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The Skin as a Mirror of Internal Disease: Comorbidities and Epidemiology of Acne Vulgaris and Adult Female Acne – A Cross-sectional Study and Current State of Knowledge

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ABSTRACT Acne vulgaris is a common skin condition affecting an increasing number of adults and might be a clue to identifying systemic disease. Objective of this study is assessment of the demographic and clinical characteristic, including comorbidities, of patients with acne with a special focus on adult female acne (AFA). This cross-sectional study analyzed the medical records of 354 patients with acne (323 outpatients and 31 hospitalized). Data concerning patient age, sex, lesions morphology and distribution on body areas, duration of the disease, Body Mass Index, and dermatologic and systemic comorbidities were collected. 61% of all patients were female, 45.37% of women were classified as AFA. The median age of patients with acne was 24 years and 32.5 years for AFA. The face was the most commonly affected area; patients with AFA had lesions on their back than less frequently non-AFA. Predominant eruptions were pustules and papules. 38.7% of patients had concomitant systemic chronic disease, 15.25% had an endocrinologic disorder, and 6.21% had thyroid gland dysfunction. Women with AFA had endocrinologic disorders more frequently (P=0.002), whereas cutaneous signs of hyperandrogenism were observed less frequently than in the non-AFA group (P=0.034). AFA possess distinct clinical features and it should raise suspicion towards possible underlying endocrinologic disturbance.

KEY WORDS: acne vulgaris, adult women, epidemiology, comorbidity, hormones

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INTRODUCTION

Acne vulgaris is a chronic inflammatory disease of the pilosebaceous units, clinically manifesting with the presence of comedones, papules, pustules, cysts, nodules, and sometimes leading to scarring (1-3). Acne occurs mainly on the face, neck, and upper trunk (1,2). Mild forms of the disease develop in approximately 85% of the population, with the remaining 15% being severe nodular forms that include acne conglobata (4).

The disease pathophysiology includes four basic processes, namely: follicular hyperkeratinization, androgen-induced hypersecretion of sebum, colonization of the hair follicles by *Cutibacterium acnes* (*C. acnes*), together with immune and inflammatory responses (2,3). Despite advances in understanding of its pathogenesis, few epidemiological studies of acne have been carried out, not just in Poland but also in other European countries (5,6).

Acne vulgaris is undoubtedly one of the most common dermatologic disorders, with an estimated global prevalence of 9.4% and the highest occurrence in adolescents; 85% of individuals between 12 and 24 years have acne at some point of their lives (6,7). Recent research has shown that acne also affects a significant number of adults (1). In the literature, adult acne is defined as acne present beyond the age of 25 and can be classified as either acne persistent from adolescence, responsible for 80% of the cases, or the late-onset type (8-10). The disease may have special features at older ages. For instance, in contrast to teenage acne, in which men tend to be affected more commonly and severely, post-adolescent acne mainly affects women and is usually mild to moderate in grade (9,11,12). We need to define whether adult female acne (AFA) should be regarded as a separate clinical entity from acne vulgaris and therefore require a different therapeutical approach.

Data also suggest that patients with severe acne are at higher risk for many somatic and psychological comorbidities, as the elements engaged in acne pathogenesis may also have an influence on organs other than skin. A role of *C. acnes* is currently postulated in the development of many different diseases, such as endophthalmitis, endocarditis, meningitis, and sarcoidosis (13). Acne may be a clue to hormonal disturbances, including polycystic ovary syndrome (PCOS) or congenital adrenal hyperplasia (14). There is reason to subject acne comorbidities in different age groups to closer scrutiny.

Objectives

The aim of the study was to assess the demographic and clinical characteristic of patients with acne vulgaris with a special regard to adult female acne. An attempt was made to establish the diseases most frequently associated with acne.

PATIENTS AND METHODS

This was an uncontrolled observational cross-sectional study that analyzed the medical records of 354 patients with acne vulgaris from Dermatology Clinic of Jagiellonian University Medical College. The data comprise 323 outpatients (from January 2016 until December 2018) and 31 hospitalizations that occurred due to acne (from January 2013 until December 2018). 10 people were included in both groups (outpatients and hospitalized). The discrepancy between the time of analysis for the groups was due to lack of electronic medical documentation for the outpatient department before January 2016.

The estimated minimal sample size was 246 patients, assuming 80% prevalence of acne in the Polish population. Patients were men and women aged between 12 and 69 years old.

