Isotretinoin-unresponsive acne as a sign of a congenital disorder: a case of 21-hydroxylase deficiency

Elisa Marzola, Vincenzo Bettoli

Department of Medical Sciences, Section of Dermatology and Infectious Diseases, University of Ferrara, Italy

Abstract

Acne is a multifactorial and common disorder among young people and a frequent reason for dermatology consultation. When moderate-to-severe acne is not responsive to conventional treatments, oral isotretinoin is a very effective solution. However, there are cases in which this treatment fails to produce the expected results. In this case, an 18-year-old male patient with acne, unresponsive to traditional acne therapies, experienced only a partial benefit from oral isotretinoin. Endocrinology consultation and hormonal work-up revealed androgen metabolism anomalies suggestive of a non-classical form of congenital adrenal hyperplasia due to 21-hydroxylase deficiency. In this case report, the authors discuss when to suspect, how to diagnose, and how to manage similar cases.

Correspondence: Vincenzo Bettoli, Section of Dermatology and Infectious Diseases, Department of Medical Sciences, University of Ferrara, via Ludovico Ariosto, 35, 44121, Ferrara, Italy.
Tel.: +39.0532236390 - Fax: +39.0532238524.
E-mail: vincenzo.bettoli@gmail.com

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Introduction

Acne is one of the most frequent skin disorders managed by dermatologists. According to the Global Burden of Skin Disease study, it is ranked as the eighth most prevalent disease globally, affecting 85% of people in the age range 12-25.[1] In fact, 15-20% of adolescents experience a moderate-to-severe form of acne.[2] It is a multifactorial disease caused by the inflammation of the pilosebaceous unit, with hyperseborrhoea, hypercornification of the pilosebaceous duct, and *C. acnes* playing significant roles. Sebum is synthesized and released by the sebaceous glands, which are stimulated by various factors, including androgens.[3]

In female patients with acne, it is relatively easy to determine whether acne is a sign of underlying hyperandrogenism, because it is often accompanied by hirsutism and menstrual cycle alterations. However, in males, acne could be the only manifestation,[4,5] and in male patients with acne, hormonal assessment is very rarely performed.

If patients do not respond to conventional treatments (topical medications, oral antibiotics), the subsequent step is oral isotretinoin, which is indicated by the Food and Drug Administration for severe acne unresponsive to traditional therapies.[6] Patients treated with isotretinoin frequently show complete clearance of acne. However, when this therapy fails, hormonal imbalance may be the cause. Here we report the case of an 18-year-old male patient with acne showing only a partial response to two courses of isotretinoin treatments; the endocrine workup revealed an inherited genetic alteration.

Case Report

An 18-year-old male presented as having been affected by acne for 6 years. He had a family history of severe acne, but his own medical history was negative for significant diseases. His acne was classified as moderate-to-severe (Figure 1), and he underwent one course of oral lymecycline (300 mg daily). After 12 weeks, the clinical response was only 60%, so he was switched to an initial course of daily 10 mg oral isotretinoin, at the highest tolerated dosage (0.25 mg/kg/day).[7] Cheilitis was at level 2 out of 4.[8] After 13 months of treatment, an improvement of 80% was observed, and a second course of oral isotretinoin was begun in

June 2020, finishing in February 2021. However, even after this course of treatment, his acne was incompletely cleared, and a hormonal workup was therefore performed. Blood tests showed increased levels of dehydroepiandrosterone sulphate at 591.5 µg/dL (N. value 70-400 µg/dL), 4-androstenedione at 4.30 ng/dL (N. value for males between 18 and 40 years old 0.30-3.10) and 17-hydroxy-progesterone (17OHP) at 8.57 ng/mL (N. value <0.9 ng/mL). The adrenocorticotropic hormone (ACTH) stimulation test result was positive, and 17OHP levels scored over 20 ng/mL. These values led us to suspect a non-classical form of congenital adrenal hyperplasia (CAH) syndrome. The 21-hydroxylase deficiency was confirmed by genetic analysis, which revealed two heterozygous pathogenic variants in the gene encoding for 21-hydroxylase (CYP21A2, chromosome 6): p.Arg357Trp (allele inherited from the mother), associated with the classical form, and p.Pro454Ser (allele inherited from the father), associated with the non-classical form. Magnetic resonance imaging was performed. The left adrenal gland appeared slightly globular but the right was within the normal range. The treatment proposed consisted of low-dose corticosteroids: 0.2% oral dexamethasone drops, 4 drops (0.25mg) on alternate days, which led to a substantial improvement (Figure 2).

Discussion

According to the guidelines, isotretinoin is the first-line therapy for severe papulopustular acne and moderate-to-severe nodulocystic acne/acne conglobata.[6,9] Although it is the most effective therapy for acne, however, some patients may not respond. Responsiveness to isotretinoin may be less than optimal in the presence of large, blocked comedones, long-lasting acne, family history of severe acne, acne onset before 16 years, cessation of the treatment before the scheduled time, and hormonal alterations principally involving androgens.[10]

