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Acne-Associated Syndromes

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Abstract

Introduction: Acne, a chronic inflammatory disorder of pilosebaceous unit, is characterized by comedones, pustules, papules, nodules, cysts, and scars. It affects nearly 85% of adolescents. High sebaceous gland secretion, follicular hyperproliferation, high androgen effects, propionibacterium acnes colonization, and inflammation are major pathogenic factors. Systemic disease or syndromes that are associated with acne are less commonly defined. Therefore, these syndromes may not be usually recognized easily.

Research methods: Acne-associated syndromes prove the nature of these diseases and are indicative of pathogenesis of acne. Polycystic ovary (PCOS), synovitis-acne-pustulosis-hyperostosis-osteitis (SAPHO), hyperandrogenism-insulin resistance-acanthosis nigricans (HAIR-AN), pyogenic arthritis-pyoderma gangrenosum-acne (PAPA), pyoderma gangrenosum-acne vulgaris-hidradenitis suppurativa-ankylosing spondylitis (PASS), pyoderma gangrenosum-acne conglobate-hidradenitis suppurativa (PASH), seborrhea-acne-hirsutism-androgenic alopecia (SAHA), and Apert syndromes are well-known acne-associated syndromes. Endocrine disorders (insulin resistance, obesity, hyperandrogenism, etc.) can be commonly seen in these syndromes, and there are too many unknown factors that must be investigated in the formation of these syndromes.

Conclusion—key results: If we are aware of the component of these syndromes, we will recognize those easily during dermatological examination. Knowledge of clinical manifestations and molecular mechanisms of these syndromes will help us to understand acne pathogenesis. When acne pathogenesis is explained clearly, new treatment modalities will be developed.

Keywords: acne, syndrome, PCOS, HAIRAN, PAPA, PASH, Apert, SAPHO, SAHA, acne-associated syndromes

1. Introduction

Acne vulgaris is a common chronic inflammatory disease of the pilosebaceous unit. Acne is typically thought as an adolescent disease but it is also seen in adulthood anymore [1].

Although there are lots of studies about the pathogenesis of acne, all pathogenetic factors are not known very well. Four main pathways are described in acne pathogenesis: increased sebum production, abnormal keratinization, *Propionibacterium acnes* colonization, and inflammation [2]. Acne is a multifactorial disease and sometimes associated with systemic disorders. Acne may be a potential skin marker of internal disease or a component of syndromes such as PCOS, HAIR-AN, PAPA, PASH, SAPHO, SAHA, and Apert. To know about the pathogenesis of those will help us to understand the acne pathogenesis [3, 4].

Herein, we aim to mention about acne-associated syndromes and their clinical and pathogenetic features.

2. Polycystic ovary syndrome (PCOS)

Polycystic ovary syndrome (PCOS) is an ovarian disease characterized by hyperandrogenism, chronic anovulation, and polycystic ovaries. It is one of the most common endocrinopathy that affects 4–12% of women of reproductive age [5].

Its etiology is unknown, but it was first described by Drs Irving Stein and Michael Leventhal in 1935. They discovered polycystic ovaries in seven patients who had anovulation during surgery and described this disorder as the name of Stein-Leventhal syndrome [6]. Later diagnostic criteria were developed.

The National Institutes of Health (NIH), the Rotterdam, and the Androgen Excess Society Criteria are used for the diagnosis of PCOS [7, 8]. Nowadays, NIH criteria are the preferred diagnostic criteria in adolescents [9].

NIH criteria are the presence of oligoovulation or anovulation and biochemical or clinical signs of hyperandrogenism [9]. Before the diagnosis with using these criteria, some conditions must be excluded that result in anovulation and hyperandrogenism, such as congenital adrenal hyperplasia, Cushing's syndrome, and androgen secreting tumors [9]. Thyroid disease, hyperprolactinemia must also be excluded.

