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Food Allergy: Only a Pediatric Disease?

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Abstract

Epidemiologic studies report an increase in food allergies in industrialized countries, but mainly focus on children and young adults. This leads to the impression that food allergies do not occur in the older population. However, age-related changes dramatically affect both the innate as well as the adaptive immune system – a phenomenon known as immunosenescence. Deficiencies in micronutrients, especially zinc and iron, as well as vitamin D, in the elderly may also contribute to the development of allergies. A further risk factor of the elderly in developing food allergies could also be the decreased digestive ability of the stomach due to atrophic gastritis or anti-ulcer medication. In these settings, undigested proteins may persist and become allergenic. In fact, mouse models indicate that these pharmaceuticals support the induction of Th2 responses not only in young adult, but also in aged animals. Previous reports have already suggested that allergies are underdiagnosed among the elderly. Based on our own recent study conducted in a geriatric nursing home, we also suggest that food allergies may be underestimated.

Keywords

Food allergy; Immunosenescence; Micronutrient deficiency

Population studies indicate that food allergies have become a major health concern in industrialized countries in the last decade with increasing awareness among physicians and patients. Approximately 25% of people are convinced to suffer from food allergy, whereas the true prevalence appears to be around 3.5–4% in American [1] and German populations [2]. A recent American study indicated an even higher prevalence of 9.1% of people self-reporting food allergy with 5.3% of them being positively diagnosed by a physician [3]. Interestingly, food allergy seems to be a disease especially of pediatric age with a prevalence of 6% among children under 3 years [1]; its occurrence in the aged population is often underestimated [4]. Thus, it is not surprising that most prevalence studies focus on children and young adults, which leads to the impression that allergic disorders do not affect the elderly. Even though the occurrence in the aged population might be underestimated [4] due

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to lack of epidemiological data, the question arises whether Th2 immune responses towards allergens might at all be possible in advanced age.

Immunological Changes due to Ageing Processes

The role of allergic diseases in the elderly is often a matter of controversy in the literature because of the physiological changes of the immune system that accompanies ageing. The so-called ‘immunosenescence’ was shown to affect both the innate and the adaptive immune systems. Therefore, the elderly are prone to the development of more severe and chronic infectious diseases, vaccine failure, autoimmunity and cancer [5]. One of the most dramatic immunological changes is the involution of the thymus which has its maximal activity during puberty and begins to shrink at the age of 20. At the age of 50 only 10% of the initial mass of lymphoid tissue is left. The relative reduction of naïve T cell number leads to a preponderance of memory T cells, which are of lower affinity and have a decreased potential to protect against new antigens [6]. The lower expression of CD28, the co-stimulatory molecule of T cells, accounts for a more anergic and apoptotic response, also resulting in a loss of responsiveness upon antigen triggering. Among memory T cells, the CD4+ T cells (in particular) proliferate and differentiate poorly [7]. There is controversy in the literature how the balance between the Th1 and Th2 branches are affected by the ageing process. [8]. Mouse studies indicated that Th2 dominance in senescence is supported by increased IL-4 levels and a higher production of IL-5 [9]. This was confirmed in humans by recent data showing that a shift towards a Th2 profile is not only present in childhood but also in mid-to-later life [10]. The differentiation of B cells is affected by immunosenescence, whereas the number of B cells in the periphery seems to be unchanged. However, the humoral immune response is deficient because of the diminished T cell help as well as the defects in class switch recombination, as reviewed by Frasca and Blomberg [11]. Although antibody serum concentrations do not change with age, the generated antibodies are of lower affinity because of a shift from IgG to IgM [12]. Furthermore, it was reported that the expression of the two most distinguishing antibodies for allergic responses in mouse studies, IgG1 and IgE, is decreased six-fold and twelve-fold, respectively, compared to young animals [13], which gives the impression that allergies may play a minor role in senescence.

Ageing not only affects the systemic immune system, but it also has an impact on local immune responses, especially on the gastrointestinal mucosa. The induction of mucosal tolerance is one of the most important protective responses against new dietary antigens. The development of opsonizing secretory IgA antibodies against food antigens represents one of the first counter mechanisms of mucosal immunity by reducing attachment, penetration and invasion of antigens across the mucosa [14]. It is well known that newborns are protected against many pathogens and toxins by the secretory IgA supplied to the infant via breast feeding. This mechanism leads to transient tolerance/immunity against oral antigens, but also trains the infant’s IgA response. With advanced age this mucosal first-line defense mechanism seems to be altered. It has been reported that orally induced antigen-specific IgA responses are weakened in aged animals [15]. Mouse studies have shown that mucosal tolerance induction was impaired in aged animals compared to young ones. However, if oral tolerance is once established in young age, it will also be maintained in senescence [16]. This indicates that ageing affects the induction, but not the effector phase

of oral tolerance. Based on these data, the ingestion of new dietary proteins may not induce oral tolerance in the elderly, but rather make them prone to de novo sensitization and type I food allergy.