Data concerning patient age, sex, lesions morphology (presence of comedones, papules, pustules, cysts, scars, hyperpigmentation), and their distribution on body areas were collected for all groups. For hospitalized patients, additional data were available for analysis: duration of the disease (years passed before admission to the hospital) and the patients' Body Mass Index (BMI) – defined as weight/height squared (kg/m^2).

Other forms of acne, such as rosacea, ance inversa, and infantile acne, are not discussed in this article.

Statistical analysis

Statistical analysis of collected data was performed using STATISTICA 12.0. The normality of data was analyzed using the Shapiro-Wilk Test. All numerical variables were presented as numbers with percentages, median (Me) with interquartile range (IQR) or mean ± standard deviation (SD). Pearson's Chi-squared and U-Mann Whitney tests were used to assess the relationship between variables, and statistical significance was defined as $P<0.05$.

RESULTS

Demographic and general characteristics

The median age of the 354 people treated for acne vulgaris at our Clinic was 24 years (IQR 20-31). Cases from the outpatient department had a higher median age than cases from the hospital (24 years, IQR 20-31 versus 20 years, IQR 17-29; $P=0.02$). There was a significant number of older individuals in our

Table 1. Acne lesions localization and types of acne eruptions

	Total		AFA		Non-AFA		*P*-value
	N	(%)	N	(%)	N	(%)	
Lesions localization							
Face	292	(82.48)	84	(85.71)	208	(81.25)	0.28
Back	140	(39.55)	27	(27.55)	113	(44.14)	0.003
Chest	73	(20.62)	24	(24.49)	49	(19.14)	0.27
Neck	32	(9.04)	12	(12.24)	20	(7.81)	0.2
Shoulders	26	(7.34)	6	(6.12)	20	(7.81)	0.58
Head	23	(6.5)	4	(4.08)	19	(7.42)	0.25
Buttocks	5	(1.41)	1	(1.02)	4	(1.56)	0.99
Other	17	(4.8)	4	(4.08)	13	(5.07)	0.79
Lesions morphology							
Comedones	128	(36.16)	32	(32.65)	96	(37.5)	0.26
Pustulo-papular	276	(77.97)	77	(78.57)	199	(77.73)	0.55
Acne conglobata	64	(18.07)	19	(19.39)	45	(17.58)	0.81
Inflammatory acne-ONS	19	(5.37)	3	(3.06)	16	(6.25)	0.2
Hyperpigmentation	96	(27.11)	21	(21.43)	75	(29.3)	0.08
Other	40	(11.23)	15	(15.3)	25	(9.77)	0.17

AFA – adult female acne, ONS – other non-specified

Missing data: for acne lesions localization on mean level 4.87%; for acne lesions morphology on mean level 7.32%

study: 69 adults aged 30-39 years, 20 adults aged 40-49 years, and 6 between 50 and 69 years. The median age for patients with AFA was substantially higher than for the remaining acne population, at 32.5 years (IQR 28-38 versus 22 years for non-AFA patients, IQR 19-25; $P<0.001$). Women suffered from acne more frequently than men, comprising 61% of all patients with acne, with 45.37% of them – 98 women in the study (27.6% of the analyzed population) – classified as AFA. Women constituted 62.3% of outpatients . In the inpatients group, there was a slightly higher prevalence of men (53.33%), but the differences were not statistically significant ($P=0.13$). One of the outpatients was in the middle of a gender change process, but was classified as female in our records. Median duration of the disease before admission to the hospital was 3 years (IQR 0.92-5.00).

Acne morphology

The three most frequently affected body areas in all the analyzed groups were the same: the face (affected in 87.49% of all patients), followed by the back and chest. Women with AFA had lesions less frequently on their back compared with non-AFA subjects (27% versus 44.14%; $P=0.003$). The vast majority (70.62%) of all patients had a limited form of acne (defined as presence of eruptions on a maximum of 2 different body areas). Women with AFA were not found to have more extensive disease compared with the rest of the population ($P=0.12$).

As far as acne lesions morphology was concerned, most patients presented with more than one lesion type. The most frequent eruptions were pustules and papules (present in 276 patients; 77.97%). There was no difference in inflammatory lesion prevalence for the AFA group compared with non-AFA (for papulo-pustular acne: 78.57% vs 77.73%; $P=0.55$).