Although pathogenesis of PCOS is not understood very well, it is thought that hormonal pathways contribute to this process. The pulse frequency of gonadotropin-releasing hormone (GnRH) increases in PCOS and stimulates to the anterior pituitary gland to secrete luteinizing hormone (LH) more than follicle-stimulating hormone (FSH), resulting in an increased ratio of LH to FSH. The increase in LH relative to FSH stimulates the ovarian theca cells to synthesize androstenedione. Consequently, the net ovarian androgen production increases [10]. Insulin has also a role in the pathogenesis of PCOS by stimulating the ovarian theca cell to secrete androgens as LH and also inhibits hepatic production of sex hormone binding globulin (SHBG). As a result, free and total androgen level increases.

Obesity is another component of this syndrome and contributes pathogenesis via insulin resistance [10].

Insulin resistance and hyperandrogenism are responsible for the cutaneous involvement of PCOS. Insulin resistance causes acanthosis nigricans (AN), and hyperandrogenism leads

to hirsutism, acne, oily skin, seborrhea, and hair loss (androgenic alopecia). It is estimated that 72–82% of women with PCOS have cutaneous signs [11]. PCOS has also multisystemic effects and is associated with lots of diseases including infertility, endometrial cancer, obesity, depression, sleep-disordered breathing/obstructive sleep apnea (OSA), nonalcoholic fatty liver disease (NAFLD), and nonalcoholic steatohepatitis (NASH), type 2 diabetes mellitus (T2DM), and cardiovascular diseases [9]. Patients with PCOS are usually first seen by a dermatologist. Because of the above comorbidities, dermatologists should know the diagnosis and clinical findings of PCOS very well.

Cutaneous findings in women with PCOS are related to abnormalities of the pilosebaceous unit. Increased androgen levels activate abnormal development of the pilosebaceous unit, and hirsutism, acne or androgenic alopecia. Androgenic alopecia is luckily rare among women with PCOS because of its complex etiology. Acanthosis nigricans (AN) and skin tags are the other skin disorders in PCOS [12].

Although acne, hirsutism, and AN were the most common skin manifestations, hirsutism and AN were the most sensitive for PCOS diagnosis [13]. In previous reports, the range of acne prevalence in PCOS is 15–95%. While hirsutism affects 5–15% of women in the general population, previous reports showed hirsutism prevalence between 8.1 and 77.5% in women with PCOS. In patients with PCOS, hirsutism is also a sign of metabolic abnormalities [13].

AN is also associated with substantial metabolic dysfunction (increased insulin resistance, glucose intolerance, body mass index, and dyslipidemia).

Therefore, the presence of AN and hirsutism should warn us regarding a patient's potential metabolic risk factors. A broad range in the prevalence of AN among women with PCOS (2.5% in the United Kingdom, 39.5% in Turkey, 16 and 17.2% in China) were observed [13].

Although patients with PCOS frequently refer to dermatologists with cutaneous concerns, it is important to educate them about the metabolic and fertility-related implications of PCOS.

Hormonal therapy (combination estrogen and progesterone oral contraceptives, antiandrogens: spironolactone, cyproterone acetate, drospirenone, flutamide, and inhibition of peripheral androgen conversion: finasteride), insulin-sensitizing agents (metformin, thiazolidinediones), and nonhormonal therapy (standard acne, hirsutism, androgenetic alopecia therapy) are treatment options [14].

Pharmacologic treatment is not every time necessary for all patients with PCOS. Mild forms of hirsutism, acne, and androgenetic alopecia may be controlled with standard nonhormonal agents and life style changes (weight loss, diet, exercise, glucose control) [14].

3. Hyperandrogenism-insulin resistance-acanthosis nigricans syndrome (HAIR-AN syndrome)

Hyperandrogenism-insulin resistance-acanthosis nigricans syndrome (HAIR-AN syndrome) is a subphenotype of polycystic ovary syndrome. It is clinically characterized by acne, obesity, hirsutism, and acanthosis nigricans. It usually manifests in early adolescence. Although

etiology is not known very well, genetic, environmental factors, and obesity are estimated to cause HAIR-AN syndrome. The primary abnormality in patients with HAIR-AN syndrome is thought to be severe insulin resistance. In those patients, insulin levels increase and stimulate the overproduction of androgens in the ovaries [15].

