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Relationship between vaccination and atopy

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Background. The rising prevalence of atopic diseases during last decades brings concern for the "Western life-style" countries. Although there is general consensus on the importance of the genetic predisposition for atopic disorders (asthma, allergic rhinitis, atopic dermatitis), only changes in environmental factors can explain the rise of allergic diseases during the last forty years. Vaccinations in infancy have been incriminated as an additional risk factor for development of atopic diseases. A potential relationship between vaccination and atopy could be analysed by two directions: either by activation of the Th2 network in the vaccine-specific memory response, or exposition to (attenuated or inactivated) pathogens or their components at a very young age of vaccinated children and possible promotion of Th1 proliferation.

Materials and methods. The major electronic databases (Medline, Cochrane Library) were searched using key words: vaccination, atopy, relationship and children. Recent studies analysing a relationship between atopic disorders and vaccination in infancy were reviewed. Moreover, possible mechanisms of immune response to vaccines in atopic children were analysed.

Results. Available evidence is rather convincing that the current regular childhood vaccination does not increase the risk of atopic disorders. Large epidemiological, prospective, cohort and multi-central studies all over the world published in last 10 years with quite large proportions of unvaccinated children included showed that vaccination in infancy was not related to development of atopic conditions starting from the first year of life up to the middle age. Even conversely, some studies detected that vaccinated children had a moderately reduced rate of atopic diseases. It was also denoted that atopy could be suppressed due to high vaccination coverage.

Conclusions. Allergic or atopic children just like non-atopic children require routine immunization to be protected from serious life and health threatening viral and bacterial infections. The risks of infection by vaccine avoidance outweigh by far the possible minimal risks of immunization, moreover, anti-infectious treatment or natural infection (like pertussis) *per se* could be potential triggers of atopic disorders.

Key words: vaccination, atopy, relationship, children, immune response

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INTRODUCTION

Allergic diseases represent an increasing problem in public health in most modern societies and

developing countries as their prevalence has risen markedly during recent decades. It is estimated that 20 percent of the world population suffer from allergic diseases (1). In developed countries more than a half of adult population is sensitized to at least one common allergen and approximately 40 percent of children by 6 years of age manifest Th2-associated memory against at least one inhalant allergen (2). Nevertheless, the causes of the allergy burden and its prevalence from country to country are not yet fully explained (3). Rising prevalence of allergies coincided with global planned infant immunization. In this context early childhood vaccination as a possible additional factor to the allergy burden has driven the attention (4). Until now this question remains worth of debates.

Following the national vaccination programs during the first year of life a child receives the biggest number of vaccine shots. It seems logical to speculate that such extensive vaccine coverage with a direct effect on the immune system should impact on other conditions related with the immune dysfunctions (5).

Early childhood immunization has been described as a promoter of the atopy (6), as well as a surrogate for infections with the inhibition of atopy (7). Two mechanisms have been proposed by which vaccination could influence development of atopic diseases: first – direct allergy inducing immune effects (4), second – by preventing possible protective effects of natural infection. Immunization, by preventing the natural infection, has been suggested to contribute the hygienic environment that permits domination of atopic immune responses (8).

Both sides of this debate have been changed by now. Meta-analysis of scripts of hygiene hypothesis concluded that positive association between viral infections and atopic dermatitis found in a part of studies appeared to be confounded by antibiotic prescription, which has been consistently associated with an increase in eczema risk, but no association with vaccines detected (9).

