ACNE AND SYSTEMIC DISEASES

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ABSTRACT

Acne is a very common, multifactorial, complex, and chronic disease of the pilosebaceous unit that affects approximately 85% of adolescent patients and 3% of adult patients. The roles of sebaceous glands, androgens, follicular epithelial cells, *Propionibacterium acnes*, immune mediators, environmental factors, and genetic factors are well known in acne pathogenesis. Although it is not a life-threatening disease, it is closely associated with low quality of life and psychological depression. Moreover, acne can also be associated with hypovitaminosis, or may present as a part of systemic syndromes such as: congenital adrenal hyperplasia; seborrhoea-acne-hirsutism-androgenetic alopecia syndrome; polycystic ovary syndrome; hyperandrogenaemia, insulin resistance, and acanthosis nigricans syndrome; Apert syndrome; synovitis-acne-pustulosis-hyperostosis-osteitis syndrome; pyogenic arthritis, pyoderma gangrenosum, and acne syndrome; metabolic syndromes; and Behçet's syndrome. These syndromes must be excluded in patients with severe and recalcitrant acne.

Keywords: Acne vulgaris, hyperandrogenaemia, insulin resistance, systemic diseases.

INTRODUCTION

Acne is a very common multifactorial disease of the pilosebaceous unit. The roles of androgenic stimulation of sebaceous glands, hyperproliferation/hyperkeratosis of follicular infra-infundibulum, inflammation, and increased colonisation of *Propionibacterium acnes* are classically well known aetiological factors in acne pathogenesis.[1] Abnormalities in androgenic steroid metabolism, insulin resistance, cell–cell signalling pathways, and uncontrolled inflammation may result in different clinical symptoms, including acne vulgaris.[1,2] The role of dietary factors and some genetic mutations are also demonstrated in recent studies.[3] Acne affects approximately 85% of adolescent patients and 3% of adult patients between the ages of 35 and 44 years all over the world.[1] Although acne is not a life-threatening disease, it is associated with low self-esteem, low quality of life, and depression. Aside from these effects, it can also be a component of systemic disorders such as hypovitaminosis, systemic syndromes (congenital adrenal hyperplasia [CAH], seborrhoea-acne-hirsutism-androgenetic alopecia syndrome [SAHA], polycystic ovary syndrome [PCOS], hyperandrogenaemia, insulin resistance, and acanthosis nigricans syndrome [HAIR-An], Apert syndrome [AS], synovitis-acne-pustulosis-hyperostosis-osteitis syndrome [SAPHO], pyogenic arthritis, pyoderma gangrenosum, and acne syndrome [PAPA]), metabolic syndromes, and Behçet's syndrome.[4,5] These syndromes should be borne in mind when considering children or adolescents with severe and/or treatment-resistant acne, a female who has never had acne but who suddenly develops severe acne as a late-onset disorder, when there is failure to respond to conventional therapies, and in cases with acne and other signs of hyperandrogenism such as hirsutism, irregular menstruation periods, changes in voice, Cushingoid features, increased libido, development of acanthosis nigricans, resistance to insulin, or androgenetic alopecia. This review addresses the pathogenesis of acne and several systemic syndromes with genetic mutations.

ACNE AND SYSTEMIC SYNDROMES

Congenital Adrenal Hyperplasia and Acne

CAH is an autosomal recessive disorder that is usually related to 21-hydroxylase deficiency due to mutations in the *CYP21A2* gene. This mutation leads to decreased production of cortisol and mineralocorticoids, as well as excessive production of androgens.[6] CAH may be classified as one of two groups depending on whether there is a complete loss of enzyme function (as in the severe, classical form) or whether they present as milder, non-classical forms. Dermatological symptoms are usually associated with excessive androgen production and present in many different ways, such as rapid early childhood growth, advanced skeletal age, early appearance of facial, axillary, and pubic hair, premature adrenarche, acne, impaired fertility in both sexes, hirsutism, androgenetic alopecia, seborrhoea, and menstrual disorders in female patients.[7,8] These manifestations may be progressive with age. Severe recalcitrant cystic acne in the peripubertal-to-adult period may be associated with CAH, especially with non-classical CAH.[9] It can be difficult to differentiate CAH from PCOS clinically, and therefore serum concentrations of 17-OHP should be investigated after adrenocorticotropic hormone stimulation (17-OHP60) in women with persistent acne in adult life.[9] Treatment of CAH with oral glucocorticoids and fludrocortisone reduces increased androgen levels in patients.

