

Preventive effect of feeding high-risk infants a casein hydrolysate formula or an ultrafiltrated whey hydrolysate formula. A prospective, randomized, comparative clinical study

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In a prospective study of a 1-year birth cohort of 158 high-risk infants the effect of feeding breastmilk, a casein hydrolysate (Nutramigen®) or a new ultrafiltrated whey hydrolysate (Profylac®) on the development of cow milk protein allergy/intolerance (CMPA/CMPI) was assessed and compared. All the infants had biparental or severe single atopic predisposition, the latter combined with cord blood IgE ≥ 0.5 kU/L. At birth all infants were randomized to Nutramigen or Profylac, which was used when breastfeeding was insufficient or not possible during the first 6 months of life. During the same period this regimen was combined with avoidance of solid foods and cow milk protein. All mothers had unrestricted diets and were encouraged to do breastfeeding only. Moreover, avoidance of daily exposure to tobacco smoking, furred pets and dust-collecting materials in the bedroom was advised. The infants were followed prospectively from birth to 18 months of age. All possible atopic symptoms were registered and controlled elimination/challenge studies were performed when symptoms suggested CMPA/CMPI. A total of 154 (97%) were followed up and 141 followed the diet strictly. Eighty-eight (62%) of the infants were breastfed for at least 6 months, 20 (14%) were breastfed exclusively, 59 and 62 had varying amounts of Nutramigen or Profylac respectively. CMPA/CMPI was diagnosed in 1/20, 1/59 and 3/62 in the breastfed, the Nutramigen and Profylac groups respectively, but 1 of the latter also had Nutramigen. None of the infants showed reactions against Nutramigen or Profylac. In 4 infants symptoms were provoked by breastmilk when the mother ingested cow milk and in 1 only by cow milk. The incidence of CMPA/CMPI among the infants who followed the dietary prevention programme was 3.6% (5/141) which was a significant reduction compared to 20% (15/75) in an identically defined high-risk group without dietary preventive measures. None of the infants in the prevention group developed CMPA/CMPI after the age of 6 months. We conclude that feeding breastmilk, an extensively hydrolysed casein formula (Nutramigen) or an ultrafiltrated whey hydrolysate (Profylac) combined with avoidance of solid foods during the first 6 months of life in high-risk infants significantly reduced the cumulative incidence of CMPA/CMPI during the first 18 months of life. No difference was noted whether the infants were fed breastmilk, Nutramigen or Profylac and a diet period of 6 months seems sufficient. Both formulae were well tolerated and accepted by the infants.

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Atopic disorders are significant contributors to illness in infancy and childhood, and represent an increasing health problem. In infancy the main atopic manifestations are atopic dermatitis, gastrointestinal symptoms and recurrent wheezing. Adverse reactions to foods, mainly cow milk protein, are most common in the first years of life, whereas allergy to inhalant allergens mostly occurs beyond this period.

The presence of atopic disease in first degree relatives, especially biparental predisposition, and high levels of IgE in cord blood increase the risk of development of atopic symptoms. Moreover, there is evidence that the development of atopic disease/allergic sensitization may be related to early exposure to allergens and to several other factors which may facilitate or protect against sensitization. The development and high prevalence of cow milk protein allergy/intolerance (CMPA/CMPI) during infancy is suggested to be due to an incomplete mucosal barrier, increased gut permeability to large molecules, and immaturity of local and systemic immunological responses (1). Human colostrum/milk facilitates maturation of the gut and provides passive protection against bacteria, virus and antigens (1). In infancy sensitization to cow milk proteins is usually due to ingestion of cow milk based formula, and a recent prospective study indicates an association between early neonatal cow milk formula feeding and development of CMPA/CMPI in high-risk infants (2).

Previous prospective studies have shown a protective effect of feeding breastmilk (3–10) or an extensively hydrolysed casein, whey or soy formula (7, 9, 11, 12) on the incidence of atopic symptoms and food allergy in high-risk infants, when the period of the diet included at least the first four to six months and solid foods were not introduced until the age of four months. Recently, data were published which indicated a protective effect of a partially hydrolysed whey formula compared to conventional cow milk formula and soy-milk based formula (6, 8, 13, 14). In none of these studies the possible protective effect of this partially hydrolysed whey formula has been compared to an extensively hydrolysed formula. The varying study designs, study populations, definitions, diagnostic criteria and control for confoundings (environmental factors) in the previous studies do not allow a comparison of the effect of the different dietary regimens and hypoallergenic hydrolysed formulae.

