



Prevalence of atopic diseases and the use of topical corticosteroids. Is there any connection?

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Summary The prevalence of atopic diseases (atopic dermatitis, bronchial asthma, allergic rhinitis) has considerably increased for the last 40 years. This tendency has coincided with the beginning of the epoch of the use of the topical corticosteroids, which have a potent immunomodulation action. This fact itself as well as a number of research results has allowed to formulate the following hypothesis: the use of topical corticosteroids in children of early age contributes to the increase of prevalence of atopic diseases in the developed countries. The offered hypothesis can explain lower prevalence of atopic diseases in rural areas and in children from families with the anthroposophic life style. In other side this hypothesis also capable to give explanation of increased level of atopic diseases among people with high socioeconomic level and in children from 1 child families. It is of a note that corticosteroids use in developing countries is limited due to economic reasons and active use of complementary medicine.

If the proposed hypothesis is correct, a revision of the therapeutic approaches is necessary concerning the attitude towards application of topical corticosteroids in children suffering from various forms of eczema. The direct proof of this hypothesis can be found during prospective studies.

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The increase of prevalence of atopic diseases today is one of the serious problems of public health services. Epidemic of an allergy became apparent with the generation that was born after 1960 [1]. Since that time the increase of incidence of atopic dermatitis from 3–5% up to 12–16% [2,3], allergic rhinoconjunctivitis from 9% up to 15% [2], bronchial asthma from 4% up to 9–10% [2,4] has been observed. The prevalence of asthma in children and young adults has tripled and quadrupled in many industrialized countries during the last two decades [5]. The increase of prevalence of atopic der-

matitis in children is first of all observed at much older age, whereas the incidence of atopic dermatitis among infants of the first year of life has not practically changed in comparison with the results of the similar examinations 20 years ago [6]. It is necessary to accentuate, that atopic dermatitis, allergic rhinitis and bronchial asthma are considered as diseases associated with predominance of Th2-type of immune response.

Most frequently the increase of prevalence of atopic diseases is related to the "western" style of life, which is characterized by low frequency of viral and bacterial infections, modification of diet (decrease of the consumption of $n - 3$ unpolysaturated fatty acids, antioxidants) and change of the intestine

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microbiocenosis [7]. Moreover, this tendency is connected with the appearance of the "new" allergens, increase of the exhaust gases in cities' atmosphere etcetera [1,8].

The proposed hypotheses were based on a combination of results of both epidemiological and pathophysiological studies. At the same time, all above-mentioned factors could not unambiguously explain the existing tendency.

Early childhood is the most sensitive period for the development of sensitization and induction of Th1/Th2-type immune answer imbalance [9]. During the pregnancy the immunologic environment of a placenta constantly induces the predominance of the immune answer of Th2-type in fetus [10–12], then in the period of early childhood the deviation of the immune answer towards Th1-type is observed. Postnatal maturation of immune system, which in atopic patients is characterized by the development of imbalance towards Th2-type of immune response, is genetically determined and is modified by the environment [13]. The delay of the maturation of Th1-type answer has resulted in increase of Th2 cytokines' releasing, that promotes the persistence of the fetal status including predominance of Th2-type of immune response [14]. It is shown, that the decrease of the ability to produce γ -interferon that is synthesized by Th1 cells during neonatal period correlates closely to the increasing risk of sensitization and development of atopic diseases and is the most reliable prognostic criterion for their development [15–17]. The generalized immaturity or suppression of both Th1 and Th2 types of the immune answer may be revealed at birth in children, which have increased risk of further allergy development [18].

The possible factors that may cause disorders of development of balance of the immune answer of Th1/Th2-type in children of early age are infectious diseases, drugs (antibiotics), vaccination, probiotics and changes of diet.

It is a paradox that increase of prevalence of atopic diseases has first of all coincided with the radical changes of their therapy, with an epoch of application of topical corticosteroids in children of early age suffering from atopic dermatitis. Taking this fact into account, as well as series of both epidemiological and pathophysiological studies the following hypothesis was formulated: the use of topical corticosteroids in children of an early age suffering from an eczema contributes considerably to the increase of prevalence of atopic diseases in the developed countries.

Considering a possible role of therapeutic intervention, including corticosteroids, on the course of

atopic dermatitis, one can come to a rather strange conclusion about practical absence of significant data related to this problem [19].

