The long-term effect
of a partial whey hydrolysate formula
on the prophylaxis of atopic disease

Abstract At the age of 5 years, the
prevalence of atopic manifestations
was analysed in 58 formula-fed “at
risk” infants because of a history of
atopic disease in at least two first
degree relatives. Infants were randomly
assigned to receive either a partial
whey-hydrolysate formula (n: 28) or
a regular cow’s milk formula (n: 30)
during the first 6 months of life;
thereafter, feeding was unrestricted.
Only non-breastfed infants were in-
cluded. The groups did not differ in
risk factors or in known confounding
factors possibly influencing the inci-
dence of manifestations suggestive
of atopic disease. At 6 months, the
prevalence of cow’s milk protein
(CMP) sensitivity was significantly
decreased in the hydrolysate group
(7% versus 43%; P: 0.002). At the
age of 12 (21% versus 53%; P:
0.029), 36 (25% versus 57%; P:
0.018) and 60 months (29% versus
60%; P: 0.016) there was still a sig-
nificant difference in the number of
atopic manifestations, if calculated
cumulatively. There was no differ-
ence between the groups if only the
new cases after the age of 6 months
were considered. Eczema was less
frequent in the whey-hydrolysate
group, but only during the 1st year
of life, suggesting a decreased preva-
ience of CMP sensitivity. During the
first 6 months, diarrohea of non-in-
fecious origin occurred in 8/30 in-
fants (27%) of the adapted formula
group, and in no infant in the hy-
drolysate group. “Colic as single
manifestation” was considered of
“allergic” origin in 1/28 infants in
the hydrolysate group, and in 4/30
infants in the adapted formula group.
If gastro-intestinal symptoms such as
“diarrohea and colic as single mani-
festation” are not considered, the
number of infants with CMP sensi-
tivity remains only significant for the
first 6 months (P: 0.004). At 12, 36
and 60 months, differences are not
significant (0.106, 0.116 and 0.07,
respectively). The results of this
study support the hypothesis that
allergy prevention is antigen spe-
cific.

Conclusion If mother’s milk is not
available and other studies confirm
these results, there might be an in-
dication for partial hydrolysates in
infants with a family history of
atopy, since these formulae reduce
the incidence of CMP sensitivity.

Key words Food allergy · Atopic
disease · Hydrolysate · Prevention

Abbreviations AF-Gr adapted
formula group · CMP cow’s milk
protein · WH-Gr whey hydrolysate
group
Table 1 Incidence of cow’s milk allergy in unselected populations. All papers regard prospective studies, and cow’s milk allergy is documented by at least one challenge.

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Follow-up</th>
<th>N° infants</th>
<th>Cow’s milk allergy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bock [3]</td>
<td>Specific</td>
<td>480</td>
<td>5.2</td>
</tr>
<tr>
<td>Forget et al. [8]</td>
<td>Specific</td>
<td>579</td>
<td>5.2</td>
</tr>
<tr>
<td>Jakobsson and Lindberg [17]</td>
<td>Specific</td>
<td>328</td>
<td>3.7</td>
</tr>
<tr>
<td>Hëst et al. [16]</td>
<td>Specific</td>
<td>86</td>
<td>3.5</td>
</tr>
<tr>
<td>Ruuska [22]</td>
<td>Specific</td>
<td>336</td>
<td>5.9</td>
</tr>
<tr>
<td>Schrander et al. [27]</td>
<td>Health care services</td>
<td>1158</td>
<td>2.8</td>
</tr>
</tbody>
</table>

Table 2 Composition of both formula in g per 100 ml

<table>
<thead>
<tr>
<th></th>
<th>Partial whey hydrolysate</th>
<th>Adapted formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peptides</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Casein/Whey</td>
<td>1.6</td>
<td>1.65</td>
</tr>
<tr>
<td>Fat</td>
<td>0/100</td>
<td>40/60</td>
</tr>
<tr>
<td>Carbohydrates</td>
<td>7.4</td>
<td>7.4</td>
</tr>
<tr>
<td>Lactose</td>
<td>5.2</td>
<td>7.4</td>
</tr>
<tr>
<td>Dextrin-maltose</td>
<td>2.2</td>
<td></td>
</tr>
<tr>
<td>KCal</td>
<td>67</td>
<td>67</td>
</tr>
</tbody>
</table>

During the first 6 months of the study, 8 infants dropped out for various reasons: change of residence in 3 (2 WH-Gr, 1 AF-Gr), refusal of blood sampling at 6 months in 4 (1 WH-Gr, 3 AF-Gr), a switch to soy formula in 1 (1 WH-Gr). Between 6 and 12 months, 2 infants dropped out because of change of address. From the age of 3 years on, 58 infants remained in the study: an additional 7 infants had been lost during follow-up because of change of residence. No new drop-outs occurred during the last 2 years of the study. The final drop-out rate was 23%.

