Role of Hydrolysates in Prophylactic and Therapeutic Diets for Food Allergy

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INTRODUCTION

Food allergy is frequently associated with other atopic manifestations during infancy and early childhood. Proteins of hen's egg and cow's milk represent the most common clinically relevant allergens. While pharmacotherapeutic approaches to food allergy up to now have not given convincing results, diets have been shown to be useful tools both in preventing early sensitization to foods and the early manifestation of atopic symptoms and in reducing food-related symptoms in children with clinically relevant sensitizations.

For several decades, extensively hydrolyzed cow's milk protein formulas have been used for the treatment of children with cow's milk allergy and several other gastrointestinal disorders. In recent years, other products from different protein sources have become available and marketed for both the treatment and the prevention of allergic disorders. This chapter focuses on the role of these products in the treatment and prevention of food allergy in infancy and childhood.

WHAT IS HYPOALLERGENICITY?

Hydrolysate formulas have been developed with the aim of decreasing the allergenicity of allergenic proteins. The use of these formulas is based on the premise that predigested proteins, when fed as amino acids and peptides, provide nutrients in a nonallergenic form. Protein hydrolysates are processed using three main technologies: heat treatment, enzymatic hydrolysis, and a combination of the two. Heat treatment mainly affects the conformation of proteins, while enzymatic hydrolysis causes progressive destruction of allergenic proteins, especially their sequential epitopes. Sometimes ultrafiltration is added to remove high molecular weight peptides and proteins. According to the source of proteins and according to the degree of hydrolysates, there are several types of formula available on the European market.
TABLE 1. Hypoallergenic formulas

<table>
<thead>
<tr>
<th>Type</th>
<th>Extensively hydrolyzed</th>
<th>Partially hydrolyzed</th>
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<tbody>
<tr>
<td>Hydrolyzed bovine casein</td>
<td>Alimentum®</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nutramigen®</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pregestimil®</td>
<td></td>
</tr>
<tr>
<td>Hydrolyzed bovine whey</td>
<td>Profylac®</td>
<td>Beba H.A.®</td>
</tr>
<tr>
<td></td>
<td>Hypolac®</td>
<td>Good Start®</td>
</tr>
<tr>
<td></td>
<td>Pepti-Junior®</td>
<td>NAN H.A.®</td>
</tr>
<tr>
<td></td>
<td>Alfare®</td>
<td>Nidina H.A.®</td>
</tr>
<tr>
<td>Mix of hydrolyzed bovine casein/whey</td>
<td></td>
<td>Nutrilon Pepti®</td>
</tr>
<tr>
<td>Hydrolyzed soy/bovine collagen</td>
<td></td>
<td>Nutrilon Pepti Plus®</td>
</tr>
<tr>
<td></td>
<td>Pregomin®</td>
<td>Aptamil H.A.®</td>
</tr>
</tbody>
</table>

* The same product marketed under two different brand names.

* Similar products marketed under different brand names in different countries.

(Table 1). In contrast to extensively hydrolyzed formulas, partially hydrolyzed formulas contain a high proportion of nondegraded or only partially degraded proteins (in the molecular weight range of 8 to 40 kDa).

The allergenicity of a formula is the ability of its proteins or peptides to induce allergic reactions in sensitized individuals by binding to cell-bound immunoglobulin E (IgE) molecules on effector cells and thus triggering mediator release. The allergenicity can be determined by (a) \textit{in vivo} methods (skin tests and provocation tests); these tests require at least two epitopes on an allergen, which are necessary to cross-link IgE molecules on the surface of mast cells or basophils; and (b) \textit{in vitro} methods (IgE binding tests), which in general need only one epitope.

Peptides with one epitope do not induce allergic reactions; thus, the total amount of antibody-binding epitopes on the peptides can be determined by \textit{in vitro} methods, whereas \textit{in vivo} methods give an estimation of the allergenicity of a formula.

As an additional \textit{in vitro} method, the leukocyte histamine release test has been used; however, there are potential methodological problems with this method, since peptides may interfere with the assay or induce nonspecific, non-IgE-mediated histamine release, especially in atopic individuals.

Hydrolyzed formulas differ enormously in their content of intact proteins and their allergenicity (1). It has been shown that partially hydrolyzed whey formulas still contain relatively large amounts of β-lactoglobulin compared to extensively hydrolyzed formulas.

