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Testosterone-induced acne fulminans in twins with Kallmann's syndrome

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Key words: acne fulminans; Kallman's syndrome; testosterone; twins.

INTRODUCTION

Acne fulminans is a rare and severe form of acne characterized by the development of painful and inflammatory nodules on the face, chest, and back. Systemic signs are associated with the onset, including fever, chills, and musculoskeletal pain. Erythema nodosum, liver or spleen enlargement, myositis, or aseptic bone involvement have been reported more rarely. Its etiology remains unknown. It is assumed that a strong activation of the cutaneous innate immunity induced by *Propionibacterium acnes* antigens could be involved. Another hypothesis is that it could be a dysregulation of some receptors expressed by sebaceous glands and keratinocytes, in particular, the androgen receptors. Moreover, these abnormalities could be genetically determined.

CASE REPORT

We report the case of an 18-year-old patient seen in the outpatient setting for severe acne on his back. In 2013, given the presence of delayed puberty and anosmia, the diagnosis of Kallmann syndrome was established and confirmed by olfactometry. The serum testosterone level was 0.3 ng/mL (normal range, 3-10 ng/mL); the luteinizing hormone level was 0.2 IU/L (normal range, 1.7-8.6 IU); and the follicle-stimulating hormone level was 0.1 IU/L (normal range, 2.0 - 14.1 IU/L). His twin brother also had Kallmann syndrome. The twins were born from a diamniotic pregnancy with one placenta, so they



Fig 1. Acne fulminans on the back with nodular and necrotic lesions.

could be mono- or dizygotic twins. We noted a family history of acne in the father and oldest brother. The twin brothers had been treated with monthly injections of testosterone for delayed puberty starting at the age of 17. Under treatment, the testosterone level reached normal range. Nine months later, nodular and necrotic acne lesions suddenly developed on the patient's back (Fig 1) associated with

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Table I. Demographic and clinical data of patients with testosterone-induced acne fulminans

Reference	Sex	No. of patients	Age	Clinical context	Therapeutic regimen	Therapy received for acne fulminans
Genetic Disorders						
Hartmann and Burg, 1989 ¹	M	1	19	Klinefelter syndrome	Testosteron enantat 500 mg every 2 wk over 18 mo	Isotretinoin therapy over 16 weeks
Wollina et al, 2005 ⁴	M	1	12	Marfan syndrome	Testosterone 50 mg every 2 wk for 6 mo	Clindamycin 300 mg, prednisolone 1 mg/kg, and isotretinoin 0.5 mg/kg. Prednisolone switched for dapsone 100 mg/d (disagreement of patient's mother to continue steroid treatment)
Current case	M	2	18	Kallmann syndrome	Testosterone 250 mg once a mo over 10 mo	Systemic corticosteroid 0.5 mg/kg/d, isotretinoin 0.06 mg/kg/d
Tall Stature Treatment						
Traupe et al, 1988 ²	M	3	13-16	Excessively tall stature	High doses of testosterone	Oral isotretinoin and topical steroid (2 cases) Systemic corticosteroid (1 case)
Weimann and Bohles, 1999 ³	M	1	13	Hereditary tall stature treated with high dose of testosterone	Testosterone 250 mg once a wk over 6 mo	Isotretinoin therapy (0.3 mg/kg/d), methylprednisolone and cefaclor

moderate acne on the face without nodules. The development of these lesions was associated with general malaise but no fevers or musculoskeletal pain. The injections of testosterone were discontinued. Simultaneously, severe nodular acne developed on the back of the twin brother, which was treated in another center using lymecycline, 300 mg/d, and topical treatment. Given the interest of these rare cases, cultures of the back lesions were taken. Results showed the presence of fully susceptible *P acnes* belonging to phylotype II in our patient and phylotype IB in his twin. Corticosteroid therapy (0.5 mg/kg/d) was initiated, resulting in disappearance of necrotic lesions at 1 month, allowing initiating tapering of corticosteroids and introducing a very low dose of isotretinoin (5 mg/d = 0.06 mg/kg/d). After 2 months of isotretinoin treatment, the severe ulcerative acne lesions were significantly reduced (by more than 50%) leaving atrophic scars. Corticosteroids were discontinued, and isotretinoin dose was increased to 10 mg/d. The treatment is still ongoing. Because acne fulminans is a rare adverse event of testosterone therapy, the case was reported to the clinical pharmacology department.

DISCUSSION

A few cases of testosterone-induced acne fulminans have been described in the literature (Table I), but this is the first case reported in twins.¹⁻⁴ These types of cases have been described only in 2 situations: self-medication of anabolic steroids in bodybuilders⁵ or testosterone treatment given for excessively tall stature.¹⁻⁴ Acne fulminans appeared between 3 and 18 months after initiating the treatment with testosterone in 5 cases and after the end of the treatment in 1 case.³ This delay could be due to the time necessary for the testosterone treatment to accumulate in the blood to a level triggering skin androgen receptors. The 2 genetic cases are similar to that of our patient. The first one was a 19-year-old boy with Klinefelter syndrome¹ and the second one was a 12-year-old boy with Marfan syndrome,⁴ both with tall stature and treated with testosterone. In a large prospective study, 23 boys treated with androgens (Triolandren) in the context of an expected body height of more than 200 cm (but without a known genetic disorder), severe acne developed in 5 patients and progressed toward acne fulminans in 1.⁶ According

to these results, the estimated incidence is approximately 4%.

The identification of 2 different phylotypes of *P acnes* in our cases does not suggest a relationship between acne fulminans and a specific *P acnes* cluster. It could be assumed that the treatment increased the level of free testosterone in the blood and thus in the skin. This testosterone increase could have activated the skin androgen receptors. In the context of twins, a genetic factor (mutation in the androgen receptor gene) could have played a role. The possible role of genetic factors influencing acne is based first on the observation that a family history of acne could be associated with an increased risk of acne. Second, a large twin study including 458 pairs of monozygotic and 1099 pairs of dizygotic twins found that 81% of the acne variance was attributable to additive genetic effects.⁷ Three reports of acne fulminans in twins are published in the literature. The first report presented 14-year-old monozygotic twin boys born in Tenerife (Spain) with no family history of acne fulminans.⁸ The second publication detailed the case of a different set of 15-year-old twin boys, also from Tenerife, who both had acne fulminans. The outcome was favorable with isotretinoin treatment in both patients and prednisolone treatment in the first twin.⁹ A third case was reported in a brother and sister with the same human leukocyte antigen type, supporting a genetic predisposition.¹⁰ Our observation of acne

fulminans in twins triggered by testosterone treatment strengthens the hypothesis of a genetic abnormality in connection with skin androgen receptors.

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