Patients may also present with amenorrhea and signs of virilization. Although adrenal function is normal, the levels of insulin, testosterone, and androstenedione may be high. Adolescents with HAIR-AN syndrome usually have normal levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) but the ratio of LH to FSH is usually more than one [16].

Clinical findings are related to insulin resistance and hyperandrogenism so patients first refer to dermatologist, endocrinologist, or gynecologist with hyperandrogenism signs (hirsutism, androgenic alopecia, male body habitus, acne, menstrual dysfunction, increased libido, clitorimegaly) or insulin resistance signs (polydipsia, polyuria (often subclinical), acanthosis nigricans, skin tags, and obesity [17] (**Figure 1**).



Figure 1. Acanthosis nigricans, from Nahide Onsun's photos.

Polycystic ovary syndrome (71–86%), congenital hyperplasia of the adrenal (3–10%), adrenal and ovarian tumors (0.3%), and idiopathic hirsutism (10%) are, respectively, the most common reasons of hyperandrogenism. Except those, HAIR-AN syndrome should also keep in mind as a reason of hyperandrogenism that is seen in almost 5% of females with hyperandrogenism [18].

For HAIR-AN syndrome diagnosis and follow-up, in addition to history and physical examination, a complete blood cell count, thyroid screen, serum prolactin, glucose and insulin measurements, serum electrolyte, and lipid panel should be evaluated [17] because Cushing's syndrome, Hashimoto's thyroiditis, Grave's disease, and congenital adrenal hyperplasia may accompanied with HAIR-AN syndrome [4]. To investigate the origin of hyperandrogenism, total testosterone, levels of 17-hydroxyprogesterone, dehydroepiandrosterone sulfate (DHEAS), levels of luteinizing and follicle-stimulating hormones, and morning cortisol after a low dose of dexamethasone should be analyzed [17].

High level of DHEAS should warn us about the possibility of an androgen-producing tumor of the adrenal gland. Increased 17-hydroxyprogesterone is usually seen in congenital adrenal hyperplasia. Patients with Cushing's syndrome have elevated levels of circulating androgen, and abnormal secretion of cortisol. In those, increased basal levels of cortisol and failure of suppression after stimulation with dexamethasone are observed. In polycystic ovarian syndrome, LH/FSH ratio is usually >2.5 (may see in normal patients as well). Although there is not an underlying virilizing tumor (ovarian or adrenal) in HAIR-AN syndrome, plasma testosterone level is high [19].

In the treatment, lifestyle changes like exercise, lower-calorie diet rich in fiber and protein are advised to patients. Metformin can also be prescribed. Other choices are estroprogestatif pills and antiandrogens [20].

4. SAHA syndrome

SAHA syndrome was first described in 1982, characterized by seborrhea, acne, hirsutism, and androgenetic alopecia [21]. The SAHA syndrome is classified into four types: idiopathic, ovarian, adrenal, and hyperprolactinemic [21], and it can be associated with polycystic ovaries, cystic mastitis, obesity, insulin resistance, and infertility [4, 21].

In the pathogenesis of SAHA, increased androgen synthesis in adrenals and ovaries, disturbed peripheral metabolism of androgens, or induction of metabolism and activation of androgens in the skin may play important role [4].

Approximately 20% of the patients have all four major signs of SAHA syndrome. Seborrhoea is observed in all of patients, androgenetic alopecia is seen in 21% of the patients, and acne in 10% and hirsutism in 6% of the patients [4].

The management of disorder resembles HAIR-AN and PCOS [22].

5. APERT syndrome

Apert syndrome is a rare congenital type I acrocephalosyndactyly syndrome (acrocephalosyndactyly type I). It was first described in 1906 by the French physician Eugène Apert, characterized by the premature fusion of the craniofacial sutures and syndactyly of the hands and feet [23].

The syndrome is inherited in an autosomal dominant fashion, a rare congenital disease. It is caused by a genetic mutation in the FGFR2 gene, and approximately 98% of all patients have specific missense mutations of FGFR2 [24].

FGFR2 is responsible for the development of embryonic skeleton, epithelial structures, and connective tissue [25]. Craniofacial deformities, hypertelorism, dental and palatal abnormalities, proptosis of the eyes, different skeletal deformities, hydrocephalus, abnormal brain development, mental retardation, blindness, cardiovascular, urogenital, gastrointestinal, respiratory, and skin abnormalities can be seen in patients with Apert syndrome [25].