Micronutrients Modulate Immune Responses

Antioxidants and micronutrients, such as zinc and iron, are well recognized for their modulating effect on the immune system. Zinc deficiency, which is widespread among the aged population, supports thymic atrophy. Low zinc levels were responsible for the accumulation of immature B cells in spleens of zinc-deficient mice. In contrast, the number of immature T cells was generally lower in the periphery. The animals also showed decreased antibody responses, particularly of the IgM, Ig-G2a and IgA subclasses, whereas the levels of other IgG subclasses were even increased [17]. Human studies have reported that zinc levels are decreased particularly in stress situations due to pro-inflammatory cytokines (such as IL-6 and TNF-α) which bind zinc ions and release them subsequently. In the geriatric population, this stress situation seems to be a permanent one; moreover, no subsequent release of zinc from the cytokines occurs, leading to reduced zinc bioavailability and, consequently, altered immune responses [18]. Decreased levels of zinc are responsible for a reduction of Th1 cytokines (IFN-γ, IL-2 and TNF-α) while the Th2 branch (IL-4, IL-6 and IL-10) is not affected [19] or even enhanced. Thus, zinc deficiency in aged individuals could favor the development of allergic diseases [17].

Iron deficiency is most often found in children and pregnant women, but is also prevalent in the aged population [20]. A reduction of iron leads to diminished antibody responses, especially of the IgG4 subclass [21], known to prevent activation of effector cells by capturing the allergen before it can cross-link cell-bound IgE. Taken together, the above data suggest a direct effect of micronutrients on the immune response favoring a development of Th2 type responses.

Does Vitamin D Deficiency in the Elderly Support Allergies?

Besides zinc and iron deficits, vitamin D deficiency is also very common in elderly. Serum concentrations of vitamin D are generally lower in older compared with younger subjects; however, in residents of nursing homes the vitamin D levels are extremely low [22]. Consequences of vitamin D deficiency are impaired mineralization of bone and a parathyroid hormone-mediated increase of bone degradation resulting in enhanced risk of fractures. Vitamin D is a prohormone; its active form – 1,25 dihydroxyvitamin D_3 or calcitriol – is produced by two hydroxylation steps. First, it is hydroxylated on position 25 and then on position 1 alpha. In addition to its central role in the regulation of bone and calcium homeostasis, calcitriol has a variety of noncalcemic target cells such as myocytes, cardiac muscle cells, lymphocytes and monocytes. There is evidence that calcitriol has immunomodulatory properties; in animal models the hormone prevents the development of autoimmune diseases. In a recently published study, Hyppönen et al. [23] found a U-shaped relationship between 25-hydroxyvitamin D and IgE levels: both the lowest and highest 25-hydroxyvitamin D levels were associated with high IgE concentrations. Moreover, an association between the CYP27B1 (the enzyme responsible for the synthesis of calcitriol)

genotype and IgE levels was seen. In a rat model, calcitriol was found to prevent allergic asthma [24], but contrasting in vitro data from our laboratory indicate that calcitriol could predispose toward T_h/T_c2-mediated allergic reactions [25]. Thus, although the underlying mechanisms remain unclear at present, calcitriol appears to have a bimodal effect on allergic reactions. In view of the high prevalence of vitamin D deficiency on the one hand and the recommendation to supplement elderly subjects with vitamin D on the other hand, further studies on the possible role of calcitriol in the pathogenesis of allergic diseases in elderly are clearly required.

