The Concept of Hypoallergenicity for Atopy Prevention

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Abstract

Infancy represents the period in which an individual may be at the highest risk of sensitization. During the first year of life around 2.5% of neonates experience hypersensitivity reactions to cow’s milk protein, which is highly associated with early exposure to cow’s milk. Attempts to avoid sensitization in this very early period of life and to prevent allergic diseases focus on diets with reduced allergenicity and possibly on the induction of oral tolerance. Hydrolyzed infant formulas are characterized by a reduced allergenicity and thus recommended as substitute or supplementary to breastfeeding during the first 4–6 months of life for infants at high risk of developing atopic diseases. This concept of hypoallergenicity has been shown effective in clinical studies. Both partially and extensively hydrolyzed formulas have demonstrated a potential in protecting from allergic diseases, mainly atopic eczema and food allergy. The in vitro characterization of allergenicity by the degree of hydrolyzation and peptide size, however, does not necessarily predict the immunogenic effect in humans, as it could be shown that the preventive effect seems to be dependent on the process rather than on the degree of hydrolyzation, which could be best explained by a possible production of tolerogenic epitopes.

Introduction

The worldwide increase in the prevalence of allergy and atopic disorders especially in the pediatric population over the past several decades has become a cardinal target for the research of pediatric allergologists [1]. Results of large epidemiological studies have helped to better understand the natural course of allergic diseases and to identify at least some risk factors which play a role in the complex interaction between genetics and the environment [2].
Amongst others exposure to food allergens in early infancy often represents the most important risk factor in children with a genetically determined disposition for atopy.

Food proteins are per se immunogens, characterized by the capacity to either initiate the production of specific IgE antibodies and/or T cell immune responses, or to induce oral tolerance. Whether an immunogen is going to be allergenic or tolerogenic is influenced by the genetic disposition of an individual, by the dose and the time point of the first introduction of the immunogen and by environmental factors like passive smoke exposure, infections, the microbial gut composition and others, which can be either promoting or protecting against the development of allergy.

Infancy represents the period in which an individual may be at the highest risk of sensitization. In line with this is the development of food allergy and especially cow’s milk allergy, which is highly associated with early exposure to cow’s milk and quite common in early childhood; around 2.5% of neonates experience hypersensitivity reactions to cow’s milk protein during the first year of life [3]. Thus, the counterregulatory processes of primary allergy prevention measures should exert their effects very early in life or even prenatally.

Consequently, the main approach in attempts to prevent allergic diseases focuses on elimination diets and on diets with reduced allergenicity in order to avoid sensitization in this very early period of life.

National and international guidelines for infant nutrition, therefore, concentrate on prolonged breastfeeding for 4–6 months and late introduction of solid foods for all children to prevent the development of allergic diseases. For high-risk children recommendations additionally include protein hydrolysates in case of insufficient breastfeeding during the first 4–6 months of life [4–8].

Breastfeeding always was and still is the gold standard for optimal infant nutrition and may – in addition – protect children from the development of atopic diseases, especially children at high risk of allergies as shown in a recent meta-analysis [8, 9]. However, it seems that the specific phenotype in the child’s family history further modifies the effect of breastfeeding in those children at high risk. Results from the German Infant Nutritional Intervention study (GINI) clearly demonstrated that in children with a positive family history of atopic dermatitis the prevalence of atopic dermatitis in the exclusively breastfed offspring was significantly higher than in children with other atopic phenotypes such as asthma or allergic rhinitis in their immediate relatives [10].

Attempts to reduce the allergenicity of breast milk also included an allergen-reduced diet for the pregnant and the lactating mothers. The rational behind this is that specific IgE to food allergens [11] and T cell responses to milk and egg proteins as well as to inhaled allergens were detected in fetuses and in newborns [12]. The rational for an allergen avoidance diet for the lactating mother is based on several observations. Food allergens were detected in breast milk, and early sensitization to hen’s egg and cow’s milk protein as well
as to other food allergens was observed in up to 6% of exclusively breastfed children [13]. In addition, in children with cow’s milk allergy, the provocation with breast milk was positive in 16 out of 17 patients [14].

