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Letter to the Editor

Fatal anaphylaxis to wheat after gluten-free diet in an adolescent with celiac disease

Dear Editor

Food allergy is the primary cause of childhood anaphylaxis. It has been hypothesized that restriction diets in food allergic children may induce an increase of food-specific IgE (sIgE) levels and the risk of anaphylaxis.[1] Accordingly, we report the case of a 16-year-old boy who experienced a fatal anaphylaxis to wheat proteins after an exclusion diet due to celiac disease.

The patient was born in 1993. Starting from early infancy, he was diagnosed a severe atopic dermatitis, several inhalant allergies and recurrent wheezing bronchitis followed by persistent allergic asthma; he also showed immediate symptoms (hives, angioedema, tingling mouth and/or abdominal pain or vomiting, indicating mild-to-moderate anaphylactic reactions) at ingestion of cow's milk, fish, kiwi and hazelnut, so that, at 5 years, he was on a diet free of these foods, while he was normally eating and tolerating egg and wheat (Fig. 1). At the age of 9, routine screening labs showed the presence of anti-human tissue transglutaminase IgA (24 UA; positive >7); despite the absence of clinical symptoms, a duodenal biopsy confirmed the diagnosis of celiac disease (villous atrophy compatible with Marshall type 3a). Consequently, the patient began a gluten-free diet. Thereafter, from age 10 y to 16 y, celiac disease was clinically and serologically well controlled, suggesting a good compliance to gluten-free diet, as also stated by the parents. However, asthma was only partially controlled and required long-term persistent treatment with inhaled budesonide (400 mcg/day). His atopic dermatitis had highly improved since the first years of life; the boy still underwent rare episodic flares that required only short courses of topical corticosteroids for remission. He started eating and tolerating cow's milk. One year after beginning the wheat-elimination diet, wheat-sIgE rapidly and progressively increased, those to codfish remained very high and those to hazelnut declined (Fig. 1). Given the rise of food-sIgE levels and worsening asthma, the patient was prescribed self-injectable epinephrine and he and his parents were taught on its use.

At the age of 16, during a lunch at a restaurant, the patient ate a packaged ice-cream containing wheat (Supplementary Table 1). He immediately felt itch in his mouth and started having progressive respiratory impairment and a sense of impending death; after a few minutes (<20) he collapsed and lost consciousness. Despite his parents injected a single dose of epinephrine 330 mcg IM (Fastjekt®) in the vastus lateral immediately after collapsing, the patient died some minutes later at the restaurant before emergency services could arrive. The autopsy confirmed the cause of death to be anaphylactic shock and excluded other possibly responsible illnesses.

Months after death, a molecular analysis of serum samples collected when the child was 14 was performed by means of ISAC ImmunoCAP® (Thermo Scientific, Uppsala, Sweden), expressing results as ISAC Standardized Units (ISU) (negative <0.3, low 0.3–1, moderate 1–15, high ≥15) (Supplementary Table 2). Strong sensitization was observed to Tri a 14 (7.9 ISU) and Tri a aA_TI (5.1 ISU), but not to Tri a 19. Sensitizations to components of codfish (Gad c 1, 49 ISU), Brazilian nut (Ber e 1, 6.3 ISU), walnut (Jug r 1, 6.1 ISU) and kiwi (Act d 1, 3.4 ISU) were confirmed. No sensitization to peanut allergens was detected.

Several arguments strongly support the hypothesis that wheat allergens contained in the packed ice-cream were the cause of the patient's fatal anaphylaxis. A) Wheat proteins and no other possible causative allergens, such as tree nuts, are mentioned in the ice-cream package list of foods; B) no scoop or dish had been used for serving the ice-cream, which had been given packaged and sealed to the patient and accidental cross-contamination to tree nuts was therefore not possible; C) a reaction to any other food that may have contained or be contaminated by food proteins to which the patient was allergic (e.g. fish, hazelnut) can be reasonably excluded, given that the lunch menu of the child had been thoroughly decided and controlled by the parents (with the exception of the ice-cream, which had been unawares served to the child in the absence of the parents) and any food to which the patient was allergic had been carefully excluded; D) the reaction started immediately (<1 min) after the ingestion of the ice-cream; E) alternative diagnoses (mastocytosis, hereditary angioedema) were excluded by the autopsy.

Wheat contains several allergenic proteins. Tri a 19, also known as Omega 5-gliadin, is a major allergen[2]; interestingly, our patient was not sensitized to it, but to Tri a 14 (a lipid transfer protein that can induce severe, systemic reactions and is a major allergen among Italian patients[2]) and to Tri a aA_TI (mainly involved in baker's asthma, but also responsible for symptoms of food allergy in children[3]). Which of these molecules was responsible for the fatal anaphylaxis attack cannot be said. Nevertheless, our longitudinal data clearly show that the wheat-sIgE levels started dramatically and progressively increasing since wheat was excluded by the patient's diet because of his celiac disease. The rise in sIgE against an offending food after an elimination diet in tolerant children has been previously reported[4–6] with subsequent anaphylactic reactions (non-fatal, near-fatal or even fatal).