IMMUNE SYSTEM RESPONSES

T-cells play a key role in atopic diseases. There are two subsets of T helper (Th) cells, referred to as Th1 and Th2. After birth recognition of microbial signals from the uterine environment progressively up-regulates Th1 function towards the adult-equivalent range. Immune (T-cell) responses to allergens are initiated very early in life, but adult-like patterns of allergen specific Th2 memory are usually established by the end of the preschool years (10). Th1 cells mainly produce the cytokines interferon (IFN)-γ, tumour necrosis factor (TNF)-α and interleukin (IL)-2, and are essential to mount a protective response against infectious agents. Th2 cells secrete IL-4, IL-5, and IL-10, and are involved in allergic responses and humoral immunity. Cytokine responses have been demonstrated to be different in atopic and non-atopic individuals. Children who are at high genetic risk of atopy development are designated to slow Th1 cell function maturation, and to Th2 memory elevation (11). Th2 associated first type or immediate hypersensitivity reactions (develop in less than 1 hour after exposure to antigen) involve immunoglobulin E (IgE) – mediated release of histamine and other mediators from mast cells and basophils. Type I reactions underlie the following atopic disorders: allergic asthma, eczema, allergic rhinitis, conjunctivitis.

FACTORS INFLUENCING ATOPY DEVELOPMENT

There is a complex interaction of genetic and environmental factors in the development of asthma, allergic rhino-conjunctivitis or atopic eczema (12). Although heredity factors and indoor tobacco smoke are evident risk factors, environmental humidity, poor ventilation, indoor pets and frequent use of antibiotics during the first year of life are possible risk factors, they cannot explain the increase in allergy during the last decades, especially in countries with a "Western life-style" (1, 13, 14). In this context early childhood vaccinations as planned immunological interventions have attracted interest because they may alter the cytokine milieu and thus theoretically render the children more or less susceptible to IgE formation (4, 15) and subsequent IgE-mediated allergy against otherwise harmless environmental antigens.

SPECIFICS OF IMMUNE RESPONSE TO VACCINATION IN ATOPIC CHILDREN

Slow maturation of Th1 function in children at high risk of atopy appears to be associated with a range of

sequels in infancy and early childhood (16). These include reduced cellular and humoral responses to some vaccines (17) and increased susceptibility to severe respiratory infections (18). Accordingly it is important to know that transient atopy-associated deficiency in Th1 function in childhood can be successfully overcome by appropriate vaccination and boosting regimens (19). The immune response formation after vaccination could be impaired not only because of atopic genotype, but also by atopic child exposure to noxious environment. Parental smoking interacts with genes associated with atopy and tends to impair IgG formation and T-cell responses to diphtheria / tetanus vaccine (20).

RELATIONSHIP BETWEEN ATOPIC DISORDERS AND VACCINES

Relationship between atopic disease and immunisation has been studied for various vaccines, mostly for BCG, measles, and pertussis.

An epidemiological study of German preschool children demonstrated a weak protective effect of BCG vaccination against asthma and skin prick test (SPT) positivity (21, 22). It was noticed that the timing of BCG vaccination may be also important for Th1/Th2 balance in infancy (23). In Lithuania one prospective study of 48 children, who were vaccinated with BCG vaccine at different age: at the first 24 hours after birth (24 children) or at the age of 3 months (control group of 24 children), was conducted. After the follow up visit at the age of 6 years the authors found out that in the group of children who were vaccinated later the prevalence of atopic eczema was less (n = 4 vs n = 9), but after statistical analysis the difference between the groups found out to be non-significant (p = 0.104) (24). Recent studies of BCG vaccination and atopic manifestation association do not confirm either protective or provocative vaccination effect to atopy in childhood (25). But this statement is still debatable (26).

There are only few studies on allergic disorder risk after hepatitis B immunization (HBV). The active substance of hepatitis B vaccine is the HBs antigen of hepatitis B virus, therefore Th1 oriented response is not as intense as in live attenuated vaccines like BCG (23).

Acellular pertussis is a vaccine which induces Th2 responses parallel to Th1, therefore it has been suggested that immunization with such vaccines may predispose some children to atopic disease. Pertussis toxin specific-IgE significantly increases after booster immunization in 4–6 year old both atopic and non-atopic children, but the prevalence of positive skin prick tests stays unaffected (27). Randomized clinical trial involving both whole cell and acellular pertussis vaccines did not show any enhancement of atopic manifestations in children at the age of 7 years (28). In the German cross sectional study (n = 1 673, 5–7 years children) whole cell pertussis vaccination was shown as protective against asthma OR 0.55 (95% CI: 0.31–0.98) and against symptoms of eczema in boys (29). Recent study on the genomic-based approach to assessment of vaccine safety and immunogenicity in children showed that in immune responses to diphtheria-acellular pertussis-tetanus (DPaT) vaccine and pneumococcal polysaccharide conjugate vaccines, potentially antagonistic Th1/INF associated and Th2-associated gene networks coexist in an apparent state of dynamic equilibrium, whereas in Th2-dominant allergen specific responses of atopic people the Th1 and INF networks are respectively disrupted and down-regulated (30).