The reduction of milk, milk products and hen’s egg in the maternal diet during the third trimester of pregnancy did not show any beneficial effect on early sensitization and prevention of early allergic manifestation [15]. This has recently been confirmed in a study, where rigorous dietary egg exclusion, starting already before 20 weeks of gestation (17–20 weeks), did neither eliminate the transplacental passage of egg allergen nor its passing into breast milk. It could be shown in this study that ovalbumin in blood and breast milk was not related to the maternal dietary intake or atopic predisposition [16].

The results of the studies with an allergen-reduced maternal diet during lactation are contradictory. The study by Hattevig et al. [17], where mothers avoided egg, cow’s milk and fish during the first 3 months of lactation, showed a 50% reduction of eczema in the offspring at 3, 6 and 48 months of life, but not at 12 and 120 months of age. Sensitization to cow’s milk and hen’s egg was lower at 3 months only. This is in contrast to the study by Herrmann et al. [18], where mothers avoided eggs and cow’s milk until their infants were 6 months of age, which did not result in any difference between the intervention and the control group regarding the cumulative incidence of eczema and sensitization to cow’s milk and hen’s egg.

According to the guidelines hypoallergenic formulas based on cow’s milk protein are recommended for primary prevention in children at high risk of allergy who need a milk supplement to breastfeeding in the first 4–6 months of life [4–6, 8].

**Hydrolyzed Infant Formulas**

Hydrolyzed infant formulas as a milk substitute, primarily invented for infants with cow’s milk allergy, have later been adapted for primary allergy prevention. The concept of introducing hydrolysates in an attempt to prevent allergic diseases focuses on the reduction of the antigenicity and allergenicity of milk proteins [19]. The residual allergenicity of an infant formula, defined as the capacity of the molecules (allergens) to initiate an allergic response, is affected by molecular weight, chemical complexity, ‘foreignness’, dose and other factors such as route of exposure and yet unknown species-specific genetic factors [20]. Different processing of foods can alter its antigenicity. Heat treatment of cow’s milk protein does affect the conformational epitopes and facilitates their hydrolysis. To produce the least allergenic formulas, cow’s milk protein can be modified by enzymatic hydrolysis with progressive destruction of sequential epitopes [21]. Dependent on the degree of enzymatic hydrolysis, ultraheating and ultrafiltration protein hydrolysates are
differentiated in partially hydrolyzed (pHFs) or extensively hydrolyzed formulas (eHFs), and dependent on the protein source in whey and casein hydrolysates [partially hydrolyzed whey formula (pHF-W), extensively hydrolyzed whey formula (eHF-W), and extensively hydrolyzed casein formula (eHF-C)].

One way to classify the allergenicity of infant formulas is the molecular-weight profile. The molecular-weight profile of pHF ranges between 3,000 and 10,000 Da; peptides in the eHF have in >90% a molecular weight <3,000 Da. It could be shown that formulas containing considerable proportions of peptides >6,000 Da showed significantly more positive skin prick test results when compared to eHFs or an amino acid formula [22].

Allergenicity of a formula is also assessable by several in vitro and in vivo tests. Most suitable methods for determining the residual allergenicity of hydrolyzed infant formulas include tests for RAST or EAST inhibition and skin prick tests, while the protein content of the formula and the molecular weight alone have been shown not to be predictive for the clinical outcome [23].

According to data from the literature a declining ranking of infant formulas with regard to their allergenicity was found to be cow's milk formula, pHF-W, partially hydrolyzed casein formula, eHF-C and amino acid-based formula [23].

**Hydrolyzed Infant Formulas for Therapy and Prevention**

Hydrolyzed infant formulas, mainly based on cow's milk, have been intensively tested in numerous allergy prevention studies and in animal models. Both infant pHFs and eHFs could be demonstrated to be hypoallergenic, which means nothing but less allergenic.

However, by the definition of the American Academy of Pediatrics a hypoallergenic formula needs to fulfill three criteria: (1) the antigenicity of the protein must be reduced, (2) it should be successfully used in patients with documented cow's milk allergy and (3) the immunogenicity of the product must be reduced [5]. Following this definition, eHFs have a higher potential of being classified as hypoallergens than pHFs, because they can be successfully used in children with cow's milk allergy.

A further differentiation of hypoallergenic formulas in 'formula for therapy' and 'formula for prevention' was necessary, when a pHF, which was marketed as hypoallergenic, had caused anaphylactic reactions.

