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A MICROBIOLOGICAL APPROACH TO ACNE VULGARIS

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The present article gives a concise survey of contemporary opinions on acne vulgaris, its etiopathogenesis, clinical forms and laboratory diagnostics. In particular, the value of microbiological diagnostics and possibilities of local as well as general therapy are discussed. Moreover, our experience is described with vaccinotherapy to manage serious clinical forms and cases when current herapy fails.

INTRODUCTION

Acne vulgaris is a chronic inflammatory disease of the pilosebaceous unit (sebaceous glands and hair follicles) frequently occurring in a large part of mainly younger population groups. In principle, it is a disorder of adolescence, but it persists until the middle age in a minority of individuals. Acne vulgaris occurs in several clinical forms. Severe forms of acne are often therapy-resistant which has mostly a very negative impact on the patients.

The disorder of the pilosebaceous unit is of a multifactorial character. The proportion of individual pathogenic factors including genetic ones can differ with a resulting variability of clinical forms of acne. In many cases, the influence of various etiopathogenic factors is combined[13, 11, 15, 24, 45, 50].

ETIOPATHOGENESIS

In patients, an increased production of sebum is manifested, and its quantity and quality varies depending on the hormone regulation. Besides direct hormonal effects, there is also involved a genetically conditioned sensitivity of sebaceous glands to the influence of androgens which is higher in persons suffering from acne. In general, androgens stimulate the formation of sebum, while estrogens reveal a suppressive effect on it. The activity of sebaceous glands is thus dependent on the ratio of estrogens and androgens[24, 45]. The increased level of androgens in adolescence is known to be a starting point for the development of juvenile acne. The amount of triglycerides in sebum increases up to 50% and together with their quantity, population of propionibacteria is enlarging, too[48].

In acne, keratinization is also impaired. An increased production of keratinizing cells in follicular canals together with a decrease of their elimination leads to the accumulation of sebaceous matter. The primary manifestation of acne is formed – a comedo. In the formation of comedos, essential fatty acids are also involved. Decreased local concentration of linoleic acid is joined with follicular hyperkeratosis[10, 48].

In the pathogenesis of acne, the natural skin microflora plays a marked role too, namely the gram-positive anaerobic rod *Propionibacterium acnes*, in a lesser extent also *Propionibacterium granulosum*, event. other species. Propionibacteria present a number of enzymatic activities. Their lipases cleave sebaceous diacylglycerols and triacylglycerols to glycerol and free fatty acids that induce proliferative hyperkeratosis in the follicular canal, thus producing a comedogenic effect. Its irritating effect (pH decrease) lead to the impairment up to the rupture of comedo covering[19]. Proteases of propionibacteria enable the permeation of follicle content through its wall and hyaluronidases support its spreading in the dermis. The clinical consequences of these processes are papules, pustules, induration and abscesses[19].

Propionibacteria influence both cellular and humoral components of the immune system[24, 36]. They are able to persist in macrophages and increase chemotaxis of polymorphonuclear leukocytes. They are also cytotoxically active, are able to activate the complement in an alternative way and bring about the hypersensitivity of early or late type[45, 47]. Other products of propionibacteria are phosphatases, neuraminidases, deoxyribonucleases and namely substances close to prostaglandins with marked importance in the formation of inflammatory manifestations of acne[5, 49, 51].

Other bacteria of cutaneous microflora [namely *Staphylococcus epidermidis*] can also produce the above given enzymes and get involved in the acne etiology[5, 16, 19].

Immune mechanisms also contribute to the formation of reactive inflammation. An intradermal test with the suspension of killed propionibacteria in patients with the severe form of acne shows after 48 hours a significantly greater inflammatory reaction than in healthy persons. In these patients, an increase of specific antibodies is also registered[4, 17, 40, 41, 42].

DIAGNOSTICS OF ACNE

Diagnostics of acne is based on the clinical picture and laboratory evidence of *Propionibacterium* and *Staphylococcus* bacteria whose quantity in the examined pus is usually increased. The technique of sampling is very important – it is necessary to get a sample of pus formed in the bottom part of the inflamed follicle. The obtained material is inoculated on appropriate cultivation soils for anaerobic bacteria (Wilkins-Chalgren agar, Schaedler agar, Clostridial agar and others), usually enriched with 5% of ram blood. On properly withdrawn samples, non-sporulating rods of propionibacteria grow after 48-hour incubation at 37 °C, forming huge white or yellowish colonies, often surrounded with a zone of complete hemolysis. Microscopic image is described as gram-positive slightly club-like rods. The species identification utilizes biochemical tests (Anaerotest 23 Lachema, ApiA Bio-Mérieux etc.) and the prevailing finding is *Propionibacteium acnes*. This strain is typical by the production of catalase and indol[2, 15, 29].

For the determination of staphylococci, the material is inoculated on agar soil (e.g. Columbia Blood Agar Base also enriched with 5% of ram blood). Staphylococci grow after 24-hour incubation at 37 °C in aerobic atmosphere as typical white or yellow pigmented colonies, often with a zone of complete hemolysis. They are identified with the help of biochemical test kits (Api Staph Bio-Mérieux, Staphy 16 Lachema and others). Latex identification tests are used for fast identification of *Staphylococcus aureus* strain.