Due to their expression of several receptors, sebocytes are affected by several hormones, in particular glucocorticoids, corticotropin, somatotropin, oestrogens, IGF-1 and insulin. The alteration of one or more of these factors could lead to the development of certain syndromes, including polycystic ovary syndrome (PCOS), Cushing's syndrome, acromegaly, and CAH.[11] CAH is an autosomal recessive syndrome caused by an alteration in the enzymes involved in cortisol synthesis. In about 95% of cases, this condition is caused by a mutation in the gene encoding the 21-hydroxylase enzyme (CYP21A2). The deficiency or complete absence of this molecule, essential for cortisol and aldosterone production, leads to a reduction in cortisol levels. Cortisol secondarily stimulates the secretion of adrenocorticotropin (ACTH) and adrenal cortex activity; the intermediate metabolites produced during these processes are redirected to synthesize adrenal androgens.[12-14] CAH can be divided into classical and non-classical forms. The incidence of classical CAH is 1:14,000 to 1:18,000, whereas the non-classical form is a more common disease, with an incidence of 1:200 to 1:1000.[15] In the classical form, the cortisol and aldosterone deficits are so severe that in 75% of the cases, there is a salt-wasting condition with a potentially fatal outcome due to a hydroelectrolytic disorder (hypovolemia, hyperkalaemia, shock). In the remaining cases, the disease is observed as a simple virilizing form, in which the aldosterone is adequate but cortisol is decreased; genital ambiguity may be seen in newborn females and males, with signs of androgen excess. In the non-classical form, the alterations detectable through laboratory test are more limited, with only moderately increased levels of sex hormones. The onset is late, with hyperandrogenism symptoms (acne, hirsutism, and alterations in the menstrual cycle) normally being detected during puberty.[14] The diagnosis is based on laboratory tests showing an increase in the precursors of the metabolic pathway in which the enzyme takes part, in particular 17OHP. A concentration of this molecule greater than 200 ng/dL is indicative of the diagnosis. Because the level of 17OHP is correlated with the amount of enzyme deficiency, a concentration greater than 10,000 ng/dL is usually indicative of the classical form of CAH. If, on the other hand, the 17OHP level is borderline (200 to 1000 ng/dL), corticotropin stimulation testing (ACTH test) is recommended. This is considered positive when it reveals a 17OHP value higher than 1000 ng/dL. Diagnostic confirmation is obtained by genetic analysis to detect mutations in the gene involved.[15-17]

Treatment for the classical form consists of mineralocorticoid and glucocorticoid replacement (prednisone or dexamethasone) to adjust the deficiency and suppress the hypothalamic-pituitary-adrenal axis, thereby reducing androgen synthesis.[18] In the non-

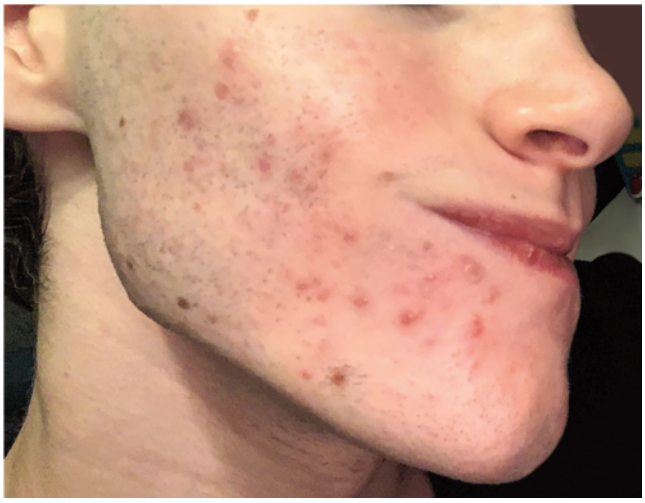

Figure 1. Clinical picture of the patient's moderate-to-severe acne before therapy.

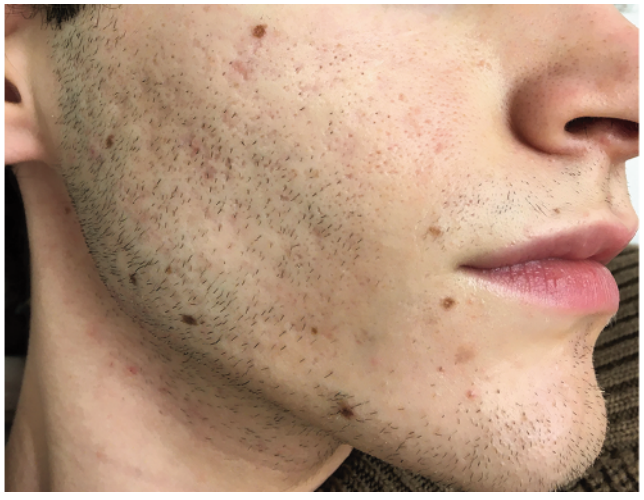

Figure 2. Improvement in the patient's clinical picture after the second course of isotretinoin..

classical form, the less severe enzyme deficit guarantees a sufficient blood concentration of cortisol and mineralocorticoids; therefore, the goal of the therapy is limited to achieving ACTH suppression. Low-dose glucocorticoids (prednisone 2.5-5 mg daily or dexamethasone 0.25-0.75 mg daily), to be taken before sleep for 6 months, are generally sufficient for this purpose.[4]

Conclusions

It is reasonable to request 17OHP testing in patients with acne when standard therapies (isotretinoin included) have proved ineffective, and when female patients show clinical features of PCOS (hirsutism, androgenic alopecia, oligomenorrhea), because the signs and symptoms of PCOS could be similar to those of non-classical CAH.[15] Furthermore, hyperandrogenism may be suggested by some features of acne, such as the rapid onset of severe nodulocystic acne in a patient with a family history of severe acne.[19]

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