A formula suitable for being classified as a 'formula for therapy' of cow's milk allergy/intolerance has to fulfill several clinical and preclinical criteria. This includes a double-blind, placebo-controlled food challenge, followed by 7 days' feeding with the respective formula to prove that 90% (with 95% confidence) of children with documented cow's milk allergy/intolerance can tolerate the formula without developing allergic symptoms [5].
The definition of a hypoallergenic ‘formula for prevention’ of allergic diseases includes that the formula should be tested in a high-risk population defined by a positive family history, that children should be exclusively fed with the formula from birth to at least 6 months of age in a controlled randomized fashion and followed until 18 months of life with validated clinical scoring systems, where any allergic symptoms should be verified by double-blind placebo-controlled food challenge, and finally that a significantly lower prevalence of allergy should be documented in these children [5].

While several eHFs and amino-acid-based formulas fulfill the criteria of a ‘formula for therapy’, neither the eHFs nor the pHFs fulfill all criteria to be classified as ‘preventive’, because no clinical study exist which verifies all criteria according to the definition.

eHFs, primarily intended for the therapy of cow’s milk allergy/intolerance some 60 years ago, have later been adapted for allergy prevention as well, while pHFs have always been reserved for the use in primary prevention due to their comparatively higher residual antigenicity.

Dietary primary allergy prevention aims at avoiding early sensitization to foods, mainly to milk proteins by induction of oral tolerance [24]. There is some scientific controversy as to whether a partial hydrolysate with its moderately reduced antigenicity or a hydrolysate with extensively reduced antigenicity is more beneficial for prevention. However, the optimal extent of hydrolysis and the amount of residual allergenicity needed to induce oral tolerance are not known.

In a mouse model it could be shown that prefeeding with a pHF-W had a suppressive effect on the IgE anti-β-lactoglobulin production at repeated feeding with cow’s milk, while prefeeding with an eHF-W resulted in a similar antibody production to prefeeding with H2O, which is interpreted by the authors as specific induction of oral tolerance due to the presence of tolerogenic peptides in the pHF-W [25, 26].

These and similar data are the reason for an ongoing discussion of whether the use of pHF should be recommended for allergy prevention in order to not only mimic as far as possible the amount of allergenic proteins like in breast milk, but also to induce oral tolerance, or whether the use of eHF is favorable to avoid an immunologic response. From the results of the GINI study, however, it must be suggested that factors – like the producing process itself – other than the degree of hydrolyzation alone are also associated with the expression of allergic reactions. Here the pHF-W and the eHF-C significantly reduced the incidence of atopic dermatitis, while the eHF-W had no preventive effect [10].

Some recent data from large intervention studies indicate less sensitization to cow’s milk in children fed a partial hydrolyzed formula compared with children fed an eHF, which may be an indication for induction of specific oral tolerance [27]. Hence the guidelines on nutrition of infants at risk for allergy
recommend both, eHF and pHF as a supplement for or a substitute to breastfeeding in the first 4–6 months.

**Infant eHF and pHF in Clinical Studies**

eHF fulfill the criteria to be classified as a formula for therapy, but they are also recommended by the American and the European Pediatric Societies for allergy prevention [4, 5].

The most intensively tested eHF is based on 100% casein (eHF-C). Its allergy-preventive effect has been investigated in several birth cohorts of high-risk infants and compared with breast milk, cow's milk formula and pHF [10, 27–34], and in two of these studies also with eHF-W [10, 27].

Most of the pHFs available today are based on 100% whey (pHF-W). The pHFs fulfill 2 of 3 criteria for the definition to be ‘hypoallergenic’ as recommended by the American Academy of Pediatrics [5]: they have a reduced antigenicity of the protein and induce limited immunological reactions. However, they are not suitable for the therapy of cow’s milk allergy/intolerance. Nevertheless, in several clinical studies pHF has demonstrated a potential for prevention of allergic disease, and here mainly with regard to atopic dermatitis and food allergy [8, 28, 34–36].

Taking together the results of the intervention studies with hydrolysates, a preventive effect with regard to the prevalence and the cumulative incidence of allergic manifestations, mainly atopic dermatitis and food allergy could be demonstrated for both eHF and pHF [28].