Moreover, 27.97% of all our patients suffered from acne scars. Among all the patients with scars, 53 (53.5%) were men and 46 (46.5%) were women ($P<0.001$). Table 1 depicts the acne morphology results in detail.

Acne comorbidities

38.7% of patients with acne suffered from at least one systemic chronic disease. The most frequent comorbidities were endocrinologic disorders, present in 54 individuals (15.25%), of which thyroid gland dysfunction was most frequently reported, i.e. by

Table 2. Chronic systemic and dermatologic comorbidities

	Total		Outpatients		Hospital		p-value	AFA		Non-AFA		p-value
	N	(%)	N	(%)	N	(%)		N	(%)	N	(%)	
Chronic systemic comorbidities												
Thyroid gland disfunction	22	(6.21)	21	(6.5)	1	(3.22)	0.71	10	(10.2)	12	(4.69)	0.08
Other than thyroid endocrinologic disease*	32	(9.03)	27	(8.36)	5	(16.12)	0.18	16	(16.33)	16	(6.25)	0.003
Hormonal disease (total)	54	(15.25)	42	(13)	6	(19.35)	0.41	24	(24.49)	24	(9.3)	0.002
Diagnosed towards endocrinologic disorders	15	(4.24)	15	(4.64)	0	0	0.38	5	(5.1)	0	0	0.57
Other chronic disease**	83	(23.44)	68	(21.05)	15	(48.39)	<0.001	27	(27.55)	56	(21.88)	0.26
No systemic disease reported	74	(20.9)	59	(18.27)	15	(48.39)	<0.001	14	(14.29)	60	(23.43)	0.06
Dermatologic comorbidities												
Hyperandrogenism associated disorder***	56	(15.82)	53	(16.4)	3	(9.68)	0.44	22	(22.44)	34	(13.28)	0.03
Eczema	21	(5.93)	21	(6.5)	0	0	0.24	4	(4.08)	17	(6.64)	0.36
Other disorder	70	(19.78)	67	(29.74)	3	(9.68)	0.14	21	(21.42)	49	(19.14)	0.63
No dermatologic disease reported	222	(62.71)	196	(60.68)	26	(83.87)	0.01	56	(57.14)	166	(64.84)	0.18

*Including: diabetes mellitus, impaired glucose tolerance, insulin resistance, PCOS, biochemical hyperandrogenism, hyperprolactinemia, premature ovarian insufficiency

**For hospitalized population: systemic lupus erythematosus, granulomatosis with polyangiitis, Crohn's disease, Still's disease, thrombocytosis, aplastic anemia, mitral valve incompetence, hypertension, depression, hyperlipidemia, SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis, osteitis), chronic idiopathic meningitis, retrobulbar neuritis

*** Including: seborrhea, seborrheic dermatitis, acne inversa and androgenetic alopecia

6.21% of all patients. There was no significant difference between the frequency of endocrine disorders between hospitalized patients and outpatients (P=0.32). Women constituted the majority of all patients with acne who had an underlying endocrinopathy (87.5% vs 12.5% men; P<0.001). Women with AFA had a concomitant endocrinologic disorder more frequently than patients without AFA (P<0.001), specifically other than thyroid hormonal disease, but not thyroid dysfunction alone (P<0.001, P=0.08 respectively). In the hospitalized population, comorbidities other than endocrinologic chronic diseases were reported significantly more often than in outpatients (P<0.001).

Some patients reported having additional chronic dermatologic conditions. Predominantly, 15.82% of patients had androgen-associated disorders. There was no correlation between presence of hyperandrogenism and the disease extent (P=0.72). Interestingly, patients with AFA had cutaneous signs of hyperandrogenism less frequently than the non-AFA group (P=0.03).

We did not observe an increase in BMI in hospitalized patients. Mean BMI in the study was within a normal range (21.64 kg/m^2, SD 3.40; minimum value 16.54 kg/m^2, maximum 30.45 kg/m^2). Mean BMI for both sexes was 22.08 kg/m^2 (SD 3.14 for women, SD 3.66 for men, P=0.47). A summary of systemic and cutaneous comorbidities acne is presented in Table 2.

DISCUSSION

Acne vulgaris is ranked among top three most prevalent dermatologic conditions and is the eight most prevalent disease in the general population worldwide (7,15). Acne affects 80-100% of people aged between 11 and 30 years old, but recent studies have shown that acne is affecting an increasing number of adults, particularly woemn (2,4). There was a significant number of older participants in our study (total of 95 people ≥30 years old).