Seborrhoea-Acne-Hirsutism-Androgenetic Alopecia Syndrome and Acne

SAHA syndrome was first defined in 1982 and characterised by the tetrad: seborrhoea, acne, hirsutism, and androgenetic alopecia. It is classified as one of four groups according to the aetiopathogenesis: idiopathic, ovarian, adrenal, and hyperprolactinaemic types.[8,10,11] Hyperandrogenaemia or increased sensitivity of the pilosebaceous unit to normal circulating androgen levels may lead to skin manifestations. This syndrome is more common in middle-aged female patients and can be associated with PCOS, cystic mastitis, obesity, insulin resistance, and infertility.[11] Acne severity is usually not related to serum androgen levels and hormonal therapies such as oral contraceptives, antiandrogens, and insulin-sensitising medications are helpful in treatment.

Polycystic Ovary Syndrome and Acne

PCOS is one of the most common endocrine disorders in females of reproductive age. It is clinically characterised by an accumulation of incompletely developed follicles in the ovaries due to anovulation and multisystemic symptoms such as irregular menses and other clinical signs of hyperandrogenism including acne, seborrhoea, hirsutism, infertility, and female-type androgenetic alopecia.[12] As reported in the Rotterdam criteria, the menstrual cycle and endocrine dysfunction with hyperandrogenism are more important for diagnosis than ultrasound findings. PCOS affects approximately 10% of women attending gynaecology clinics, but the prevalence in the population varies from 10–20%, depending on which diagnostic criteria are used.[12] PCOS is also associated with hirsutism, infertility, acne, weight gain, Type 2 diabetes, cardiovascular disease, and endometrial hyperplasia. Hyperandrogenaemia, altered gonadotropin secretion, insulin resistance, and vitamin D deficiency are the most important factors in PCOS pathogenesis.[8] More recently, PCOS has been considered to be a major risk factor for metabolic syndrome.

Increased circulating androgen levels are seen in 60–80% of patients, with serum free testosterone being the most sensitive biochemical marker. Adrenal function is usually normal. Acne is seen in approximately one-third of women with PCOS and these patients usually have severe, late-onset, persistent, and/or treatment-resistant acne vulgaris.

Lifestyle modification, insulin sensitisers, oral contraceptives, and vitamin D supplementation are the most common therapeutic agents for the management of PCOS.[12-14]

Hyperandrogenaemia, Insulin Resistance, and Acanthosis Nigricans Syndrome and Acne

HAIR-An syndrome is widely accepted as a subphenotype of PCOS. Clinical manifestations in young women include irregular menses, hyperandrogenic symptoms such as oily skin, hirsutism, acne, androgenetic alopecia, deepening of voice, clitorimegaly and changes in muscle mass, and insulin resistance with diabetic symptoms.[15] Patients have elevated insulin levels, and elevated or high-normal levels of testosterone and androstenedione. Adrenal function is usually normal. Hyperinsulinaemia directly affects the androgen levels. Hyperinsulinaemia and hyperandrogenaemia stimulate epithelial proliferation and melanin

accumulation. Weight loss and antiandrogens such as spironolactone and flutamide are traditional treatment options for HAIR-An syndrome.[15,16] Insulin sensitisers, such as metformin, rosiglitazone, and pioglitazone, are very important components of the treatment of HAIR-An syndrome as they improve hyperandrogenism and ovulation. In recalcitrant cases, surgical biliopancreatic diversion or bilateral wedge resection of ovaries and hormonal gonadotropin suppression may be an effective treatment approach.

Apert Syndrome and Acne

AS is a rare genetic and congenital disease characterised by craniosynostosis and syndactyly of fingers and toes. AS was first described by Wheaton in 1894 and then reviewed extensively by the French physician Apert in 1906. AS has a dominant inheritance pattern, but most of the cases are sporadic and exhibit a paternal effect. Dermatological manifestations of AS are hyperhidrosis, oily skin, resistant acne, interrupted eyebrows, excessive forehead wrinkling, lateral plantar hyperkeratosis, skin dimpling over joints, and oculocutaneous hypopigmentation.[17] The association between AS and acne vulgaris was first reported by Solomon et al. in 1970. A possible mechanism is end-organ hypersensitivity to circulating androgens.[18] More than 98% of AS cases are caused by *de novo* mutations (S252W and P253R) in the gene encoding fibroblast growth factor receptor 2 (FGFR2).[17] Increased FGFR2 signalling has a major pathogenic role in follicular hyperkeratinisation and sebaceous gland hypertrophy in acne, and effective anti-acne drugs increase FGFR2 signalling.[19] Increased FGFR2 signalling activity is seen in AS, which upregulates the activity of phosphoinositol-3-kinase/Akt and mitogen-activated protein kinase signal-transduction pathways. This results in a nuclear deficiency of the transcription factor forkhead box protein O1, which is thought to be a key transcription factor in the pathogenesis of acne vulgaris.[7]

