Acne and ‘Mild’ Adrenal Hyperplasia

A Short Critical Review

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Acne is one of the most common cutaneous disorders. It can affect up to 85% of adolescents to various degrees [1] and has considerable psychological and economic consequences. Acne is an infectious, inflammatory disease of the sebaceous glands with local excessive sebum production; heredity is a prognostic factor for severe acne [2]. The role of hormones, in particular steroids and androgens, as a trigger of sebum production, either by individual hypersensitivity or by excess quantity, has been well known for decades. Consistent with this, patients suffering from Cushing syndrome or from androgen-secreting tumors may present with acne as the unique clinical symptom [3, 4]. One example of excessive hormone production is congenital adrenal hyperplasia (CAH). CAH is a hereditary disease in which a key enzyme of adrenal steroid production is partially or completely inactive, thereby leading to an accumulation of adrenal steroid precursors with androgenic activity. It has been described that patients suffering from CAH may clinically present with acne as the only manifestation [5]. However, CAH is a very heterogeneous disease where the dysfunction of the enzyme can range from a total lack of enzyme activity – known as classical adrenal hyperplasia (and early clinical symptoms such as virilization of the female fetus or early puberty in boys) – to less severe symptoms (partial defect of the enzyme known as nonclassical CAH). Furthermore, variants exist where the mild enzymatic defect has no clinical relevance (cryptic CAH).

This concept has now been extended by some investigators who suggest that even mild CAH could be a major contributor in the development of acne, even in patients

with no other clinical manifestations of CAH. In a recently published paper [6], the authors postulate that there appears to be enough evidence to screen for the presence of nonclassical CAH in healthy young men presenting with acne as the sole clinical feature, as this may represent an indication for an inhibitory therapy with exogenous corticoids. However, while this concept appears appealing at first sight, it is fraught with some serious problems and inconsistencies.

That patients with acne of various degrees of severity had significantly higher plasma levels of 17-OH-progesterone with regard to controls [6] was already described 20 years ago in men with cystic acne [7], whereas no changes in 17-OH-progesterone levels were found in men with persistent acne vulgaris [8]. No correlation was found between the circulating levels of adrenal steroid precursors and the severity of acne, thereby weakening the case for a causal link [6].

The interpretation of the circulating hormone levels is also problematic. The authors performed an adrenocorticotrophic hormone (ACTH) stimulation test in patients suffering from acne and describe a surprisingly high prevalence of over 12% of CAH by using unconventional diagnostic criteria. Most specialists agree that the diagnosis of classical or nonclassical CAH is established when the circulating levels of 17-OH-progesterone after an ACTH stimulation test exceed 10,000 ng/dl or lie between 1,000 and 10,000, respectively, whereas values of <1,000 ng/dl are present in unaffected or asymptomatic carriers [9]. In contrast, if one uses the ACTH-induced increment in plasma 17-OH-progesterone levels (mean

increase 160 ng/dl from a mean basal value of 200 ng/dl) as a diagnostic tool [6], it is likely that this change in the diagnostic criteria will lead to an increased diagnosis of apparent CAH, which may in fact be false-positive or clinically irrelevant findings.

Even more debatable are the therapeutic implications. Degitz et al. [10] thus reported on 3 young men with refractory acne and possible CAH. Consistent with their hypothesis of mild CAH being responsible for the acne, the authors instituted treatment with pharmacological doses of glucocorticoids to suppress ACTH secretion, thereby inhibiting the putative production of excess androgens by the adrenals. Clinically, the patients appear to have improved the symptoms of their acne. While this observation might prove the authors' hypothesis (*ex juvantibus*) correct, this is at odds with the current concepts of the treatment of CAH. In order to efficiently inhibit the ACTH-dependent production of adrenal androgens, the glucocorticoids must be given at relatively high doses. Clearly, the doses used by the authors in their study (short high-dose prednisolone and then prednisolone 4 mg every other day or only prednisolone 4 mg every other day) are highly unlikely to inhibit even partially the pituitary-adrenal axis, since it is generally accepted that 5 mg of prednisolone constitutes a nonsuppressive, phys-

iological replacement dose, e.g. in patients with adrenal failure. Hence, the effectiveness of the suppression of serum ACTH should be documented by an associated decrease in the plasma levels of 17-OH-progesterone, and these data are unfortunately not available. Taken together it appears likely that the observed positive effect of low-dose prednisolone on the symptoms of acne should probably be attributed to its anti-inflammatory effect rather than to the inhibition of adrenal steroid production. Finally, the glucocorticoid doses required to suppress the pituitary-adrenal axis very often result in the development of iatrogenic Cushing syndrome, with all its well-known and potentially dangerous complications, including the development of acneic lesions.

In conclusion, we do not think that there is currently enough evidence to justify screening healthy men with refractory acne as the sole clinical symptom for CAH; moreover, the effective treatment of CAH requires doses of glucocorticoids which often have adverse effects on acne. Nevertheless, the concept proposed by Degitz et al. [10] is conceptually intriguing and certainly requires more careful and systematic evaluation; until these data become available, endocrinological investigations in patients with acne should be limited to those presenting with additional evidence for an endocrine disorder.

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