In general it is not possible to compare these dietary intervention studies because of methodological differences in their design and their performance [28, 34, 36]. All of these studies were performed in children at risk of atopy; however, not always with the same level of risk (uniparental, biparental). All of the studies mentioned in the reviews tried to randomize the children to the study formula that would be fed as a supplement if breastfeeding was insufficient. However, some children were randomized before birth [29], some at birth [10], at weaning [30] or by the day of randomization (even, uneven) [27]. Not all of the studies were blinded, and only two of them were double-blinded [10, 30]. In case the formula is tested versus breast milk, blinding and randomization are not possible for ethical reasons. Additional differences between the studies are the result of the time of weaning and duration of feeding study formula, as well as of co-interventions such as recommendations for the diet of the lactating mother, solid food introduction, or avoidance of inhalant allergens. And not least important are the differences in the outcome definitions and the criteria for diagnosis in the various studies.

A direct comparison between eHF and pHF was performed only in two studies, showing that, with regard to the reduction of atopic dermatitis and food allergy, mainly cow’s milk allergy, eHF was borderline significantly superior
over pHF [27, 30, 34]. However, from results of the GINI study, where the allergy-preventive effect of three different hydrolysates (pHF-W, eHF-W and eHF-C) was compared with a regular cow’s milk formula in children at high risk of atopic diseases, it became obvious that the effect of a formula was modified by the specific allergic phenotype in the child’s immediate family. While the incidence of atopic dermatitis in children without atopic dermatitis in a first-degree family member was reduced with all 3 hydrolysates – and even significantly so with pHF-W, a significant reduction of atopic dermatitis in children with atopic dermatitis in the family could only be shown with eHF-C. This finding may have implications for the cost/benefit ratio, as pHF-W is much cheaper than eHF-C. The use of eHF-C should be reserved for infants at the highest risk of developing atopic dermatitis.

In conclusion, the concept of hypoallergenic infant formulas for atopy prevention in children at high risk of developing atopic diseases has been demonstrated efficacious in reducing the incidence of allergic manifestations, mainly atopic dermatitis and food allergy, in infancy and early childhood. So far there has been no evidence for a preventing effect of hypoallergenic infant formulas on respiratory allergic diseases.

References

von Berg

Discussion

Dr. Saavedra: When we look at strategies for prevention we probably should start thinking about breastfeeding. We continue to discuss breastfeeding as a way to prevent allergy, and in relative risk tables we use breastfeeding as the nonexclusive standard and then we look at the effect of breastfeeding in reducing allergy. Nobody would agree that the standard should be nonexclusive breastfeeding. The right question here is how does nonexclusive breastfeeding increase the risk of atopy. I think that this changes our mind set regarding where we need to go if we admit that there are risks associated with nonexclusive breastfeeding. It is not that breastfeeding reduces the risk of allergy, it is that nonexclusive breastfeeding increases it. For example these hydrolysates don’t reduce or prevent allergy, they just cause less than what would be caused if we did not use these hydrolysates.

Dr. von Berg: You are absolutely right, it should be the other way round. We should have breastfeeding as gold standard and compare other foods in case breastfeeding is not sufficiently available. The aim of this study was not to compare hydrolysates versus breastfeeding, instead we wanted to find out in the case of insufficient breastfeeding, which kind of hydrolyzed formula is best for allergy prevention. This is one reason why the results in the breastfed group were not included in the analysis [1].

Dr. Wahn: I still like this GINI study, I think it is a wonderful study telling us a lot, and I recall the good old days of the study by Zeiger et al. [2]. It appears to me that the key messages are very similar. You followed 3 phenotypes, one was atopic dermatitis, one was asthma and one was specific sensitization. Please correct me if I am wrong, you saw a transient effect on the incidence of atopic dermatitis, the incidence afterwards was the same as the cumulated prevalence of atopy?

Dr. von Berg: Yes, the incidence was reduced in the first year with pHF-W and eHF-C, and in the second and third year the incidence was not different between the 4 study groups. This confirms the findings by Vandenplas et al. [3] and Zeiger et al. [2], who in their studies also saw the preventive effect developing early, in the first 6 and 12 months of life, respectively.

Dr. Wahn: You were unable to describe any effect on airway diseases, and this is also the case in Dr. Zeiger’s study. You saw effects with regard to specific IgE responses as you found a reduced IgE response to cow’s milk and also to hen’s egg in one case.