HYDROLYSATES AS COMPONENTS OF THERAPEUTIC DIETS IN ALLERGIC DISORDERS

In allergic diseases, therapeutic diets are indicated whenever allergenic proteins have to be eliminated. A necessary prerequisite for any elimination diet, however,
is a positive challenge test, preferably a double-blind, placebo-controlled food challenge. Substitution of eliminated proteins can be achieved by feeding other protein sources with a comparable nutritional value, for example, soy instead of cow's milk, or by the use of hydrolysates with a reduced allergenicity (2).

Nonspecific dietary interventions in allergic disorders like atopic eczema, which are occasionally recommended, lack any scientific basis and should be abandoned.

In the vast majority of children with cow's milk allergy, casein hydrolysates have been shown to be safe and effective, although a few cases of allergic reactions have been reported (3). Recently, there have been reports on extensively hydrolyzed whey formulas. Their clinical effectiveness should be further documented.

A hydrolyzed formula based on the hydrolysate of soy and bovine collagen has been in use for a few years. The possible clinical value of this product in cow's milk allergy still has to be documented.

In general, partially hydrolyzed whey formulas are not suitable to be fed to cow's-milk-allergic children, since several cases of allergic reactions to these products have been reported.

Our own studies in cow's-milk-sensitive children (4,5) indicate that both the IgE-binding capacity of hydrolysates and the allergenic activity, as determined by IgE binding and \textit{in vivo} tests (skin test, titrated oral challenge tests), show considerable variations between the different types of hydrolyzed formula (Figs. 1 to 3 and Table 2). Therefore, we recommend that before a hydrolysate is introduced into the diet of a sensitized infant or child, its safety should be tested, preferably by \textit{in vivo} methods.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Results of skin puncture tests with whole cow's milk and six different hydrolysates in 17 cow's-milk-sensitive children.}
\end{figure}
FIG. 2. Specific serum-IgE antibody binding to cow's milk and six different hydrolysates.

ROLE OF HYDROLYSATES IN PREVENTION

It is generally accepted that the mode of feeding in early infancy influences both the risk of specific sensitization and the natural course of atopic disease in high-risk infants (infants with at least one first-degree relative with documented atopic disease). Breast-feeding in combination with avoidance of cow’s milk and solid foods during the first 4 months has resulted in a significant reduction in the prevalence of atopic disease.

FIG. 3. Total percentage of radioallergosorbent test (RAST) inhibition measured with cow’s milk and six different protein hydrolysate extracts, with the use of sera from cow’s-milk-sensitive patients and cow’s milk allergen disks.
Table 2. Titrated oral provocation test in eight cow's-milk-allergic children

<table>
<thead>
<tr>
<th>Test product</th>
<th>Number of positive reactions</th>
<th>Negative reactions</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.2 ml</td>
<td>1 ml</td>
<td>2 ml</td>
</tr>
<tr>
<td>Whole cow’s milk</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Casein hydrolysate I</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Casein hydrolysate II</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Whey hydrolysate I</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Soy-collagen hydrolysate</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Whey hydrolysate II</td>
<td>0</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Whey hydrolysate III (ultrafiltrated)</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

* Level of significance in comparison to whole cow’s milk.

dermatitis and food allergy during the first 2 to 3 years of life. Early introduction of solid foods into the diet of high-risk infants is associated with a higher prevalence of atopic dermatitis in the first year of life (6).

During recent years several prospective studies have been published in international journals on a possible preventive effect of hydrolyzed formulas on the natural course of atopic disease (7–14). The end points used as markers for the efficacy of prevention differ from study-to-study and include (a) prevention of specific sensitization (induction of serum IgE antibodies), (b) prevention of food allergy (proved by challenge tests), and (c) prevention of clinical manifestations (eczema) that may or may not be induced by allergic reactions.

At present, it can be concluded from the different studies that, in high-risk infants, extensively hydrolyzed and partially hydrolyzed formulas are both able to reduce skin symptoms transiently, especially atopic dermatitis, during the first years of life, to a degree similar to breast-feeding. In contrast to extensively hydrolyzed formulas, partially hydrolyzed formulas have not been convincingly shown to prevent IgE-mediated sensitization to cow’s milk in infants at high risk of developing atopic disease. Further studies comparing the preventive effect of different hydrolysates, especially partially and extensively hydrolyzed formulas, are urgently needed.

