE) levels, or pulmonary function indices. We also excluded three athletes with complications (e.g., anemia and irritable bowel syndrome) and five athletes who underwent ICS or ICS/LABA combination therapy within 6 months. A total of 104 athletes (80 men) who were nonsmokers and had continued ICS therapy or ICS/LABA combination therapy for at least 6 months were enrolled in this retrospective analysis.

Athletes in this study were individuals who were competitive at the regional to national level and trained approximately 20 h/week. Sports types were categorized as endurance/nonendurance sports, winter/summer sports, and indoor/outdoor sports based on the work of Alaranta *et al.*[18] (Table 1). This study was performed in accordance with the Ethical Principles for Medical Research Involving Human Athletes, the Declaration of Helsinki, and with the approval of the Ethics Committee of Niigata Institute for Health and Sports Medicine (Niigata City, Japan).

Clinical assessment

Before treatment, all athletes underwent a physical examination; pulmonary function testing; methacholine provocation tests; measurements of the FeNO level, peripheral blood eosinophil count, and total IgE level; and a radioallergosorbent test (RAST) for mites, ragweed, and cedar pollen. Pulmonary function testing was performed using a spirometer (SpiroSift SP-470; Fukuda Densi, Tokyo, Japan) in accordance with the American Thoracic Society guidelines.[19] The FeNO level was measured using a nitric oxide (NO) analyzer (Kimoto Denshi, Osaka, Japan) with an online method. The method of measuring FeNO conformed to a previous mutual consensus statement from the American Thoracic Society/European Respiratory Society.[20] The methacholine challenge involved 2 min of tidal breathing of methacholine, and the PC_{20} was determined.[21] A PC_{20} < 8 mg/mL was defined as a positive response in this study. The athletes also underwent the Asthma Control Test (ACT) in the clinic. The details of the procedures are provided in the Supplementary Methods.

Table 1
Sports classifications of the athletes.

Sport classification	Sport (percentage of athletes)
Endurance	Cross-country skiing (27.9), canoeing (2.9), badminton (2.9), track and field (1.9; >800 m runners), tennis (1.9)
Winter	Cross-country skiing, alpine skiing (11.5), figure skating (2.9), snowboarding (1.0)
Indoor	Judo (8.7), badminton, figure skating, basketball (1.9), fencing (1.9), volleyball (1.0), karate (1.0), kendo (1.0)
Other	Baseball (12.5), soccer (7.7), track and field (5.8), archery (1.0), ultimate frisbee (1.0)

Assessment

The athletes were treated with an ICS alone or an ICS/LABA combination for at least 6 months, based on a physician's judgment. Briefly, athletes who had a relatively lower (i.e., <85%) percent predicted FEV_1 (%FEV_1) or some symptoms unrelated to exercise underwent ICS/LABA treatment rather than ICS treatment alone. The response to treatment was assessed using the physician's Global Evaluation of Treatment Effectiveness (GETE), as previously described.[10,22,23] An overall clinical evaluation of asthma control from 3 to 6 months was judged from all available information, which included patient interviews, physical examinations, pulmonary function tests, and FeNO levels. Asthma treatment was stepped down if the GETE rating for 6 months was “excellent” (i.e., complete control of asthma) or “good” (i.e., marked improvement of asthma), whereas therapy was stepped up if the GETE rating for 6 months was “poor” (i.e., no appreciable change in asthma symptoms) or there was a worsening of asthma at any time. The definition of step-down and step-up are described in the Global Initiative for Asthma guidelines.[24] The data from pulmonary function testing and the FeNO after treatment were also compared to the baseline data.

Statistical analysis

A hierarchical cluster analysis using Ward's method was conducted to generate a dendrogram to estimate the number of clusters. Previous research[12] has consistently revealed important variables for cluster establishment such as age at onset, eosinophilic inflammation, airflow variability, and IgE levels. One-half of the athletes in this study had a history of pediatric asthma, although all athletes had reached at least clinical remission during their elementary school years and were therapy-naïve patients. Therefore, we determined that their age at onset was when they were newly diagnosed. Furthermore, age and sex were indispensable variables; however, the age composition in this study was limited and male athletes were overrepresented. Therefore, these factors may drive the hierarchical clustering results. We applied the