Available data has shown acne prevalence for people aged 20-29 to be 64%; for those between 30 and 39 years old it is 43%, and between 40 and 49 years it is 3% for men and 5 % for women (6). Even for people over 59, acne incidence was as high as 13% (3). As far as adult female acne is concerned, its prevalence varies highly from 14% in clinical studies to 54% in surveys (12,16).

The peak age of acne incidence ranges between 16 to 20 years of age, according to different studies (2,7). Over recent decades, the average age of people with acne has increased from 20.5 to 26.5 years (11,17). This finding is in accordance with our results, where the median age of patients was 24 years. On the other hand, individuals with more severe acne requiring hospitalization were younger (median 20 years old) than outpatients.

27.6% of our study population were classified as AFA, which is similar to a Chinese study (25%) (3). AFA mean age ranges from 26.5 to 33.9 years in the literature (18). In our study, the median age for this acne subtype was 32.5 years, which was therefore closer to the reported upper age range. Acne has been increasingly recognized as a chronic disease, especially regarding AFA chronicity, which may persist until the postmenopausal period (10,19). The median duration of acne before admission to the hospital was 3 years in our study, which is longer than the global average duration of the disease (mean 2 years, median 1 year) (7).

The sex ratio of reported visits to a dermatologist due to acne was evaluated in literature to be 5:3 women to men (15). In our study, women constituted the majority (62.3%) of outpatients, but the most severe cases of acne that required hospitalization were predominantly men (53.33%). Studies evaluating sex have shown that women are more often affected at younger ages and in adult acne, whereas men are more frequently affected during adolescence and with more severe forms of the disease (4,7,20).

Several aspects of acne morphology were assessed in our study. The distribution of the lesions was mostly in accordance with the available literature. The face was by far the most common site of acne involvement (up to 100 % of individuals according to some studies). The extrafacial areas are affected at slightly different rates depending on the study, with the second most common location being the upper back (52%), followed by the upper chest (30%), lower back (22%), shoulders (16%), and neck (8%) (7).

The majority of our patients had a disease restricted to two body areas. Women aged more than 25 years in our study differed from the whole acne population, having acne eruptions less frequently on their back. In a study by Di Landro *et al.*, 96.8% of women with AFA had lesions on the face (mainly on the cheeks and chin) and 30.4% had lesions on the trunk (17). Recent studies have questioned the classic localization on the lower third of the face, instead reporting involvement of multiple facial areas and a 48.4% prevalence of truncal lesions vs 11.2 % on the mandibulum (10,11).

Apart from the lesion distribution, we also analyzed their morphology. The probability of having inflammatory acne was postulated to increase with patient age, although in some studies up to 93.7% of AFA had comedones and patients with comedonal acne were older than those with the inflammatory type (1,2,10,17,21,22). In our study, inflammatory papulo-pustular eruptions were the most frequent. This was true for all groups: younger patients, hospitalized and older patients, and outpatients. Furthermore, there was no difference in eruption type between the AFA group and the other patients.

Scarring is the most concerning and disfiguring sequela of acne. The predominance of acne scars varies highly from study to study (from 26.1% to 95%) (23). A significant number of patients suffered from scarring in our study, but, in contrast to some data that suggest more frequent scarring in female patients (14% vs 11%), we noted that men predominated among all patients with scars (53.5% in men vs 46.5% in women) (24).

To our knowledge, the global prevalence of concomitant diseases in acne patients has not yet been estimated. There are single studies available; for example, comorbidities were found in 4.3% of women with adult female acne (18). Acne might be an indicator of hormonal disturbances, including syndromes such PCOS or congenital adrenal hyperplasia, as well as other systemic disorders such as Behcet syndrome, Apert syndrome, or hypovitaminosis (14). Comorbid disorders associated in the literature with severe forms of acne in children and adolescents also include sinopulmonary disorders (asthma, sore throat other than streptococcal infection) and upper gastrointestinal diseases (13). According to some studies, psychiatric comorbidities accompany acne, but the data are not consistent (13,15,17,25).

In our study, 38.7% of the total population with acne suffered from at least one systemic chronic disease. Hospitalized patients had significantly more concomitant systemic diseases than outpatients. The presence of a severe comorbidity such as collective tissue disease, vasculitis, or inflammatory diseases as in our inpatient population, might be a factor contributing to more severe acne course.