**CONCLUSION**

Both preventive and therapeutic diets should be limited to specific risk groups. An unrestricted use of hydrolyzed cow’s milk formulas in the general population is not recommended, as pointed out in a recent position paper of the European Society of Pediatric Allergy and Clinical Immunology (15). There is no evidence that non-atopic children might benefit from hydrolyzed cow’s milk formulas. Similarly, among children with atopic dermatitis or atopic disorders, only the subgroup with a clinically relevant allergy, as demonstrated by a positive challenge test, should be candidates for specific elimination diets.
REFERENCES


DISCUSSION

Dr. Strobel: Can I just specify the role of the elimination diet and the therapeutic diet. I think that before you embark on the diet, you have to identify the antigen that you are trying to eliminate. So you have to approach the problem in a clinical way, eliminating a lot of antigens and then introducing them serially; otherwise, you end up on a very bizarre diet.

Dr. Wahn: That is exactly right; we call this a diagnostic diet. That means that we eliminate foods in a nonspecific way in order to see whether any effect occurs, and then we rechallenge before we decide on the therapeutic diet.

Dr. Chandra: I am very impressed with the range of things that you are measuring. My question is about management of children who have definite atopic dermatitis. Did some of them receive specific treatment, and, if so, how does that influence the calculation?

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Dr. Wahn: I consider it unethical not to give any treatment. We are well aware of the fact that we may change variables that we are interested in by treatment, but I don’t think there is any other solution. The term “nonintervention” is perhaps somewhat idealistic. I feel that any kind of intervention will reduce skin manifestations. This may or may not be related to specific sensitization or to food allergy. We should be very careful to differentiate what we are talking about.
Dr. Chandra: So some of the infants may have received local treatment and some perhaps even systemic treatment?

Dr. Wahn: Some received local treatment, while systemic treatment was always avoided.

Dr. Sampson: So when children have atopic dermatitis you intervene and start therapy. Do you mean that you then attempt to diagnose the food allergy or some other environmental allergens are concerned before starting any other treatment, as far as possible.

Dr. Molkhou: Do dermatologists send you those children suffering from severe eczema?

Dr. Wahn: Occasionally, but not for this study. It is the privilege of the pediatrician to know the patients before they get sick. We have them in the premorbid situation, followed up from birth, and no dermatologist would ever like to interfere.

Dr. Marini: Your study is in some way similar to one we have done, a multicenter study with no intervention in which we screened 36,000 babies. We did a regression analysis of the factors influencing the presence of symptoms. Our data show that some foods are really important in causing allergic symptoms. When we looked at the symptomatology, we found that the major factor was the early introduction of cow's milk—not adapted formula—and solid foods. Other less powerful factors included introduction of beef before 7 months or citrus fruit products before 4 months. When we evaluate such data we must bear in mind that there are many confounding factors due to the diet. If you are not really sure about the diet, it is very difficult to come to the conclusion that IgE is important, since it depends on what the baby is eating.

Dr. Wahn: We have been facing the same problems. Although it turned out that the atopic state of the parents is a determinant for the mode of feeding, which means that atopic children are breast-fed longer, we tried not to intervene. The only thing we could do was to document what was happening. My personal prejudice now is that in the third year of life food is not the most important determinant for the long-term state of a child.

Dr. Schmitz: You took great care in discriminating between sensitization, which was determined by cord blood IgE, and eczema, which was not and was mainly determined by maternal eczema. What is the determinant of eczema on which hydrolyzed formula may play a role, as has been claimed at this meeting, if it is not IgE?

Dr. Wahn: We should now be looking for subgroups and dividing these to see what happens, in terms of prevention, to the group with very transient and mild eczema, what happens to the group with chronic and severe eczema, and what happens to the group with eczema that is associated with food sensitivity. It turned out in our study that the family history of the mother was the prime predictor for early manifestations of eczema in the first 18 months, but it was especially impressive if the mother had eczema herself and not hay fever or asthma. This was also true for asthma. If one of the parents had asthma, there is obviously a second genetic determinant that has nothing to do with sensitization.

Dr. Schmitz: But what would be the immunological mediator that would not be the IgE?

Dr. Wahn: I don't know.

Dr. Chandra: In terms of family history of the two parents, is there any evidence that past history is as relevant as current history of eczema or asthma? If so, I think it would be useful to interview the grandparents because I am sure many adults have forgotten if they had childhood diseases.

Dr. Wahn: I don't know the answer, but the idea of the grandparents is very attractive.