Meta-analysis of observational studies (7 studies: n = 186 663 and 5 studies: n = 41 579) detected no association, provocative or protective, between receiving the BCG or whole cell-pertussis vaccine and risk of asthma in childhood and adolescence (31).

In an international study of asthma and allergies in childhood (ISSAC) conducted in 29 centres of 21 countries of the world between 1995 and 2005, 54 943 schoolchildren of 8–12 years of age were randomly selected. No associations of pertussis and measles infection with symptoms of asthma, rhino-conjunctivitis and eczema were found in both affluent and non-affluent countries. Pertussis infection by itself was related to asthma-like conditions (ORad 1.68; 95% CI 1.44–1.97) and rhino-conjunctivitis (ORad 1.63; 95% CI 1.33–2.00) exacerbations. Measles infection was associated with wheeze (OR 1.26; 95% CI 1.10–1.43) and eczema exacerbations (OR 1.22; 95% CI 1.08–1.39). There was no association between infections and SPT positivity detected (32). Bernsen and van der Wouden found a statistically significant positive association between measles infection and atopic disorders (ORad 1.77; 95%

CI 1.20–2.61) in MMR-vaccinated children and a negative association between rubella infection and eczema in unvaccinated children (ORad 0.57; 95% CI 0.38–0.85) (33). Another cross-sectional study (n = 14.893), including children of farming and anthroposophic families in 5 European countries, indicated inverse associations between measles infection or vaccination and atopic sensitization in the whole population (34).

VACCINATION STATUS AND ATOPY

In recent 10 years a number of scientific articles were published investigating potential associations between vaccination and atopy.

Prospectively followed atopy risk-enhanced birth cohort study in Germany revealed no evidence for allergy promoting effect of common childhood vaccines. Moreover, children with complete vaccination coverage seem to be better protected against development of atopy at their preschool years (35). But these conclusions could be misleading as no information about parent refusal to vaccinate their children was given. Spanish studies showed that children with the risk of atopy were inadequately immunized: incompletely or not vaccinated at all because of the social believe that vaccination could cause allergies and asthma (36, 37).

KOALA Birth Cohort study in Netherlands (included 2 764 families) revealed that infants until the age of 6 months with incomplete schedules or not vaccinated at all did not differ significantly in eczema risk or recurrent wheeze compared to infants with standard vaccinations against diphtheria-tetanus-pertussis (DTP), poliomyelitis (IPV), *Haemophilus influenza* type b (HiB) (38). These findings were confirmed by Grüber et al. in a multi-central randomized clinical trial of infants (aged between 11.5–25.5 months) with active atopic dermatitis. Received cumulative vaccine doses were inversely associated with eczema severity (p = 0.0107). Also there was no association between severities of eczema neither in allergic sensitization to food nor inhalant allergens and exposure to common vaccines (39).

Investigators from the prospective cohort study in Australia, which started at 1986 and data recollected at 2004, did not find any association between common childhood immunizations and risk of asthma and other atopic disease at the age of 44 years (40).

Despite the parental fears (41) that vaccination weakens the immune system of a child and some doctors' reservations about vaccines, studies show that the frequency of infections and manifestation of atopic disorders during different periods of childhood does not differ between vaccinated and non-vaccinated children (42). The German Health Interview and Examination Survey of Children and Adolescents with a representative sample of 17 641 subjects evaluated that children depending on the status of vaccination differed significantly only in terms of the lifetime prevalence of vaccine preventable diseases. As it is to be expected, the risk of such diseases is notably lower in vaccinated children (43).