Dermatologic associations of Apert syndrome was not known when first described in 1906 [26]. In 1970, Solomon first reported the dermatologic manifestation of this disorder, which is severe acneiform lesions [27]. The other skin manifestations are hyperhidrosis, hypopigmentation, and hyperkeratosis of plantar surfaces [27].

In this syndrome, the pathogenesis of acne is not understood very well but increased fibroblast growth factor receptor-2 (FGFR2)-signaling is suspected to be of pathophysiological importance in acne vulgaris because it was reported that in skin cultures, keratinocyte-derived interleukin-1 α stimulated fibroblasts to secrete FGF7 which stimulated FGFR2b-mediated keratinocyte proliferation [28]. In acne pathogenesis, increased levels of interleukin-1 α (IL-1 α) are seen in comedones, and an important pro-inflammatory cytokine stimulates keratinocyte proliferation, hyperkeratinization, and decreased desquamation of comedo formation [28]. Patients with Apert syndrome usually have oily skin. Moderate to severe acne, occurring in childhood or early adolescence, affecting the forearms, which is an unusual site for conventional acne, is often observed [23, 28]. Comedones, papules, pustules, furunculoid cysts, and scars as seen in conglobate acne can be seen. It is very difficult to treat, and often unresponsive to therapy but good response to oral isotretinoin [23, 26, 28].

Although isotretinoin therapy has good treatment option, it has serious adverse effects such as teratogenicity, hepatic dysfunction, elevation of cholesterol and triglyceride levels, visual changes, pseudotumor cerebri, musculoskeletal pain, hyperostosis, mucocutaneous dryness, and dryness of the eyes. Therefore, the risk/benefit ratio in treatment of acne lesions with isotretinoin in children with Apert syndrome should be evaluated well [26].

6. Synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome

SAPHO syndrome was first defined in 1987 by Chamot et al. and its characteristic clinical findings are synovitis, acne, pustulosis, hyperostosis, and osteitis [29]. The etiology is controversial [30]. Although infections (*Propionibacterium acnes*, *Corynebacterium* sp.), seronegative spondyloarthropathies (psoriasis, sacroiliitis, enthesitis, inflammatory bowel disease, axial involvement), genetic factors, and stress were responsible for the pathogenesis, those are only hypothesis [30].

Propionibacterium acnes is estimated to play a pathogenic role in SAPHO syndrome. Productions of microbial determinants of *P. acnes* stimulate innate immune response through TLR-2. TLR-2 induces inflammatory cytokines via NF- κ B and mitogen-activated protein kinase

pathway [31]. Recent reports also showed that SAPHO syndrome had similar features with other autoinflammatory disease. IL-1 β , TNF- α , and IL-8 were suggested to be important in the pathogenesis of SAPHO [32].

Two cohort studies investigated genes PSTPIP2, LPIN2, NOD2, PSTPIP1, and PTPN22, but did not show causal mutations. Therefore, SAPHO syndrome is thought as a polygenic disease [33].

SAPHO syndrome is a rare disease so usually misdiagnosed because this syndrome have similar clinical features with infectious discitis, seronegative SpA, and psoriatic arthritis (PsA), and skin and bone lesions may appear at different times [34].

Standard diagnostic criteria are also controversial such as etiology. The commonly used diagnostic criteria of SAPHO syndrome: (i) local bone pain with gradual onset; (ii) multifocal lesions, especially in the long, tubular bones and spine; (iii) failure to culture an infectious microorganism; (iv) a protracted course for several years with exacerbations and improvement with anti-inflammatory drugs; and (v) neutrophilic skin eruptions, mostly palmoplantar pustulosis (PPP), nonpalmoplantar pustulosis, psoriasis vulgaris, or severe acne [30] (**Figure 2**).



Figure 2. Pustular psoriasis, from Nahide Onsun's photos.

