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Sudden loss of cow's milk tolerance in a long-sensitized patient

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Key words

celiac disease, cow's milk protein allergy (CMA), specific oral tolerance induction (SOTI), allergen-free diet, food tolerance

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Summary

The prevalence of food allergy and anaphylaxis in children is reported to be increasing in recent years. Evidence suggests that exposure to large doses of antigen favors the maintenance of tolerance.

We report a case of sudden loss of cow's milk tolerance in a long-sensitized girl with celiac disease after a short period of milkless diet. We hypothesize that the continuous intake of high quantities of antigen sustained tolerance despite high levels of specific IgE and that, in the presence of epithelial barrier dysfunction caused by celiac disease, the few weeks of allergen-free diet led to a rapid loss of tolerance.

Introduction

Food allergy is an increasingly prevalent disorder with potentially life-threatening complications, requiring affected individuals and families to make life-altering modifications in dietary habits and psychosocial interactions (1).

Although the detailed immunologic mechanisms underlying the development of immediate food hypersensitivity are still being fully defined, food allergy appears to be the direct consequence of a breakdown in the normal development of oral tolerance or of a breakdown in existing tolerance, resulting in deregulated T-helper type-2 (Th2) responses and immediate hypersensitivity reactions upon antigen re-exposure. Ineffective induction of regulatory T-cells (T regs) has been shown to promote the development of food allergy (2-5).

Under normal conditions the contact between allergens and the immune system, via the gut, results in immune tolerance. In fact, the intestinal mucosa is characterized by a down-regulatory microenvironment whose role is to ensure that active immune responses are not elicited against dietary proteins (5)

The intestinal epithelium acts as a selectively permeable barrier, permitting the absorption of nutrients, electrolytes and water while maintaining an effective defense against intraluminal toxins, antigens and enteric flora. The epithelium maintains its selective barrier function through the formation of complex protein-protein networks that mechanically link adjacent cells and seal the intercellular space (6).

A breakdown or impairment of the epithelial barrier has been implicated as a critical determinant in the predispo-

sition to intestinal inflammation and a number of gastrointestinal diseases, including food allergy (7).
We describe a case of sudden loss of cow's milk tolerance in a long-sensitized girl, after a short period of milk elimination diet, in course of celiac disease.

The case

A sixteen years old girl, with no family history for allergic diseases, came to our observation for an allergy work up.
The personal history showed that she had been exclusively breastfed in the first six months of life. At six months she had been weaned, and, for the first time, cow's milk was introduced in the diet, without any adverse reaction. After that, no symptoms followed the ingestion of cow's milk and dairy products.
Until some months before, she hadn't suffered from any gastrointestinal, cutaneous or respiratory allergy. Six months before the visit, following the onset of diarrhea, fatigue and weight loss, an allergist was consulted who performed Skin Prick Test (SPT) for foods. Based on the finding of a positive SPT for lactalbumin, beta-lactoglobulin, casein and fresh cow's milk, an allergy to cow's milk protein (CMA) was suspected and a diagnostic elimination diet for eight weeks recommended.
Since the diet did not improve her symptoms, the girl was addressed to our center. She showed impaired general condition, weight loss (- Kg 8), pallor and continued to suffer from severe diarrhea.
SPT with lactalbumin, beta-lactoglobulin, casein and fresh cow's milk were performed again and scored positive (mean diameter 15 mm, 13,5 mm, 14 mm and 20 mm, respectively). Specific IgE measurements by ImmunoCap (Phadia, Uppsala, Sweden) scored strongly positive: whole cow's milk > 100 KUA/l, alfa-lactalbumin 49 KUA/l, beta-lactalbumin 36,7 KUA/l, and casein >100 KUA/l).
In view of the ineffectiveness of the diet regimen, IgA anti-transglutaminase (IgA-tTG) and IgA anti-endomysial antibodies (EMA) were measured; both scored strongly positive (EMA=++++, IgA-tTG=>100 UI/ml). An intestinal biopsy confirmed total villous atrophy diagnostic for celiac disease.
After two months of gluten-free diet, combined with milk and dairy-free diet, the symptoms were completely resolved: she showed some weight–gain (+ Kg 4) and significant reduction in EMA (+) and IgA-tTG titres (=20 UI/ ml).
A double-blind, placebo-controlled food challenge (DBPCFC) with lactose-free cow's milk was carried out according to the guidelines for IgE-mediated food allergy (8). We started with 0,1 ml of CM and continued in a graded way. Ten minutes after ingesting 1 ml of milk the girl experienced severe vomiting, edema of the glottis, asthma, generalized urticaria-angioedema and shock (blood pressure 60/30 mmHg).
A strict cow's milk protein-free diet regimen was recommended, and instructions how to recognize symptoms were provided along with a prescription of self-injectable epinephrine and information about access to emergency services.
After six months on a strict gluten-free diet, proven both by negative IgA-tTG and EMA titres and further weight–gain (+ Kg 4,5), the girl experienced another anaphylactic episode following the ingestion of a cake containing traces of cow's milk. After patient's request, a Specific Oral Tolerance Induction (SOTI) was started, but had to be stopped after six months due to severe adverse reactions to small doses of cow's milk. The strict gluten-free diet regimen was continued and IgA-tTG and EMA titres remained negative.