Synovitis-Acne-Pustulosis-Hyperostosis-Osteitis Syndrome and Acne

SAPHO syndrome is a rare multifactorial systemic syndrome that usually affects children and young adults, with a female predominancy.[20] This syndrome was first described in 1987 by Chamot et al.[20,21] The aetiology of SAPHO is unknown but may include genetic, infectious, and immunological abnormalities. *P. acnes* is one of the most highly suspected microorganisms with regard to the aetiology of SAPHO syndrome.[21] As suggested by the name of the syndrome, it is characterised clinically by chronic, recurrent multifocal osteomyelitis, acute or chronic sterile arthritis associated with pustular or palmoplantar psoriasis, or sterile osteitis in the presence of a skin manifestation such as severe acne. Presence of any of these is sufficient for a diagnosis of SAPHO syndrome. Arthritis is usually seronegative. Skin manifestations include Sweet's syndrome, Sneddon–Wilkinson disease, pyoderma gangrenosum (PG), palmoplantar pustulosis, acne, hidradenitis suppurativa, folliculitis, and psoriasis. Acne is usually seen in 25% of patients with SAPHO syndrome and may present as acne conglobata, acne fulminans, or hidradenitis suppurativa.[20,21] This syndrome may also be associated with ulcerative colitis.[22] Non-steroidal anti-inflammatory drugs are generally offered as the first-line therapy option, while systemic antimicrobial therapies such as doxycycline, azithromycin, sulfamethoxazole/trimethoprim, and clindamycin can be used with anti-inflammatory and immunomodulatory effects. Other treatment options include corticosteroids, photochemotherapy, retinoids, colchicine, bisphosphonates, and disease-modifying agents such as methotrexate, sulfasalazine, and anti-tumour necrosis factor (TNF) therapy.[21]

Pyogenic Arthritis, Pyoderma Gangrenosum, and Acne Syndrome

PAPA syndrome is an autosomal dominant hereditary disease that is associated with mutations in the *PSTPIP1/CD2BP1* gene on chromosome 15q.[23] It was first described in 1997 and classified in the group of auto-inflammatory disorders. The affected protein, CD2-binding protein 1 (encoded by *PSTPIP1*), is a cytoskeletal adaptor protein that interacts with a number of other intracellular and membrane proteins such as PTP-PEST, CD2, WASP, Fas ligand, and pyrin, and was first described in 2002.[24] Arthritis is generally the initial symptom of this syndrome, followed by acne and PG, although acne and PG may not be seen in all patients. Arthritis is classified as seronegative or aseptic arthritis and usually starts between the ages of 1 and 16 years. Acneiform lesions begin at puberty.[4] PG is usually the final symptom of this syndrome and seeing a child or adolescent patient with PG is an important finding of PAPA syndrome. Systemic corticosteroids, interleukin (IL)-1 receptor antagonist, anti-TNF agents, leflunomide, sulfasalazine, and dapsone are treatment options for PAPA syndrome.

Vitaminosis and Acne

The role of diet is a very controversial topic in acne pathogenesis. Many nutrients have been incriminated in acne pathogenesis, including chocolate, sugar, multivitamins (or hypovitaminosis), dairy products, and oily and fatty foods with a high glycaemic index. Serum levels of vitamin A, vitamin E, vitamin D3, vitamin B12, folic acid, and minerals such as zinc and copper have been evaluated in patients with acne vulgaris.[25]

Vitamin A is a lipid-soluble vitamin that has a role in the keratinisation and immune regulation of the skin. Low levels of vitamin A in patients with acne vulgaris have been shown in a few studies in the literature.[25,26] Kligman et al.[27] reported that oral vitamin A (retinol) is effective in acne treatment when used in high doses (300,000 U daily for women, 400,000–500,000 U daily for men).

