

Prospective, controlled, multi-center study on the effect of an amino-acid-based formula in infants with cow's milk allergy/intolerance and atopic dermatitis

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Cow's milk allergy/intolerance is treated by complete avoidance of cow's milk proteins. Because cow's milk is an important food for infants, its avoidance may lead to an increased risk of growth impairment. Whilst there is evidence for the beneficial effects of extensively hydrolyzed cow's milk formulae (eHF) in infants with cow's milk allergy/intolerance, little is known about the effects of amino-acid-based formulae (AA) in such infants. We therefore performed a prospective, controlled, multi-center trial to study the efficacy of AA in comparison with eHF, on the growth and clinical symptoms of 73 infants (median age 5.7 months) with cow's milk allergy/intolerance and atopic dermatitis. Cow's milk allergy/intolerance was proven in all infants by double-blind, placebo-controlled food-challenge. We observed a significant improvement in the SCORAD index in both groups, from a mean of 24.6, at entry, to a mean of 10.7 ($p < 0.0001$) after 6 months. In the AA group there was a significant increase in the length standard deviation score ($p < 0.04$), whilst there was no difference in the eHF group. The weight-for-length values were stable in both groups. The energy intake during the study was similar in both groups. Both an AA and eHF resulted in a significant clinical improvement in infants with an early onset of symptoms of cow's milk allergy/intolerance. Feeding an AA resulted in improved growth compared with feeding eHF, despite similar dietary intakes, and may therefore be considered as a beneficial alternative in infants with severe cow's milk allergy intolerance.

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Cow's milk is the most common cause of food allergy/intolerance in infants and children. Prevalence rates of 2–6% have been reported (1,2). Food allergy/intolerance is often associated with atopic dermatitis (AD). In the literature, the frequency of a clinically important food allergy in children with AD has been reported to range from 33% (3) to 54% (4).

However, the clinical manifestation of food allergy includes not only eczematous reactions, but also urticaria, gastro-intestinal, and respiratory symptoms (5,6). Even fatal anaphylactic reactions are reported in patients with food allergy and AD (7).

The mainstay of treatment of cow's milk allergy/intolerance is complete avoidance of cow's milk proteins. But as cow's milk is an important food for infants, this may lead to an increased risk of growth impairment (8). Whilst there is evidence for the beneficial effects of extensively hydrolyzed cow's milk formulae (eHF), little is known about the effects of feeding amino-acid-based formulae (AA) to these infants.

We therefore performed a prospective, controlled, multi-center trial to study the effects of AA in comparison with eHF on clinical symptoms and growth in 73 infants with cow's milk allergy/intolerance and AD.

Patients and methods

Patients

Seventy-three infants (24 girls, 49 boys) were included in the study. All infants suffered from AD, as defined by the criteria of Sampson and Seymour et al. (9,10), modified from Hanifin & Rajka (11). The infants included in the study were between 1 and 10 months of age with cow's milk allergy/intolerance proven by double-blind, placebo-controlled, food challenge (DBPCFC).

Study design

After proving cow's milk allergy/intolerance by determination of cow's milk-specific immunoglobulin E (IgE) in serum and DBPCFC, infants were randomly assigned to receive either AA (Neocate[®]; SHS, Liverpool, UK) (n=31) or an eHF (extensively hydrolyzed whey formula: either Alfaré [Nestlé, Germany] or Pepti-Tutteli [Valio, Finland]) (n=42). Clinical symptoms of AD (as evaluated according to the SCORAD index), dietary intake (3-day dietary record), length (cm), and weight (g), were monitored over a 6-month time-period. The study protocol was approved by the local ethics committees, and parents gave informed consent.

Severity scoring of AD

The severity of eczema was scored according to the SCORAD (12), with assessment of 'topography' items (extent of skin area), 'intensity' criteria (extent of erythema, edema, crusts, excoriations, lichenification, dryness), and subjective parameters (degree of itch and loss of sleep). The maximum score was 103 points.

Determination of serum IgE

Concentrations of total IgE and cow's milk-specific IgE antibody titers in serum were determined by fluorescence enzyme immuno assay (FEIA) using the Pharmacia CAP-system (PCS) (Kabi-Pharmacia, Uppsala, Sweden) (13). The detection limit was 0.35 kU/l of IgE; children were regarded as sensitized if the concentration of specific IgE was above the detection limit.