Dr. von Berg: Yes, with pHF-W, we found a significant reduction of sensitization to cow’s milk at 3 years.

Dr. Wahn: You saw no effect on inhalant allergens?

Dr. von Berg: We didn’t see an effect on inhalant allergens, that is correct.

Dr. Wahn: If you saw something, an effect on hen’s egg which was not related to the hydrolysates you gave, could you speculate on the effect? Is it really a nonspecific effect which has to do with some immunomodulation or regulatory processes or what is your interpretation with regard to the hen’s egg and IgE response?

Dr. von Berg: At the age of 1 year about 30% of the cases of atopic dermatitis were associated with IgE, and most of them with specific sensitization to hen’s egg. Interestingly, this hen’s egg-associated atopic eczema was significantly reduced in the group of children fed eHF-C. If this finding is more than a statistical effect, then it has to be interpreted as a nonspecific effect likely to have something to do with immunoregulatory processes.

Dr. Fuchs: I find this fascinating. I am not an allergist or a dermatologist but in looking at the effect, as I understand it, the presence or absence of atopic dermatitis was the only clinical outcome variable. However, is all atopic dermatitis the same or
does it vary in severity and, if you look at severity, are there more striking differences
or do the differences become less significant?

Dr. von Berg: Atopic dermatitis is definitely not the same, one difference being
whether it is associated with specific IgE responses or not. Regarding severity, we
could not see marked differences between the study groups at 1 year; we have not yet
looked at it after 3 years.

Dr. Wahn: In the EPAAC trial 2,500 children with atopic dermatitis were screened
for specific IgE levels between their first and second birthday. It is quite clear that spe-
cific IgE responses are most likely related to severity.

Dr. von Berg: We have not yet related severity to IgE levels. We have just related
severity to the 4 formulas.

Dr. Fuchs: I guess my patients would be more concerned not about the IgE levels
but the degree of the atopic dermatitis.

Dr. Davidson: This is probably a naïve question from a pediatric gastroenterolo-
gist. The difference between hydrolyzed casein and hydrolyzed whey interests me
because breast milk really is a combination of whey and casein and you would expect
that that would be the ideal mix. So is there a good explanation as to why a whey
hydrolysate or a casein hydrolysate may actually have some benefit?

Dr. von Berg: I give this question over to people who actually produce the formulas.

Dr. Saavedra: This an excellent question because it is probably one of the best
declarations we have that not all hydrolysates are created equally or behave simi-
larly. It is just a clear demonstration that the percentages of casein and whey from
cow’s milk are of course totally different from the percentages of casein and whey in
breast milk. I use the analogy that casein in cow’s milk is an excellent protein for mak-
ing cheese, human casein isn’t. So these proteins are not comparable chemically or
physicochemically. Different amounts of certain types of casein are present in both
cow’s milk and human milk. The second major factor of course is hydrolysis. Not every
method of hydrolysis is the same and currently each manufacturer has its own
method, some use trypsin, some use a combination of enzymes, some use pancreatin,
some use actual pancreatic glands, and some use no pancreatic enzymes at all. So of
course these peptides are not going to look the same and I think this study does show
that the ‘degree of hydrolysis’ may be less important than the ‘method of hydrolysis’
when it comes to allergy prevention.

Dr. von Berg: This is underlined by the fact that our extensively hydrolyzed whey
showed no effect, while another extensively hydrolyzed whey formula in the study by
Halken et al. [4] had an effect similar to that of extensively hydrolyzed casein.

Dr. Lack: I was interested to see your data on specific IgE to milk, which I don’t
think I’ve seen before. You showed the reduction in cow’s milk which you say is the
only significant reduction, is that right?

Dr. von Berg: Yes, at 3 years of age. We don’t have the results at 6 years yet.

Dr. Lack: But what I don’t understand is this 20- or 30-year-old belief that chang-
ing cow’s milk composition is going to change asthma, eczema, other food allergies and
inhalant allergens. I can understand how it would affect specific IgE to cow’s milk, but
by just taking out the protein how do you think it could affect egg or how could it
affect inhalants if milk allergy was the main cause of asthma in older children?