Differential diagnostics is important for the differentiation of acne caused by external factors and acneiform eruptions. External causes of acne can be the influence of various chemical substances manifesting comedonic effects (natural oil derivatives, detergents, cosmetic products). The causes may be physical ones too – acne mechanica (efflorescence in sites of intensive mechanical contact) or Mallorca acne (reaction to an increased temperature and humidity of environment). An etiologic agent in the formation of acneiform efflorescence can be a mite (Demodex folliculorum).

Acneiform eruptions (acne medicamentosa) are provoked by various generally applied medicaments. The formation is mostly abrupt and it might appear after administration of steroids, anti-epileptic agents, sedatives, vitamins B6 and B12, preparations containing bromine and iodine, event. other agents[11, 12, 15, 24, 45].

THERAPY

Acne vulgaris often represents a therapeutic problem. In mild forms of the disease, the local therapy is advantageous, mostly reaching a very good therapeutic effect. Azelainic acid is frequently used, with antibacterial influence without bacterial resistance. Therefore, its administration is not time-limited[19]. Among other agents, tretinoin is to be mentioned (a vitamin A derivative), as well as benzoylperoxide, influencing namely inflammatory manifestations and its advantage is a faster onset of influence in comparison with tretinoin. For patients with sensitive complexion, local drug forms containing antibiotics can be effective; usually erythromycin (1–4 %) or clindamycin (1 %). A possible formation of bacterial resistance is limiting their use, so the maximum interval of treatment is 2–3 months. The resistance is usually of temporary character and the therapy can be repeated later. Another alternative is clotrimazol. It is used even as a component of a make-up (Acnecolor, Acnecolor light) with good concealing effect[11, 14, 15, 24, 31, 34, 25, 45, 49].

Severe forms of acne (large acne papulopustulosa, acne nodularis, acne conglobata, acne fulminans, acne tetrada) need the application of systemic treatment.

Complex therapy of acne involves the application of oral antibiotics, hormones, isotretinoin and bacterial vaccines.

Oral therapy with bacteriostatic antibiotics can reduce the microbial colonization of follicles by staphylococci and above all by propionibacteria. Tetracycline drugs exert a favorable influence on acne even in low doses that do not alter quantitative condition of the cutaneous microflora, but they can inhibit the synthesis of bacterial enzymes, including lipases. Other antibiotic agents are also being applied (macrolides, lincosamides), in dependence on the limits for tetracycline indication and according to the verified therapy used by various centers. Sulfonamides are utilized in the acne therapy too, but the authors' opinions on their use in this indication are different[7, 8, 11, 15, 24, 26, 31, 32, 45, 49].

Hormones are also effective in the treatment of acne. Their administration is connected with the widespread use of oral birth-control pills. In women, antiandrogen cyproteronacetate in combination with ethinylestradiol (Diane-35) can be used.

Recently, a derivative of vitamin A isotretinoin has been introduced into the therapy of acne. It decreases markedly the formation of sebum and reduces the population of propionibacteria. Its administration is limited for the most severe forms where the preceding systemic therapy was not sufficiently effective[1, 3, 11, 15, 24, 30].

Another approach to the therapy of acne is the application of auto- or stockvaccines containing inactivated strains of propionibacteria and/or staphylococci[6, 9, 33].

Their effect is based on the non-specific modulation of the immune system of patients[9, 12, 20–24, 33, 34]. The vaccinotherapy is usually applied together with external treatment and follows the systemic antibiotic therapy when the pronounced inflammatory manifestations are eliminated[43, 44]. Contrarily to wide-specter antibiotics that can cause the recession of the disease without any effect on possible recurrent attacks after the end of their application, the use of oral vaccines reveals a long-term favorable effect[23, 24].

The Teaching Hospital in Olomouc has a long history of vaccinotherapy use. Whole cell stockvaccines of standard composition are preferred (*Propionibacterium acnes*, *Staphylococcus aureus*, *Staphylococcus epidermidis* in the ratio 1:1:1). They are prepared using the cellophane technique with following inactivation of obtained germs and their lyophilization. They can be applied as subcutaneous injection or in oral forms of drops, capsules or tablets. Basing on the experience, it can be stated that the vaccinotherapy shows a very good effect without unwanted side effects in most patients. The therapy failed at less than 2 % of patients, no worsening of the state was registered. The differences in the effectiveness of individual drug forms (injections, tablets, capsules and drops) was not described[23, 37–39]. It was confirmed that the proper onset of vaccination in mild forms of acne prevents the development of severe cases with permanent consequences. Vaccines can be applied in all cases of acne papulopustulosa, conglobata, induration or abscess forms. Priors to the vaccine therapy, biochemical, hematological and immunological examinations are to be performed. When a clinical improvement is reached as the result of antibiotic therapy, it is recommendable to continue with vaccinotherapy, eventually with another immunotherapy, according to the results of immunological tests[15, 45, 46, 49].

CONCLUSION

It can be concluded that acne is a typical disease of young age and it often represents a major psychic trauma for the patients. The results of non-treated or insufficiently treated disease are frequent scars, also influencing negatively the psychic condition of patients. Regarding to the constantly improving diagnostic methods and various therapeutic possibilities, it is feasible to reach a favorable therapeutic effect in most cases. The disease can thus be influenced at its beginning, esthetic damage can be prevented and the economic costs resulting from chronic character of the process can be decreased.

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