CONCLUSIONS

The question of vaccination and allergy relationship remains important because it is undermining confidence in national and global immunization programs (44). Available evidence is rather convincing that the current regular childhood vaccination does not increase the risk of atopic disorders.

Atopic children require not only the adopted lifestyle to be protected from allergy exacerbations (45) but also additional measures. To improve the quality of life of allergic children the vaccination status should be completed by encouraging parents. Atopic children are at a greater risk of infections caused by specifics of immunity system maturation, reduced cellular and humoral responses. Allergic children are more easily infected and consequently tend to use more antibiotics than non-allergic children (46). In this way, regular and additional childhood vaccination is protective not only from health and life threatening infections, but also it could help to avoid excessive consumption of medications.

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VAKCINAVIMO ĮTAKA ATOPIJOS EIGAI

Santrauka

Pastaraisiais dešimtmečiais kelia susirūpinimą moderniose valstybėse sparčiai didėjantis alerginių susirgimų skaičius. Genetinių veiksnių įtaka atopinėms ligoms (bronchų astmai, alerginiam rinitui ir konjunktyvitui bei atopiniam dermatitui) yra neabejotina, tačiau alerginės sensibilizacijos didėjimą visuomenėje galėtų paaiškinti tik pakitusių aplinkos veiksnių poveikis. Visuotinis kūdikių skiepijimas sutapo su augančiu sergamumu alerginėmis ligomis, todėl kelia mokslininkų susidomėjimą. Vakcinavimas, veikdamas T limfocitų proliferaciją ir sąlygodamas Th1/Th2 santykio svyravimus, galėtų turėti įtakos atopinių ligų eigai. Vienos vakcinos žinomos kaip I tipo T ląstelių pagalbininkių (Th1) atsako stimuliatoriai (pvz., BCG), kitos (pvz., kokliušo) stipriau veikia II tipo T ląstelių (Th2) imuninio atsako grandį, kuri dominuoja atopijos patogenezėje.

Tikslas. Remiantis naujausios mokslinės literatūros duomenimis, analizuoti atopiškų vaikų imuninio atsako į vakcinas ypatumus bei atopijos ir vakcinavimo ryšį.

Medžiaga ir metodai. Didžiausiose medicininės literatūros paieškos duomenų bazėse (Medline, Cochrane Library) atlikta straipsnių paieška naudojant raktinius žodžius: vakcinavimas, atopija, ryšys ir vaikai.

Rezultatai. Per pastaruosius 10 metų daugelyje publikuotų epidemiologinių, prospektyvinių, daugiacentrinių mokslinių darbų pateikiamos išvados, jog kūdikių vakcinavimas neturi įtakos atopinių ligų išsivystymui nuo pirmųjų gyvenimo metų iki pat vidutinio amžiaus. Keliose studijose nurodoma, kad vakcinavimas kai kuriomis vakcinomis (BCG, tymų), o taip pat visa imunizacija pagal valstybines vakcinavimo programas ne tik neskatina atopinių ligų vystymo bei paūmėjimo, bet priešingai – sumažina.

Išvados. Šiuolaikinių vakcinų tyrimai įrodo, kad yra saugu skiepyti padidintos (su teigiama atopijos anamneze tarp pirmos eilės giminaičių) atopijos rizikos grupės vaikus. Todėl atopinėmis ligomis sergantys vaikai, taip kaip ir sveiki, turi būti skiepijami siekiant apsaugoti nuo sveikatai ir gyvybei pavojingų virusų ir bakterijų sukeliamų ligų. Infekcijos rizika siekiant išvengti vakcinacijos pranoksta galimą skiepijimo riziką. Be to, gydymas priešinfekciniais vaistais arba natūrali infekcija (pvz., kokliušas) gali savaime tapti alerginių susirgimų priežastimi.

Raktažodžiai: vakcinavimas, vaikai, atopija, ryšys, imuninis atsakas