Details of the family history, IgE determination at day 5 and possibly confounding factors are listed in Table 3, and were previously published in detail [33]. The infants were fed exclusively with the formula they had been assigned and, on demand, up to the age of 12–15 months. A semi-elemental diet was administered up to this age in these children. All children were examined at least 15 times (each month during the first 6 months of life, each 6 months between the age of 6 months and 5 years). Whenever the children were sick, they were examined by the same team.

Follow-up was blinded as much as possible: neither the parents nor the physician(s) involved in the follow-up were informed about the nature of the formula. Both formulae (hydrolysate, regular formula) were given in blinded, unlabelled package. Nevertheless, it is obvious that a “partial hydrolysate” differs substantially in several aspects from a “regular formula”.

The criteria for the diagnosis of CMP sensitivity have been published [33], and are briefly summarised here. The following manifestations were considered: gastrointestinal symptoms (recurrent colic, vomiting, and/or diarrhea, 2 episodes lasting > 2 days), when common eating problems, coincidental infections and lactose intolerance were excluded [1, 11], urticaria, angio-oedema, atopic dermatitis, allergic rhinitis, asthma, chronic cough [15, 18, 25, 33]. Since the “allergic” origin of diarrhea and “colic” is difficult to prove, the results were also analysed not accepting diarrhea or colic as single manifestation of possible atopic origin.

Laboratory tests were performed in all infants at 6 months (IgE (Phadebas IgE Prist), RAST (Pharmacia Diagnostics, Uppsala, Sweden) for cow milk, casein, lactalbumin and lactoglobulin, skin prick test for cow milk (Bencard, Brentford, England). A challenge test, between 2 and 4 weeks after disappearance of the symptoms, was performed before cow’s milk sensitivity was diagnosed: symptoms had to disappear on a semi-elemental high-degree whey-hydrolysate (Alfare, Nestlé), and to relapse when the original formula was reintroduced [25]. Lactose intolerance was excluded in infants presenting with diarrhea or colic by determination of the lactase activity in the small bowel mucosa whenever a small bowel biopsy was performed, and a lactose breath test.

Introduction

Mother’s milk is the gold standard in infant feeding. If for some reason maternal milk is not available, (adapted) cow’s milk is considered a good alternative. The estimated prevalence of cow’s milk allergy is 3% to 6% in unselected, bottle-fed infants (Table 1). As a consequence, cow’s milk proteins (CMP) are the most frequent (food)allergens during early infancy. “Food intolerance” may play a role in the pathogenesis of some “allergic” or “atopic” disorders during infancy and early childhood [9, 24]. Exclusive breast feeding gives at least partial protection [2, 23], although this is also controversial [14, 29].

Results of studies on the short-term preventive effect of feeding a partial whey-hydrolysate, identical to the formula used in this study, to infants “at risk” for atopic disease because of a positive family history, were promising: the prevalence of manifestations suggestive of atopic disease was significantly decreased in the whey-hydrolysate group (WH-Gr), and similar to the incidence during exclusive breast feeding, in comparison to a group with a “regular” cow’s milk based formula [6, 20, 26, 31–33]. Intermediary results of this study have been reported at 12 and 36 months [31, 33]. In this paper, the final data after a 5-year follow-up are presented.

Patients and methods

During a period of 14 months (1988–1989), in a total of about 2000 births, 75 infants with a positive family history in at least two first-degree relatives could be included in this study. Many parents with atopic disease refused participation because of the blood sampling at 6 months and the long-term follow-up, resulting in a particular study population. Parents and/or siblings had typical histories of atopic disease, supported by previously positive diagnostic tests. The mothers of these babies were strongly advised to breast feed. If breast feeding was refused, participation in this study was proposed. After randomisation, the infants were given one of two coded formulae (WH-Gr, or an adapted formula with native cow’s milk proteins (AF-Gr), delivered in an unlabelled package. Both formulae are marketed by Nestlé (Table 2).