Vitamin E is another lipid-soluble vitamin that is an effective non-enzymatic antioxidant, protecting the skin from the adverse effects of oxidative stress. It also has a synergistic effect with vitamin A.[28] Reactive oxygen species produced by neutrophils have a role in the inflammatory process of acne.[27] Low levels of vitamin E in patients with acne vulgaris have also been reported in the literature.[25,26]

Vitamin B12 is an essential vitamin that has a role in cellular proliferation, infertility, and nerve damage. It works together with folic acid and iron. The role of this vitamin in acne pathogenesis was first reported in 1976 by Braun-Falco and Lincke.[29] They reported that with vitamin B12 therapies, patients were developing acne and/or acneiform eruptions. These lesions may appear after initial treatment as small papules or pustules on the face, back, chest, and upper arms. All age groups can be affected, with a predisposition for females. The aetiological and pathogenic mechanisms of this reaction are not well known. Several cases of an eruption resembling acne rosacea have been reported after ingestion of high-dose vitamin B supplements. The most important consideration is that the eruption does not respond to classical rosacea treatment, but resolves quickly after discontinuation of the vitamin supplement.[30] Aside from this side effect, Karadag et al.[29,31] reported vitamin B12 and folic acid deficiency after the treatment of acne vulgaris with systemic isotretinoin.

Vitamin D is the other lipid-soluble vitamin that is also identified as a prohormone steroid with endocrine, paracrine, and autocrine functions.[32] The endocrine effects of vitamin D mainly influence serum calcium homeostasis, but it has recently been discovered that it is essential for the proper function of nearly every tissue in the body including the brain, heart, muscles, immune system, and skin. The relationship between vitamin D and acne has long been theorised: Simpson et al.[33] reported the effect of vitamin D in the treatment of acne vulgaris in 1940. In a more recent study, Agak et al.[34] reported that *P. acnes* is a potent inducer of Th17 cells, and 1,25(OH)2D inhibits *P. acnes*-induced Th17 cell differentiation, which can be an effective option for modulating acne. In this study, sebocytes were identified as 1,25(OH)2D-responsive target cells; this effect may be an option in acne therapy. In another recent study, the expression of inflammatory biomarkers has been shown to be influenced by treatment with vitamin D in cultured sebocytes. Ekiz et al.[35] also reported that high serum levels of vitamin D in patients with rosacea may lead to remission.

Zinc is an essential element for the proper development and function of the human skin. Zinc supplement-induced remission of acne was first reported in the 1970s by Michaelsson and Fitzherbert. Patients with acne vulgaris have been reported to have low levels of serum zinc.[25] Zinc has a bacteriostatic effect on *P. acnes*, inhibits chemotaxis, and may decrease production of the inflammatory cytokine TNFα.[27]

Metabolic Syndrome and Acne

Metabolic syndrome is a multiplex syndrome consisting of abdominal obesity (waist circumference >102 cm in men and >88 cm in women), hypertriglyceridaemia (≥150 mg/dL [1.69 mmol/L]), low high-density lipoprotein cholesterol (<40 mg/dL [1.04 mmol/L] in men and <50 mg/dL [1.29 mmol/L] in women), high blood pressure (≥130/85 mmHg), and high fasting glucose (≥110 mg/dL [≥6.1 mmol/L]), and which is a risk factor for coronary heart disease, as well as for diabetes, fatty liver, and several cancers. This syndrome arises from insulin resistance and abnormal adipose deposition and function.

Insulin/insulin-like growth factor 1 receptors can be expressed by epidermal keratinocytes, and hyperinsulinaemia may lead to increased proliferation of basal keratinocytes within the follicular sebaceous unit duct, inducing failure of terminal differentiation of follicular corneocytes and thus actively participating in acne pathogenesis.

Another mechanism linking insulin resistance and acne development is aggravation of the mammalian target of rapamycin complex 1 (mTORC1) signalling pathway.[36] Stimulation of the mTORC1 signalling pathway via a Western diet may be strongly associated with acne with increased body mass index, insulin resistance, and early onset of menarche.[37]

The role of insulin resistance is very well known in female patients with PCOS and acne vulgaris.[38] In addition, there are published studies that support the role of insulin resistance in male patients with acne vulgaris and in post-adolescent acne.[39,40]

These mechanisms should be kept in mind during the treatment of acne vulgaris. Stabile et al.[41] reported that insulin sensitisers not only improve the irregularity of menses and hirsutism in patients with PCOS, but also reduce insulin resistance as well as reducing the body's inflammatory response. Using insulin sensitisers in male patients with treatment-resistant acne vulgaris was supported by results of Fabbrocini et al.[42] These studies describe the importance of insulin resistance in acne vulgaris pathogenesis and underline the use of metformin and diet as a possible adjuvant therapy in this condition.

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