To the best of our knowledge, this is the first reported fatal anaphylactic reaction to wheat in a patient with celiac disease;

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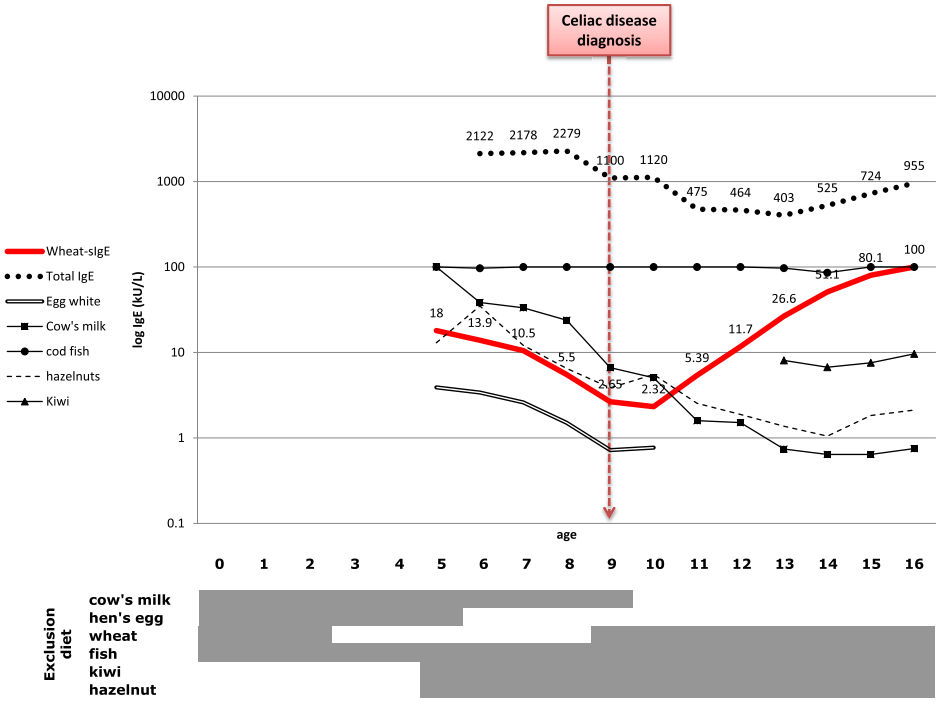

Fig. 1. Total and specific IgE levels and exclusion diet for cow's milk, hen's egg, wheat, fish, kiwi and hazelnut at different ages.

other authors only reported wheat allergic children with suspected or latent celiac disease.[7]

In our case, the rise of wheat-sIgE levels started simultaneously with the wheat elimination diet (Fig. 1), strongly supporting the idea that loss of tolerance was caused and strengthened by the elimination diet itself. The mechanisms of this phenomenon are not clear. Both food allergies and celiac disease are associated with abnormal regulation of the immune system and in particular of the T-cell subset in the GI tract. Subsets of regulatory T cells seem to play a fundamental role in maintaining self-tolerance and preventing autoimmunity[8,9]: in particular, TCR$\gamma\delta$ intraepithelial lymphocytes contribute to oral tolerance and have a regulatory potential in human celiac disease seemingly by producing TGFβ, which is also under-expressed in the gut of food allergic children.[10] A recent study showed that gluten-free diet affects multiple regulatory T cell subsets and Th17 cells in the mucosal lymphoid tissues of BALB/c mice.[11] In the reported case, the coexistence of food allergy and autoimmunity might have influenced the T cell balance and caused a substantial increase in wheat-sIgE.

In recent years, the role of atopic dermatitis epidermal skin barrier defects in inducing a transcutaneous allergic sensitization is highly debated,[12,13] possibly explaining why some children with eczema are sensitized to foods they have never eaten. It might be argued that our patient, even after eliminating wheat from his diet, was exposed to it via the skin. However, his atopic dermatitis was generally well controlled and, in our opinion, this sensitization route may have played only a minor role in this case.

On the other side, it is important to stress that the child had a particularly high risk of severe anaphylaxis because he was asthmatic and because he had already had anaphylactic reactions, even if mild or moderate, in the previous years.

A new, still debated therapeutic option for food allergic patients is food desensitization or specific oral tolerance induction, meaning a regular administration of the offending food with the aim of inducing a complete or partial tolerance. The results of the first trials are promising,[14] but at present the recommended management of food allergies in pediatrics is still food avoidance, as it is well known that several patients reach the tolerance spontaneously and because desensitization can have serious complications in terms of reactions.[15]

This case of fatal anaphylaxis can be very useful to reach some conclusions and raise hypotheses. First, it reminds that avoidance diets may not always be a valid option and that, if stronger data on its usefulness and feasibility are published, desensitization might be of utmost importance in certain patients who do not reach spontaneous food tolerance. Secondly, the natural course of sIgE in allergic patients who are on a food-free diet needs further investigation, such as the possible influence that the increasing popularity of gluten-free diets may have on the epidemiology of wheat allergy in westernized societies.[1] National and International registers of cases of fatal anaphylaxis may improve the still limited knowledge in this field. Finally, the association between celiac disease and wheat allergy might be particularly harmful due to unavoidable strict food avoidance.

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Appendix A. Supplementary information

Supplementary information associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.alit.2014.12.001.

Conflict of interest

The authors have no conflict of interest to declare.

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