The use of topical corticosteroids, effective therapeutic agents, is recommended in various consensuses on therapy of atopic dermatitis [20,21]. The topical corticosteroids, besides, are actively prescribed to children of early age with a seborrheal dermatitis, microbic eczema, napkin dermatitis etceteras. Application of topical corticosteroids in children of early age with various kinds of eczemas was constantly increased in the advanced countries for last 40 years. Moreover, a tendency to apply topical corticosteroids of higher potency is observed during the last years. Application of topical corticosteroids in early children's age is at the same time considerably less spread in the developing countries that is explained by both peculiarities of the system of national health services in these countries and the low standard of living. Cost of "the correct" treatment of a child with atopic dermatitis estimated in series of publications [22–24] makes it unreal to use the offered therapy in children in developing countries.

Moreover, the use of the recommendations of the consensus on atopic dermatitis designating the prescription of topical corticosteroids as the preparations of the first line in general practices is accepted mainly in the developed countries. As a rule, in developing countries national folk methods of therapy play an important role limiting the use of topical corticosteroids.

The proposed hypothesis is also capable to give indirect explanation of the well-known facts:

1. The relation of atopic diseases' prevalence and the social status of the patient. People with high socioeconomic level are characterized by increased level of incidence by bronchial asthma [25,26].
2. Smaller prevalence of atopic diseases in rural areas than in cities [27,28].
3. The prevalence of atopic dermatitis in children is much lower in families with more than 1 child [29].

In all three cases (children from less provided groups of population, children from rural areas, families with many children) "not enough" active medical tactics (not following the recommendations of consensus) takes place, that is resulted in more rare prescriptions of topical corticosteroids in early age.

The offered hypothesis can also explain considerably lower prevalence of allergic diseases in children from families with the anthroposophic life style [30]. The negative attitude towards the use of topical corticosteroids is one of the characteristic features of these families.

Analysis of a pathophysiological basis of the offered hypothesis makes it necessary to estimate the influence of corticosteroids to the development of Th1/Th2 types of the immune answer. It's known, the clinical efficiency of corticosteroids is connected to their ability to inhibit synthesis of such inflammatory cytokines as IL-1, IL-2, IL-3, IL-5, IL-6, IL-8, γ -interferon [31–34].

As it was found in series of the studies, corticosteroids had the ability to change the type of immune answer by CD4+T-cells towards the predominance of T-helpers of 2 type. In animal (mice) experiments it was found that dexamethazolum suppressed production of IL-2, but had no influence on IL-4 production by T-helpers [35]. In people corticosteroids have selective effect on CD4+T-cells' development [36]. Incubation with glucocorticoids Th0 of cells stimulates production IL-4 and IL-10, but suppress production IL-5 and interferon- γ [37]. The latter blocks immune response of Th2-type [38].

Corticosteroids have blocking effect on synthesis and receptor binding of IL-12 which is the inducer of development of Th1-type of the immune answer [39]. The corticosteroids inhibit production of IL-12 by monocytes, that is resulted in the decrease of γ -interferon production by these cells and in the increase of T-cells' ability to synthesize IL-4 [40]. The treatment with topical corticosteroids within 9–10 days considerably reduces the increased expression of mRNA IL-12 p40 in damaged skin of the patients with atopic dermatitis [41]. Moreover, dexamethazolum inhibits an expression of receptors to IL-12R β 2 and expression of mRNA IL-12R β 2 in mononuclear human peripheral blood cells [42].

The therapy by corticosteroids influences the production of IgE, that is one of the key markers of the atopic diseases. Thus, therapy of patients with atopic dermatitis by topical corticosteroids within two weeks resulted in the elevation of spontaneous production of IgE by B-cells in vitro [43].

The experiment has showed that corticosteroids are able to induce IgE production by B-lymphocytes when added to a culture in vitro [44–46]. A synergy of IL-4 and corticosteroids in induction by B-cells of IgE production plays, probably, some role in the influence of corticosteroids on the course of atopic diseases.

Thus, in spite of the obvious clinical efficiency of corticosteroids, there is a change of a balance be-

tween Th1- and Th2-types of the immune answer towards to Th2-type predominance under their action. One may suggest that the use of corticosteroids in children of early age who have natural predominance of Th2-immune response promotes a delay in formation of the balance between Th1/Th2-types of the immune response and causes a favorable background for the development of atopic diseases.

Probably, the ability of corticosteroids to "fix" Th2-immune response in children of early age can explain the fact that the increase of prevalence of atopic diseases is significantly related to the children from "low risk" families where there is no hereditary predisposition for atopic diseases [47,48].

If the presented hypothesis is correct, the revision of the therapeutic approaches of topical corticosteroids' application in children suffering from eczema is necessary. Direct link to this hypothesis can be found in prospective studies conducted jointly by a number of research centers.

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