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Food Allergy: From the of Loss of Tolerance Induced by Exclusion Diets to Specific Oral Tolerance Induction

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Abstract: 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 might produce a suppression of the specific IgE response, so that the continuous contact with high doses of antigens favours the maintenance of tolerance. In the same way loss of contact with allergen in children with specific IgE reactivity may favour a loss of tolerance with development of systemic reactions, while a progressive new contact with allergen may favour a specific tolerance induction. We hypothesize that widespread and uncontrolled use of elimination diets for atopic dermatitis may have played a role in the increase of allergy and anaphylaxis. Specific oral tolerance induction may be a possible therapeutic strategy. The article reviews food allergies caused by exclusion diet and also discusses recent patents related to the field.

Keywords: Food allergy, exclusion diet, specific oral tolerance induction, immunological risk.

INTRODUCTION

The prevalence of food allergy is high in early childhood and it seems to be increasing [1]. The incidence of anaphylaxis in children has been reported to be increasing as well [2]. The possible reasons of this increase have been investigated by many authors without conclusive results. We 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 [3]. Evidence suggests that exposure to large doses of antigen might produce a suppression of the specific IgE response, so that the continuous contact with high doses of antigens favours the maintenance of tolerance [4]. For example Philippe *et al.* suggested composition for Antigen-Specific Induction [5], similarly Otoo *et al.* discovered agent for suppressing production of IgE antibody for the antigen JP2007091694 [6]. One well known mechanism of allergy induction, i.e. loss of specific food tolerance, was once represented by the offer to the new born baby of cow's milk proteins in the nursery, eventually followed by exclusive breast feeding with a "classic" anaphylactic shock at 4 or 5 months when the next bottle of cow's milk was introduced.

IMMUNOLOGICAL RISK OF EXCLUSION DIET: "THE FACTORY OF ANAPHYLAXIS"

There is evidence in the literature about the risk of loss of tolerance induced by exclusion diet in children with specific IgE reactivity.

We found four papers involving 24 children with documented IgE hypersensitivity who could all previously tolerate the offending food and in which the elimination diet caused the subsequent development of immediate type symptoms [7-10]. David TJ in 1984 described 4 children who developed an anaphylactic shock after an exclusion diet

started for atopic dermatitis. Larramendi and others reported a series of patients with allergy to fish and high specific IgE who were put on an exclusion diet for an atopic dermatitis. All could eat fish before the diet and all experienced systemic reactions few months after the diet.

Flintermann recently reported about a series of 11 infants who lost tolerance after being started on a milk free exclusion diet. The same mechanism may take place in the revealing of a previously latent and asymptomatic specific IgE reactivity in children with atopic dermatitis who go through an exclusion diet for at least ten days before a challenge. After a period of exclusion diet before the challenge nearly half of the children with a positive IgE reactivity are reported with an immediate reaction that was not evident before [11-14].

We described a single patient who experienced a loss of tolerance after an exclusion diet for milk started for an eczema at the age of 12 with an eventual fatal anaphylaxis.

The core message of warning of these papers "don't forget a patient in a useless diet" is worth of being reported once more. The first striking every day clinical evidence confirmed by Flintermann's most recent experience is that, notwithstanding the official recommendations and the evidence of a significant literature, an impressive number of children with atopic dermatitis is still diagnosed as allergic to cow's milk proteins on an insufficient basis. Moreover, often these children are eventually "forgotten" for months or even years in an exclusion diet, even in front of no benefits on symptoms. In the past years, many paediatricians or general practitioners would have considered this attitude a sort of "venial pity", of little or no harm at all. On the contrary this approach may actually have worked as a "factory of anaphylaxis". We hypothesize that some IgE mediated food allergic diseases have been on the increase because of a widespread prescription of elimination diets.

Actually, the episode we reported dramatically changed our attitude. We became not only more aware of the immunological risk of exclusion diets, but also started to

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consider the possibility of inducing tolerance by forcing a slowly progressive contact with the allergen. A similar strategy has been already considered by Yousuke, which provided a method of acquiring immunological tolerance to a foreign DNA or its expression product [15].