Discussion

CMA affects from 2 to 6% of children, with the highest prevalence during the first year of age (9). About 50% of children have been shown to resolve CMA within the first year of age, and 80-90% within their fifth year (10-11). The incidence of anaphylaxis in children has been reported to be increasing (12).
The possible reasons of this increase have been investigated by many authors without conclusive results. Some believe that the dramatic increase of exclusion diets in the last years, often prescribed without a sound rationale, may at least partially explain the increase in food allergy and anaphylaxis (13).
The relationship between oral immune tolerance and tolerance to food antigens in human beings is not well established. Several recent reports have supported the hypothesized role of Treg cells, including the CD4+ CD25+ subset, in the development of normal tolerance or in the spontaneous resolution of milk allergy (14-16).
There are 2 primary effector mechanisms for inducing oral tolerance: active suppression by regulatory T cells or clonal anergy or deletion (17). The primary factor that determines what will take place is the dose of the antigen. Low doses of antigen favor tolerance driven by regulatory cells; high doses favor anergy-driven tolerance. Regulato-

ry T cells suppress immune responses through soluble or cell surface-associated down-regulatory cytokines, such as IL-10 and TGF-β (18).

Evidence suggests that exposure to large doses of antigen might produce a suppression of specific IgE response, so that the continuous contact with high doses of antigens favors the maintenance of tolerance (19).

The Gastrointestinal tract, including its gut-associated lymphatic tissue, is the largest immunologic organ in the body with an epithelial surface in constant contact with the external environment (20).

Intact barrier function and innate immune mechanisms are a vital part of the mucosal response (21).

Food allergies could result from epithelial barrier dysfunction as the impaired barrier immunity increases food antigen exposure towards the immune system, thus resulting in antigen sensitization and production of a Th2-predominant allergic response (22).

In our case, the continuous intake of high quantities of antigen in a patient sensitized to cow's milk proteins led to tolerance. The reintroduction of the antigen after few weeks of elimination diet, in the presence of epithelial barrier dysfunction caused by celiac disease, was associated with a rapid loss of the tolerance that had been achieved naturally despite high levels of specific IgE. Nevertheless, the symptoms related to celiac disease could represent only the "primum movens" to investigate of allergic sensitization that, once found, suggested allergen-free diet. In this case, dairy-free diet alone could be the cause of the loss of tolerance. In addition, the following attempt to desensitize the girl, after eight months on rigorous gluten-free diet, using low and progressive doses of antigen, was not successful suggesting a persistent loss of tolerance despite the restored normal epithelial barrier function.

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