DBPCFC

Oral food challenges were performed in a double-blind, placebo-controlled clinical setting, as previously described (4,14). Briefly, placebo or successive doses (0.1, 0.3, 1.0, 3.0, 10.0, 30.0, and 100.0 ml) of fresh pasteurized cow's milk containing 3.5% fat were administered (in Neocate) in a randomized order. Neocate was used as placebo;

and for allergen challenges, the proportion of cow's milk in Neocate was 50%. The time interval between each dose was 30 min. Provocation was stopped if clinical symptoms were observed or the highest dose was reached. The children were observed, on an in-patient basis, for at least 48 h after each allergen or placebo challenge. The food challenges were scored as positive if objective clinical reactions (such as urticaria, angio-edema, wheezing, vomiting, diarrhea, abdominal pain or exacerbation of eczema) were observed. Clinical symptoms were defined as early reactions if they occurred within 2 h after administering the highest dose and as late reactions if symptoms occurred after 2 h.

Antihistamines were withdrawn at least 3 days prior to challenge. Topical corticosteroids were allowed twice a day at a concentration of 1% hydrocortisone or 0.3% betamethasone.

Statistical analysis

SCORAD data are expressed as mean (95% CI) or median values. For statistical evaluations, analysis of variance (anova), anova for repeated measurements, the Friedman test, and the chi-squared test were used. Differences associated with p-values of less than 0.05 were considered significant.

Results

Patients

Seventy-three infants (1.6 to 9 months of age; median age 5.7 months) were included in the study. Their SCORAD values ranged from 0 to 72 (mean 24.6). Total IgE ranged from <2.0 kU/l to 4710.0 kU/l (median 16.0 kU/l). Specific IgE to cow's milk in serum ranged from <0.35 kU/l to >100.0 kU/l (median 0.6 kU/l). The two groups (AA and eHF) showed no statistically significant differences concerning gender, age, total IgE, specific IgE, SCORAD, or family history for atopy (Table 1).

Oral food challenges

Cow's milk allergy/intolerance was proven in all infants by DBPCFC. Upon oral challenge with cow's milk, 40 infants showed an early reaction, 14 a late reaction, and 19 a combined reaction. Two infants presented with anaphylactic reactions, 63 with skin symptoms (urticaria, worsening of eczema), six with gastro-intestinal symptoms (vomiting, diarrhea), and two with respiratory symptoms (bronchial obstruction).

Table 1. Relevant background data of the patients at entry

	AA (n=42)	eHF (n=31)	p-value
Gender (F/M)	13/29	11/20	NS
Age (months)*	5.5	5.7	NS
Total IgE (kU/l)*	16.0	30.0	NS
Specific IgE to CM positive	22 (52%)	15 (48%)	NS
SCORAD*	18.5	14.7	NS
Family history of atopy	36 (86%)	26 (84%)	NS

*Median values.

AA, amino acid formula; CM, cow's milk; eHF, extensively hydrolyzed formula; F, female; IgE, immunoglobulin E; M, male; NS, not significant.

Clinical symptoms of eczema (SCORAD)

There was a significant improvement in the SCORAD in all children, from baseline at entry (mean 24.6, 95% CI 20.1–29.0), through the 3-month mean (12.2, 95% CI 9.1–15.3) to the 6-month mean (10.7, 95% CI 7.1–14.2) ($p < 0.0001$). Figure 1 shows the results for the AA group and the eHF group.

Growth data

While a small, but statistically significant, increase of length standard deviation score in children of the AA group was found (Friedman test, $p < 0.04$), there was no similar significant difference in the eHF group (Fig. 2). Weight-for-length showed a stable, similar, development in both groups (Fig. 3). The energy intake during the study was similar in both groups (not significant). There was no center effect.

Discussion

Impaired growth is a common problem found in many children with AD (15). Defining growth impairment as a height below the third percentile,

prevalences of 10% (16) and 22% (17) have been reported. The growth impairment in AD may be explained by various factors: the chronic disease itself (17,18); malnutrition by unnecessary and unsupervised dietary restriction (8,19); protein loss (20); sustained allergic inflammation and poor compliance (21); loss of sleep (22); vitamin D deficiency and steroid therapy (16); and impairment of growth hormone release during stage 4 sleep (22). However, few of these factors have been proven to be responsible for growth impairment in AD.

As food allergy/intolerance may exacerbate the problem of growth impairment in AD, adequate therapy is mandatory. The mainstay of treatment of food allergy/intolerance is avoidance of the proteins responsible, and to achieve this, three possibilities may be considered: feeding an eHF; feeding a different protein source (such as soy); or feeding an AA. Whilst eHF may be regarded as the treatment of choice in infants, soy formulae cannot be recommended as a first-line treatment of allergy/intolerance to cow's milk because of subsequent sensitization and allergy in a considerable number (14%) of children (23). AA may have some additional benefit for special groups of children owing to more complete antigen elim-

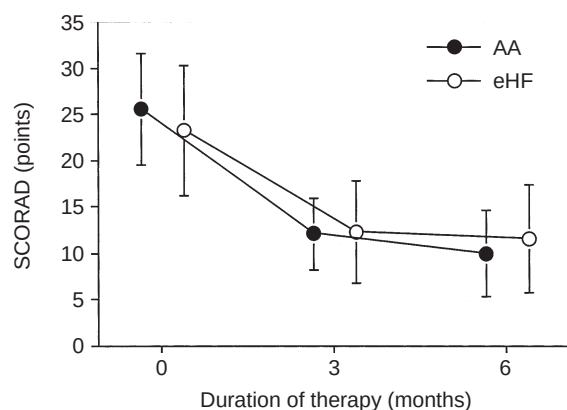


Fig. 1. Severity of eczema (as evaluated by using the SCORAD index) during treatment. Data are presented as mean (95% CI) significant improvement over time. $p < 0.0001$. AA, amino-acid-based formula group; eHF, extensively hydrolyzed formula group.