SPECIFIC ORAL TOLERANCE INDUCTION

In 1998 e 1999 Patriarca [16] and Bauer [17] reported the possibility of inducing specific oral tolerance induction (SOTI) in children with food allergy. Nowadays, more evidence in the literature shows that SOTI is a possible approach [18-23]. A good percentage of success with about 60- 70% of children reaching free diet is reported. To the best of our knowledge a good safety profile is reported so far as well, without very severe or near fatal reactions. Even though only a small number of children with very severe allergy was included in these series and no study ever selected only patients with severe CMP-induced reactions.

As a matter of fact some children allergic to cow's milk proteins present severe reactions after ingesting small amounts of antigen. The possibility of spontaneous recovery, which is almost the rule in younger children, is quite rare in such patients after the age of six in presence of very high levels of specific IgEs antibodies against the food [24]. Antigen avoiding and having epinephrine available are the current strategies for their management, but they are not completely foolproof.

We recently published a paper about a SOTI protocol [25] in sixty children that tested positive during a challenge to very small amounts of milk. All children had high IgE levels (> 85 KU/L) and an history of severe reactions. Thirty children were subjected to SOTI, while 30 were kept on a milk free diet. After one year 11 children out of 30 (36%) in treatment group tolerated large amounts of milk, 16 (54%) could take limited amounts (5 ml to 150 ml), and 3 (10%) were not able to complete the protocol because of reactions. In the diet group, the challenge performed after a year was positive in all 30 cases. The total number of reactions in the treatment group during the study was high and 4 patients required i.m. adrenaline.

In this experience, SOTI was effective in a significant percentage of cases and was perceived as an important improvement in the quality of life for these patients. The number of reactions to milk was significant and data are still needed to estimate the risk of fatal or near-fatal events in these subjects and to confirm the safety of this intervention that should therefore be restricted to highly defined assistance setting.

The immunologic mechanisms underlying SOTI are still unclear. It is not known whether this is a true, long lasting, immunity shift or whether tolerance is obtained through temporary reduction of specific IgE levels, as happens in desensitization to antibiotics. We hypothesize that oral tolerance is first achieved through an antigen specific mast cell desensitization, followed in the long term (years) by a T lymphocyte mediated process with normalization of IgE levels. For this reason, we recommend to our patients a constant intake of milk in the years after SOTI to promote the decrease of specific IgE levels and to reduce the risk of

recurrence of the symptoms if the intake of milk is discontinued.

So, where should we go from here?

In the end, it is well known that the great majority of children with food allergy gains tolerance over the years while being maintained on an exclusion diet.

At the same time, evidence from the literature tells us that antigen avoiding can be dangerous for some children while cautious and progressive contact with allergen may induce specific tolerance acquisition in a significant percentage, even with severe allergy. At the moment, we believe that SOTI should be restricted to patients with food allergy with systemic reactions, over the age of the higher chance of spontaneous acquirement of tolerance (6 years of age), with allergy to foods which are very difficult to avoid (milk, egg, grain, possibly peanuts in the USA).

CURRENT & FUTURE DEVELOPMENTS

SOTI has a defined cost benefits ratio. One should always consider that before six years of age the majority of children are due to spontaneously acquire tolerance in the forthcoming years. The benefit of intervention, that is the possibility of introducing even small amounts of the incriminated food getting out of the risk of reactions from contamination or in adverted contact, is perceived by families as a major improvement in their quality of life. This benefit must be weighted case by case with the costs of family engagement for milk administration and risk of reactions. Furthermore this approach is time consuming and requires a defined level of commitment by the staff involved.

More research is needed to further understand the biological mechanisms of tolerance and to identify criteria in order to select which patients can take advantage by contact with allergen.

CONFLICT OF INTEREST

We declare that none of the authors has received a financial contribution for the work, none of the authors has any conflict of interest to declare. No patent have been cited in stage of legal litigation.

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