Because of extensive hydrolysis the casein based hydrolysates have an unpleasantly bitter taste, and previously some infants had problems with diarrhoea due to hyperosmolarity of these products. These problems would be reduced by a less exten-

sive hydrolysis of whey proteins, which may on the contrary result in increased remaining antigenicity and a higher allergenicity. However, ultrafiltration is able to remove possible high molecular proteins from less extensively hydrolysed hydrolysates.

The aim of the present study was to examine, whether a new, less extensively hydrolysed, but ultrafiltrated whey hydrolysate (Profylac, ALK, Hørsholm, Denmark) was as protective as an extensively hydrolysed casein hydrolysate (Nutramigen, Mead Johnson, Evansville, Indiana, US) as regards development of CMPA/CMPI and atopic symptoms at present until the age of 18 months.

Subjects and methods

Study population

During 1988, all infants with atopic predisposition, born alive at Odense University Hospital and Viborg Hospital were registered at birth. A total of 158 (Odense 108, Viborg 50) infants had biparental atopic predisposition, or severe single predisposition combined with cord blood IgE (CB IgE) ≥ 0.5 kU/l. This birth cohort of high-risk infants comprised the study population and the parents were informed about the study orally and in writing. The parents of two of the infants did not want to participate in the study, and two infants never turned up for the examinations. Thus, 154 high-risk infants were included in the study.

As regards development of CMPA/CMPI, a birth cohort comprising 75 identically defined high-risk infants born in the municipality of Odense in 1985, were followed up and diagnosed prospectively by one of the authors (2). These 75 high-risk infants, not recommended any allergy prevention programme, were compared with the corresponding subgroup from the same area from our prevention group from 1988 – and with the total prevention group. Diagnostic criteria were exactly the same in these groups. The study was approved by the human research ethics committee. Informed consent was given by the parents before entering the study.

Method

All the mothers had unrestricted diet during pregnancy and lactation, and were encouraged to breast feed exclusively. If breastfeeding was not possible, or insufficient, feeding a casein hydrolysate (Nutramigen) or a new ultrafiltrated whey hydrolysate (Profylac) was advised for the first 6 months of life. At birth all high-risk infants in both hospitals were randomized to either Nutramigen or Profylac by means of time of birth. Thus, every second high-risk infant born at each hospital be-

longed to the Nutramigen group and the others to the Profylac group. The investigators were not involved in this procedure. It was recommended not to introduce cow milk, cow milk products including conventional cow milk based formula and solid foods until the age of 6 months. After the age of 6 months we recommended a normal unrestricted diet. Furthermore, it was recommended to avoid daily exposure to passive tobacco smoking, daily contact with furred pets, damp housing conditions, carpeted floor and having many dust collecting materials in the child's bedroom.

The parents of these high-risk infants were informed orally and in writing at the hospital soon after the birth. The infants were followed prospectively with careful registration of the diet, various environmental factors and any symptoms. At the age of 6, 12 and 18 months, all the infants underwent physical examination by one of two pediatricians and the children's individual case histories and data were recorded. If the infants experienced possible atopic symptoms they were also examined by the same pediatrician and at any suspicion of CMPA/CMPI controlled elimination/challenge studies were performed.

Definitions

High-risk infants were defined as having biparental predisposition to atopic disease (asthma, hayfever, atopic dermatitis or allergic urticaria), or severe single atopic predisposition combined with CB IgE ≥ 0.5 kU/l. Severe single atopic predisposition was present, when one parent and/or one or more older siblings had, or had had atopic disease with perennial symptoms or symptoms from more than one organ system.

Atopic symptoms were defined as asthma, recurrent wheezing, atopic dermatitis, urticaria $> \times 2$, food allergy, colic and or otherwise inexplicable vomiting/diarrhoea.

Recurrent wheezing was registered, when the child had a history of at least two episodes with expiratory wheezing diagnosed by a physician.