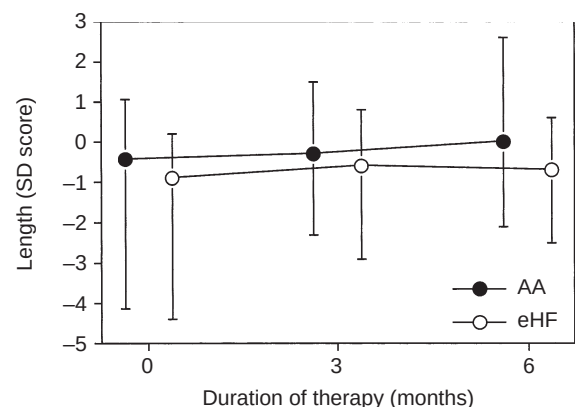


Fig. 2. Length during treatment expressed as standard deviation scores (median, range). Using the Friedman test, the results were statistically significant for the amino-acid-based formula (AA) group ($p < 0.04$), with no differences in the extensively hydrolyzed formula (eHF) group.

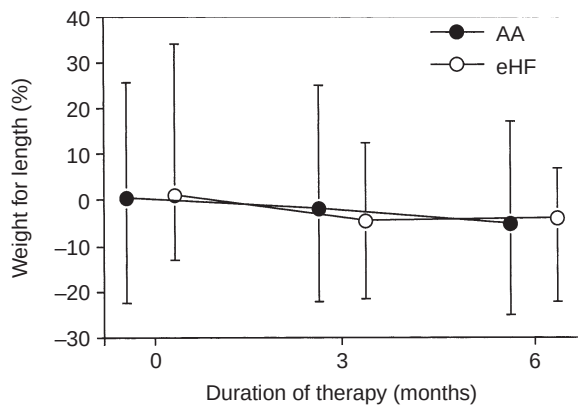


Fig. 3. Weight-for-length (%) during treatment. Data are expressed as median and range. AA, amino-acid-based formula group; eHF, extensively hydrolyzed formula group.

ination; however, to date its nutritional value has not been extensively studied.

In this study, we found that feeding an AA to children with cow's milk allergy/intolerance and AD resulted in a small, but significant, increase in the length standard deviation score, while there were no similar differences in the eHF group. The weight-for-length course was stable in both groups. In the literature, only a few investigations report studying eHF and AA in infants with cow's milk allergy/intolerance and AD: they found similar results to this study concerning growth and improvement of clinical symptoms (24).

Besides the nutritional value, acceptance by the infants is a clinically important criterion for the choice of an alternative formula. eHF have a strong, bitter taste, which is difficult to disguise. The AA used in this study was well-accepted. Furthermore, the residual allergenicity of an AA can be neglected, whereas several anaphylactic reactions to even eHF have been reported (25,26).

eHF and AA are expensive, with the AA costing $\approx 25\%$ more than eHF. Our study showed that both formulae are comparable concerning growth data. In general, eHFs are the choice for treating cow's milk allergy. Indications for preferring an AA are very severe cow's milk allergy and severe multiple food allergy.

In the literature, the frequency of a clinically important food allergy in children with AD has been suggested to range from 33% (3) to 54% (4). There are no prevalence rates in the literature extrapolated for the general population. The reported high numbers very much depend on the patients investigated. In our Department, the rate of a positive clinical reaction to at least one challenge is around 80%, owing to the fact that the inclusion criteria for performing DBPCFC

are a suspicion of food-related symptoms by the parents (5).

As a result of the good prognosis of AD and cow's milk allergy in early childhood, infants and small children may outgrow their growth impairment. Some studies have investigated this issue. One group investigated adult height in patients with childhood-onset AD and found that the growth impairment seemed to be temporary (27). Another study found that growth seemed to be dependent on the area of the skin involved (18).

In conclusion, both an AA and eHF resulted in a significant clinical improvement in infants with an early onset of symptoms of cow's milk allergy/intolerance. Feeding an AA resulted in improved growth compared to feeding eHF, despite similar dietary intakes, and may therefore be considered as a beneficial alternative in children with severe cow's milk allergy intolerance.

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