

Klinefelter syndrome and bronchial asthma: Is there any relationship between the low testosterone levels and asthma exacerbations?

Sir,

It is widely reported that the Klinefelter syndrome (KS) is one of the most frequent congenital chromosome disorders. The 47, XXY karyotype causes infertility, testosterone deficiency, and a spectrum of other symptoms and comorbidities, including varicose veins, thrombosis, embolism, type 2 diabetes, bone fractures, epilepsy, and other neurological and mental disorders.^[1] Chronic inflammatory airway disorders, such as asthma, have not been reported in patients with KS. Herein, we describe a patient with KS with frequent asthma exacerbations whose clinical course was really improved after androgen replacement therapy and standard antiasthmatic medications.

An 18-year-old male was admitted to our department for managing an asthma exacerbation. His medical history included an uncontrolled asthma which was treated by a reliever inhaler occasionally without any supervision by a pulmonary physician. The patient received 50 mg prednisolone intravenously for 7 days and nebulized short-acting bronchodilators as well as corticosteroids with significant clinical improvement. Then, he was discharged taking a controller inhaled corticosteroid (ICS)/long-acting β 2-agonist (LABA) medication (formoterol 4.5 μ g/budesonide 160 μ g two inhalations twice daily). A week later, he was readmitted exhibiting shortness of breath and wheezing. More thorough physical examination disclosed sparse facial and body hair, symmetrical gynecomastia, and small testes and penis, thus signifying a eunuchoid appearance. Moreover, the patient had had tall stature with long legs and a short trunk. Laboratory testing demonstrated low testosterone levels accompanied by high levels of luteinizing hormone and follicle-stimulating hormone. The chromosomal analysis in peripheral venous blood showed 18-year-old male, thus confirming the diagnosis of KS. Brain magnetic resonance imaging was normal whereas bone mineral density measurement revealed osteopenia. Testosterone was administered (testosterone enanthate 250 mg/every 4 weeks via intramuscular injection) in conjunction with systemic corticosteroids (50 mg prednisone intravenously) and nebulized bronchodilators/corticosteroids for the asthma exacerbation management. In addition, a calcium and Vitamin D supplement was instituted. The patient responded satisfactorily and was discharged receiving 20 mg prednisone/day with gradual tapering until its discontinuation in a 3-week period as well as a combined inhaled ICS/LABA formulation. Two months later, the patient's condition had been stabilized using the inhaled

and testosterone medications consistently. The patient is already reevaluated at 6-monthly intervals by an endocrinologist and a pulmonary physician.

Asthma has been considered a T helper 2 (T_H2) cell-driven inflammatory disease, characterized by eosinophilic inflammation, T_H2 cell-associated cytokine production, and airway hyperresponsiveness. The immune system interacts with the endocrine system. Female sex hormones aggravate asthma and other allergic diseases, whereas male sex hormones suppress such diseases, as a result of this interplay.^[2] In particular, testosterone has been shown to be an immunosuppressant and protective against immunological and inflammatory processes that trigger asthma. Page *et al.* reported that during a transient medical castration in men, not only serum testosterone but also CD4+/CD25+ T-cell numbers and CD8+ T-cell interferon- γ expression decreased, and this was prevented by testosterone replacement.^[3]

KS is strongly associated with hypogonadism and its negative impact on the functioning of several organ systems. However, there is a paucity of literature regarding the effect of hypogonadism on respiratory system in KS patients. To the best of our knowledge, only one single case study described a patient with KS, diabetes mellitus, osteoporotic rib fracture, and refractory asthma whose attacks were completely controlled using a combined inhaled (LABA/ICS) and oral testosterone formulation.^[4] So far, a unique study by Koçar *et al.* found higher absolute numbers and percentages of CD4+, plasma interleukin (IL)-2, and IL-4 in patients with KS than those in healthy controls. There was a significant decrease in cytokines' high levels after 6-month treatment with testosterone.^[5] The findings of this study indicate that the lack of testosterone in patients with KS enhances cellular and humoral immunity and that antiretroviral therapy suppresses this abnormality. That explains the effectiveness of such treatment approach in asthma management.

In conclusion, chronic inflammatory airway disorders, such as asthma, can occur in KS probably due to the negative impact of hypogonadism on lung function. The diagnosis of KS has been delayed in the present case for nearly 20 years. The syndrome remains highly underdiagnosed because of substantial variation in its clinical presentation. The rate of diagnosis during childhood is extremely low, and only 10% of cases are identified before puberty while 25% of the cases are identified during adulthood. Nonetheless, pulmonary physicians should be aware of KS, thus

improving the prognosis of patients with asthma and this congenital chromosome disease.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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