Only endocrinological comorbidities were significantly frequently noted in patients records, present in 15.25% of individuals. The relationship between acne and hormonal disfunctions has been widely discussed in literature, but the findings are not fully clear. Although it is generally agreed that there is no underlying endocrine disease in most cases of AFA, more and more studies suggest that late-onset or persistent acne suggest hyperandrogenism (18,26). Up to 70% women with PCOS, the main cause of hyperandrogenism, do have acne and the postulated causative factor of AFA is hyperproliferation of keratinocytes due to an increase in insulin and Insulin Growth Factor 1 levels (10,15,18).

In our study, the vast majority (87.5%) of all patients with acne who had an underlying endocrinologic disease were women. Furthermore, patients with AFA had a concomitant endocrinologic disorder more frequently compared with patients without AFA, although no particular hormonal disease was associated with AFA.

As for dermatologic comorbidities, patients most frequently suffered from seborrhea, seborrheic dermatitis, and androgenetic alopecia, which are conditions that might be attributed to some extend to a disturbance in androgen metabolism (10,27). Surprisingly, women with AFA had cutaneous manifestations of hyperandrogenism less frequently than non-AFA patients, which is in contrast to available studies: it has been reported that one third of AFA cases present some clinical features of hyperandrogenism (1). The explanation for this discrepancy might be that an inflammatory AFA subtype was predominant in our study, which is said to be less frequently associated with hyperseborrhea than the retentional form in which hyperseborrhea is always present (8,10). In studies on the adult acne population, alopecia was present in 1.8-7.2% of patients, but raised laboratory markers of hyperandrogenism were observed in only 3.08% cases, among which slightly elevated levels of dehydroepiandrosterone sulfate were reported most often (1,8,9,18,28). In acne, there is an altered response of skin receptors to circulating androgenic hormones and increased peripheral conversion to active metabolites (18). Insulin resistance is associated with acne independently from hyperandrogenemia, according to some researchers (29).

Some studies emphasize a positive relationship between the number of acne localizations and the presence of hyperandrogenism signs. At least two locations of acne (thorax, shoulders, jaw, neck, and cheeks) were correlated with irregular menstrual cycles and seborrhea (26). no such correlation was found in our study. However, our study demonstrated that there might be a rationale for analyzing thyroid dysfunctions in patients with acne, as thyroid dysfunction was the most frequently reported comorbidity in our study group (6.21%). The available study results remain contradictory – Tsvetanova *et al.* showed an increased risk for thyroid gland dysfunction or autoimmunity in patients with acne compared with the control group (22.86% vs 1.43%), while other studies have failed to demonstrate significant changes in thyroid parameters in adults with acne (30). Thyroid-stimulating hormone and thyroxine increase sebum secretion together with testosterone. The role of pro-inflammatory cytokines (interleukin-1, interleukin-2, interferon-alpha, interferon-gamma) elevated in autoimmune thyroid inflammation is also postulated to activate sebaceous gland function (30-32).

Finally, we did not observe an increase in BMI in hospitalized patients with acne above the normal range. Mean BMI in our study was 21.64 kg/m^2, which is lower than the mean BMI value for Poland (26.4kg/m^2, $p<0.001$) (33). There were no statistically significant sex differences in BMI, which is in contrast to some available studies. It has been shown on different populations that the risk of having acne is reduced at lower BMI (34). Some researchers have documented an association between acne and BMI in adolescent acne (stronger in men compared with women). but not in adult female acne (6,17). Acne appears to be an indicator of systemically enhanced mammalian target of rapamycin complex 1 signaling, which is responsible for obesity, insulin resistance, type 2 diabetes mellitus, arterial hypertension, Alzheimer's disease, and cancer (35).

CONCLUSION

We managed to identify some specific clinical features of patients with AFA. The median age of 32.5 years was substantially higher than for the rest of the acne population. Another feature was less frequent occurrence of lesions on the patients' back in comparison with non-AFA. We demonstrated that disease extent does not differ from other patients, which had not been previously examined. Finally, patients with AFA presented an increased risk for concomitant endocrinologic disorders and a decreased risk for manifesting cutaneous sings of hyperandrogenism. We therefore recommend treating AFA as a special clinical entity that should raise suspicion of hormonal disturbances even if no other cutaneous manifestations of hyperandrogenemia are present.

The present study had several limitations related to the methodology used, including the retrospective approach as well as information bias, missing data, and lack of suitable controls. No objective scale

such as the Global Acne Grading System was obtainable from the available data.

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