Dr. von Berg: It neither affected the inhalant allergies nor did we expect this.
However what one could perhaps expect is that if you prevent sensitization to food
allergens then maybe you can avoid the allergic march from atopic dermatitis to
inhalant allergens. We have now finished the 6-year follow-up in these children, where
we performed lung function and looked at bronchial responsiveness in a subgroup.
The results will show whether avoidance of sensitization to foods and/or atopic
eczema will cause less asthma or airway inflammation.
Dr. Szajewska: I read your results which were published at 1 year of age [1]. I understand the results for atopic dermatitis at 3 years of age are very similar. If so the number needed to treat was 13, with quite a wide confidence interval (8–51) which means that one would need to treat 13 infants with extensively hydrolyzed casein formula to prevent one additional infant suffering from any allergic manifestation. I come from Poland, a country less rich than Germany, so my practical question is: do you really think with such a number needed to treat and such a wide confidence interval that this intervention is really the best way to prevent allergic diseases?

Dr. von Berg: At 3 years we calculated the cost-benefit relation on the basis of the number needed to treat. If you take all children with a family history for atopy together, there is no difference between the extensively hydrolyzed casein and the partially hydrolyzed whey, 12 versus 13 children, respectively. However if we look into the subgroup of children with the specific phenotype atopic eczema in the family then there was a big difference: 8 children had to be fed eHF-C compared to 47 fed pHF-W. Therefore, to prevent atopic eczema in children at risk in general I would recommend the partially hydrolyzed whey, which has a better taste and costs less. But for the subgroup of children with a very high risk of atopic eczema, that is atopic eczema in an immediate relative, eHF-C would most likely be more beneficial in preventing atopic eczema.

Dr. Szajewska: But my question was not whether to choose extensively hydrolyzed versus partially hydrolyzed formula but whether with this quite large number needed to treat and especially with a wide confidence interval, is it really worth doing this kind of intervention? It might be very expensive.

Dr. von Berg: If you look at prices the difference between the partially hydrolyzed whey and normal cow’s milk formula is really not much. The difference comes up if you take the extensively hydrolyzed casein. Therefore I would suggest to carefully select whom you recommend the extensively hydrolyzed casein.

Dr. Wahn: Did you have a chance to look not only at the quality of the IgE response but also at the quantity? You obviously had a certain cutoff point above which you found an IgE response to egg or whatever. We know that there are decision points and if you have very high IgE responses then you might end up having just clinically relevant food allergy. Have you analyzed this?

Ms. Skypala: It interested me that you avoided the key food allergens also after a year. I wonder if you could speculate on how important this was in the results you had. What is your general view regarding the disparity between the American guidelines on the avoidance of key food allergens and the European guidelines that don’t give such a recommendation?

Dr. von Berg: We recommended avoiding solid foods up to the 4th month and thereafter to introduce only one new solid food per week [1]. We have some data on solid food introduction for breastfed children and for children supplemented with regular cow’s milk. It shows first that breastfeeding mothers hardly ever introduce solids in the first 4 months, while 30% of mothers in the cow’s milk group did. The percentage of atopic eczema in both groups in our study is higher when solids are introduced later and lower when more diverse food groups are given [5]. This is totally different from the results in the older study by Fergusson et al. [8, 9]. Our interpretation of this finding is reverse causality [5, 7]. Because the decision of diversity and when to introduce solids first is driven not only by the family history of atopy, mainly atopic eczema or food allergy, but also by the presence of early skin symptoms of the baby. This has been nicely shown by Zutavern et al. [6] who analyzed data from our observational LISA study. There she showed that in those children who had no early skin symptoms egg and milk were equally often introduced before or after the 6th month, but if a child...
had early skin symptoms, then egg and milk were significantly more often introduced after the 6th month. So there is an association between early skin symptoms and the time of introduction of solid foods.

Dr. Wahn: Can I just add two sentences before everybody gets confused about this. You remember that Bergmann et al. [10] wrote a paper on the risk factors of prolonged breastfeeding. They showed that it is clearly reversed causation. Everyone knows that eczema becomes manifest between 2 and 6 months, and this is when mothers decide to prolong breastfeeding.

Dr. B. Koletzko: That is exactly why the paper of Zutavern et al. [6] is so important. Their data give strong dogmatic support to the recommendation that complementary feeding should not start before the first day of the 7th month with the aim of preventing allergy. I don't think we have any solid basis for that recommendation.