The Role of Food Allergy in the Elderly

In our recent study conducted in a geriatric nursing home, 40.4% of patients (mean age 77 years) showed specific IgE to respiratory allergens and 24.8% to food allergens, which was supported by positive type I skin tests [26]. Interestingly, the positive skin prick tests correlated significantly with alcohol consumption, which has been described as a risk factor for sensitization against food allergens [27]. Besides the direct effect on the gastric mucosa by enhancing its permeability, chronic alcohol abuse is correlated with atrophic gastritis and decreased gastric secretory capacity [28]. The hypoacidic milieu is physiological in newborns and during the first months of life. In addition, hypoacidity represents the therapeutic aim in treatment of dyspeptic disorders, like esophageal reflux or chronic gastritis, and can be achieved with acid-suppressive drugs like proton pump inhibitors, antacids or H_2-receptor blockers. In our studies, we repeatedly reported a positive correlation between the intake of anti-acid drugs and the incidence of food allergy. Also the association with development of eosinophilic esophagitis is currently discussed [29]. Physiologically, the inactive pro-enzyme pepsinogen is cleaved in the acidic milieu of the gastric lumen, thereby activating its protease functions. Thus, pepsin exerts its full enzymatic activity on dietary proteins only at an optimum gastric pH between 1.8 and 3.2, whereas in hypoacidic conditions proteins remain undigested and transit to the intestine. These persisting food proteins can cross the normal intestinal mucosa in an intact conformation, enter the blood stream and elicit the production of IgE antibodies. When encountering the same food proteins after a consecutive ingestion, the allergen can cross-link IgE on effector cells (e.g. mast cells) and trigger mediator release (e.g. histamine, leukotrienes). This event leads to severe local and systemic reactions with dosage and integrity of the allergen determining the severity of the clinical reactions [30]. Therefore, it can be concluded that the digestibility under physiologically gastric (low) pH conditions is an important protective factor against food allergy, and the increase of gastric pH due to acid-suppressive medication retains the sensitizing and eliciting capacity of the allergen [31].

Furthermore, recent studies indicated that treatment with proton pump inhibitors for 8 weeks increased mucosal permeability of the upper gastrointestinal tract not only in patients with gastroesophageal reflux disease (GERD), but also in healthy controls [32], which could contribute to the development of food allergies [29]. Therefore, patients treated with proton pump inhibitors are at risk for sensitization because dietary proteins become digestion-stable and can cross the mucosal barrier more easily due to increased permeability, thus becoming allergenic.

Our hypothesis was that the elderly population may be at risk for this mechanism due to a higher incidence of atrophic gastritis and also anti-acid drug consumption [33, 34]. In order to investigate the effect of gastric hypoacidity on the development of food allergy in senescence, we used our previously established food allergy mouse model of oral immunizations under acid-suppression [35], which mimics the situation in human patients [36]. In contrast to other studies showing a defect of Th2 responses with advanced age [6, 13], our data revealed that IgE mediated food allergy can be induced in senescent mice (18 months old) including allergen-specific IgE responses, positive type I skin tests and high IL-5 levels in context with anti-acid treatment. The aged animals have not shown significant differences in IgE response or cytokine production compared with the adult control mice. Interestingly, we found significantly reduced iron and zinc levels in the aged animals compared with the adult controls, which suggested that the micronutrient imbalance supported the development of allergy in the aged mice. A further concern was to define the risk of experiencing clinically relevant allergic symptoms by defining thresholds of digested versus nondigested allergens. Indeed, only properly digested allergens showed decreased binding capacity of specific IgE in elderly patients (mean age 72 years) with food allergies, both in skin prick tests and IgE immunoblots [37]. Thus, we conclude that in senescence the stomach has an important protective function against food allergy by degrading food proteins. Consequently, hindrance of gastric digestion can support sensitization to dietary proteins and lower threshold levels of allergens in the aged population as well.

The importance of these findings for the elderly population is underlined by the fact that 25% of patients over 60 years receive acid-suppressive medication each year [34]. Furthermore, a recent Danish cross-sectional study reported that the prevalence of long-term treatment with proton pump inhibitors is 2.1% among general practitioners' patients (mean age 63 years), which was defined as >120 tablets/year. Interestingly, proton pump inhibitors were prescribed to more than 70% of these patients without a verified indication for treatment [38]. The inappropriate prescription of anti-acids by practitioners was shown to lead to long-term misuse of these drugs even after discharge of patient also due to immediate recurrence of acid-related symptoms following proton pump inhibitor withdrawal [39]. Furthermore, emerging data raise concerns on the risk of osteoporotic fractures, enteric infections and pneumonia associated with long-term proton pump inhibitor treatment [40]. Besides the intake of acid-suppressive drugs, gastric hypoacidity due to atrophic gastritis or to a decrease of gastric fluid production is found in 20–50% of the elderly [33].

We conclude that food allergy is a rising health problem in industrialized countries, and is also a concern for the aged population. So far, the role of food allergies in the elderly has been underestimated and, therefore, most likely undertreated. However, food allergic responses are evident in senescent patients and can be induced in experimental models using aged animals. Moreover, elderly are prone to develop gastric hypoacidity, which is a risk factor for de novo sensitization because harmless dietary compounds may become allergenic. Micronutrient deficiency being typically expressed in the elderly should be considered as a risk factor for the development of allergic disorders. Further studies investigating the role and mechanisms of food allergy in senescence are required for addressing this health problem of the aged population sufficiently.

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