The skin manifestations are those of different neutrophilic dermatoses. PPP is the most common skin involvement, including pustular psoriasis, representing 50–75% of all dermatologic manifestations, psoriasis vulgaris may also be seen among the dermatologic manifestations of SAPHO. One fourth of patients have acne conglobata and fulminans with men clearly predominating [34]. Hidradenitis suppurativa may also be seen.

PG, Sweet's syndrome, and Sneddon-Wilkinson disease are the other rare cutaneous manifestations. IBD especially Crohn's disease may also be accompanied with SAPHO syndrome [34].

The most of author agree about that SAPHO could be classified within the spectrum of auto-inflammatory diseases. Therefore, intra-articular or systemic corticosteroids, disease-modifying antirheumatic drugs (DMARDs) such as methotrexate, sulfasalazine, cyclosporine, and leflunomide are the treatment options but there are no randomized controlled clinical trials for the treatment. Doxycycline can also be thought as a treatment option for *P. acnes* eradication [33] Infliximab (INFX), an anti-TNF- α monoclonal antibody, has been showed effective for the treatment SAPHO patients especially unresponsive or refractory to conventional drugs. In recent case series, remarkable improvement of bone, joints, and skin inflammatory manifestations was observed with Infliximab (INFX) therapy. In resistant SAPHO cases, the IL-1 antagonist anakinra can be also tried [35, 36].

7. PAPA syndrome

PAPA syndrome (pyogenic arthritis, pyoderma gangrenosum, and acne) is an autosomal dominant, autoinflammatory disorder. PAPA syndrome was first described as a hereditary disease in 1997 [37]. There is a PSTPIP1/CD2BP1 mutation on chromosome 15q that causes an increased binding affinity to pyrin and induces the assembly of inflammasomes [37]. The caspase, a protease, is activated and converts inactive prointerleukin (IL)-1 beta to its active isoform IL-1 beta. Overproduction of IL-1 beta induces to release pro-inflammatory cytokines and chemokines. Those are responsible for the recruitment and activation of neutrophils, leading to a neutrophil-mediated inflammation [38].

PAPA syndrome is usually presents with severe self-limiting pyogenic arthritis in early childhood. Pyoderma gangrenosum (**Figure 3**) and nodular-cystic acne may be seen around puberty and adulthood [37]. Pathergy test is positive in PAPA syndrome and clinically appears as pustule formation followed by ulceration [34]. There is not a diagnostic test but acute phase reactants and white blood cell count may be elevated because of systemic inflammation [34].



Figure 3. Pyoderma gangrenosum, from Nahide Onsun's photos.

Arthritis usually gives good response to therapy with corticosteroids. Pyoderma gangrenosum is treated with topical or systemic immunosuppressant drugs. In addition, a few reports showed that anti-TNF- α and anti-IL-1 agents are effective in the treatment [39].

8. PASH syndrome

The clinical trial of pyoderma gangrenosum, acne conglobata, and hidradenitis suppurativa was described as PASH syndrome by Braun-Falco et al. in 2012. PASH syndrome clinically resembles pyoderma gangrenosum, acne conglobata, and pyogenic arthritis (PAPA) syndrome, but arthritis is not observed [40].

The molecular basis of PASH syndrome is not known very well. It is accepted as autoinflammatory disease. PAPA (pyogenic arthritis, pyoderma gangrenosum, and acne), PAPASH (pyogenic arthritis and PASH), and PASH (pyoderma gangrenosum, acne conglobata and hidradenitis suppurativa) syndromes clinically have similar components. The absence of pathogenic mutations in the PSTPIP1 gene may be used for distinguishing this syndrome from other AIDs [41, 42]. Although a genetic mutation was not discovered clearly in PASH syndrome, in some case series, NCSTN gene, NOD (nucleotide-binding oligomerization domain) genes, the immunoproteasome, and MEFV mutations were reported in PASH syndrome [41, 42].

Systemic corticosteroids, traditional antineutrophilic agents (dapsons and colchicine), and metformin may be tried at first but standard therapy options for autoinflammatory diseases are not usually enough to treat patients with PAPA and PASH syndrome whereas anti-TNF therapies and anti-IL-1 therapy are promising new treatment options for drug resistant cases [43].

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