Dr. Micskey: How long do you recommend the use of different hydrolysates?

Dr. von Berg: Until 6 months. There is no evidence in any study that there is an effect of hydrolyzed formulas on allergy prevention beyond 6 months of life.

Dr. Beyer: I like the GINI study a lot but I was always puzzled that the extensively hydrolyzed whey formula did not give the result. It is not only the rate of hydrolysates or the proteins, it might also be the way the formulas are hydrolyzed. But let's turn it around. If you now recommend a partially hydrolyzed formula for prevention of atopic diseases and use a brand produced differently, you might see completely opposite results. So should we not require a standardization in producing formulas used for treatment or prevention in order to be able to compare the results between different companies?

Dr. Haschke: In part the methods are protected by patents so it would be very difficult to proceed according to one standard.

Dr. Beyer: Patents are a real problem in the whole research field. Many things we come across in patient care are due to this patent problem.

Dr. von Berg: What we recommend for allergy prevention is to use only those formulas that have shown a preventive effect in controlled studies, and there are very few [1]. It was very surprising that the extensively hydrolyzed whey did not have an effect. We actually gave the formulas to Hugh Sampson to find the reason for this, and even he has no explanation.

Dr. Saavedra: The important question from a practical point of view is how do we apply what we know. A very appropriate question is how many children need to receive an effective hydrolysate to see the effect in a population? If we use family history as a risk factor today, given the incidence of allergy, about 30% of the general newborn population would fall under the category of risk by family history. This means that 30% of the population would theoretically benefit from risk reduction. Obviously it is very hard to argue that family history should be the one criteria for obvious reasons. One reason is the large number of children needed to screen for only 30%. The second is that we cannot get the kind of history this research needs in real life, and in the US 30% of the time the father is neither available nor would he remember.

Dr. von Berg: Your question is why should only children at risk get a hydrolyzed formula or should not all children get it. Of course this is a question all of us have. There is only one study by Exl et al. [11] looking at health and skin problems in the general population, not specifically at allergy, in two areas of Switzerland. In one area where a partially hydrolyzed whey formula was recommended, the children had less health problems than in the other area where no feeding recommendations were given at all.

Dr. Wahn: The family history, usually you have the mother available, she knows certain things about the father whether he ever wheezed and so on. So this is quite reliable information and the family history isn't too complicated.
Dr. B. Koletzko: You have omitted the data by Chandra. At this time this is probably quite appropriate with all the questions we have as to the reliability of his data. I wonder whether the president of ESPGAN has any comment to offer as to whether this has already been looked into. Particularly as it is my understanding that the Cochrane review on this issue was very much based on Chandra’s data which you now seriously question.

Dr. von Berg: This is the reason why I did not show them.

Dr. B. Koletzko: What would the Cochrane meta-analysis conclude if we were to take out Chandra’s data?

Dr. von Berg: As far as I know the results are still showing a preventive effect of the partially hydrolyzed whey and of the extensively hydrolyzed casein formula.

Dr. Lentze: I have been asked whether ESPGAN has decided to withdraw the papers by Chandra from the *Journal of Pediatric Gastroenterology and Nutrition*. The journal has two societies, a European one and an American one. From the European side we recommended withdrawing the papers immediately and writing an article as to what was going on. The American side wanted to wait until there was an answer from Chandra but in my opinion we will never get an answer and I reckon that these papers will be withdrawn from the journal soon.

Dr. Haschke: I refer to a meta-analysis we have published, which included a total of 13 clinical trials with one partially hydrolyzed formula. As you indicated, after removing the Chandra data, the results remain the same.

Dr. von Berg: But I think until the situation is solved one should not take them into consideration in the meta-analysis.

Dr. Bayhon: I would like to know if there are any studies correlating the cord blood IgE level with the development of atopic dermatitis? Could these children with high cord blood IgE levels benefit from this milk formula?

Dr. von Berg: Dr. Wahn, I think you have looked at the level of total IgE.

Dr. Wahn: Yes we did. It must be certain that the cord blood IgE is not contaminated by maternal blood because then it can be an insufficient predictor of subsequent atopic manifestation. There was a time when we were hoping that we could screen cord blood IgE and use it for prediction and also for preventive measures, but it does not seem to be the case.

References


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