Atopic dermatitis was diagnosed if physical examination showed areas of scaly, erythematous and itchy eczematous rash primarily of the face, the scalp and at the flexural folds. Only excema with at least two localisations in typical areas was registered.

Gastrointestinal symptoms were defined as recurrent colic, vomiting and/or diarrhoea (> 2 episodes lasting > 2 days) when common eating problems, coincidental infections and lactose intolerance were excluded.

Cow milk allergy/intolerance (CMPA/CMPI) was diagnosed by generally accepted criteria: a)

definite disappearance of symptoms after each of two dietary eliminations of cow milk and cow milk products, b) recurrence of identical symptoms after one challenge, and c) exclusion of lactose intolerance and coincidental infection. All challenges were open, but with equivocal results the challenge was repeated and eventually blind.

Milk challenges

The children were on a milk free diet for at least 4 weeks before milk challenge. All challenges were performed in a controlled hospital setting observed by professionals. The challenges were performed with cow milk or an ordinary cow-milk based formula (Allomin) starting with a dose of 5 ml followed by 10, 20, 40 and 80 ml at intervals of 2 h. If no symptoms occurred after 8 h (a total cumulated dose of 155 ml) the child was sent home with increasing amounts to be taken at home until customary daily intake of milk was tolerated. In the case of late reactions the patients were reexamined at the hospital as soon as possible, and at a suspected reaction the last dose was repeated once. Before and after challenge and at any adverse reaction the patients were examined and symptoms and signs were noted.

Hypoallergenic infant formula, Profylac

Profylac (ALK, Hørsholm, Denmark) is a hypoallergenic milk powder based on bovine whey. No native proteins are present in the product as proteins are hydrolysed and ultrafiltrated through a filter with a pore size of maximum 6 kD, ensuring a MW < 8 kD. Profylac is tested by means of RIE (Rocket immuno electrophoresis) in order to control any residual antigenic activity. Antibodies against bovine whey are used in the gel to precipitate remaining antigens. No precipitation must be present. An ELISA test is performed using anti bovine whey antibodies and enzyme-linked antibodies. A standard solution of bovine whey is run parallel ensuring a 30,000 times reduced antigenicity of Profylac (15, 16).

Profylac represents a full diet for infants during the first 6 months of life, contains all necessary nutrients and meets the nutritional demands of infants during the first 6 months of life. The content of protein in the mixture is 15 g/l (1.5%). Bovine fats are replaced with unsaturated vegetable fats. Saccharides like lactose and galactose are removed. All essential vitamins and minerals are present and the amount of single components are within the recommendations from WHO (17).

Table 1. Duration of breastfeeding (BF) in 141 high-risk infants.

	Number of breastfed high-risk infants		
	Total number n (%)	Exclusively or almost exclusively n (%)*	Exclusively n (%)**
< 1 month	9 (6%)		
≥ 1 month	132 (94%)	117 (83%)	66 (46%)
≥ 2 months	128 (91%)	115 (82%)	65 (46%)
≥ 3 months	121 (86%)	100 (71%)	58 (41%)
≥ 4 months	111 (79%)	82 (58%)	47 (33%)
≥ 5 months	94 (67%)	54 (38%)	28 (20%)
≥ 6 months	88 (62%)	43 (30%)	20 (14%)

* No or minor supplement of formula a few times.

** No supplements of formula at all, even not during the first few days of life.

Statistics

Analysis of statistical significance was performed with Chi-squared test. Two-tailed tests are used.

Results

Study population – nutrition – confoundings

In advance 79 infants (Odense 53, Viborg 26) were randomized to nutramigen and 79 infants (Odense 55, Viborg 24) to Profylac. Four infants were not included (refusal by parents), 9 infants were excluded because of inadvertent supplements of conventional cow milk based formula during the first week of life and 4 because they were fed conventional cow milk based formula or cow milk from the age of 2–4 months. Another 4 infants had supplements of minor amounts of conventional cow milk based formula from the age of 4 (n 2) and 5 months (n 2) of life and were not excluded. A total of 20 infants (Odense 11, Viborg 9) were exclusively breastfed, without having any supplement of formula during the first 6 months of life, even not during the first few days until breastfeeding was established (Table 1). Hence 59 infants (Odense 38, Viborg 21) were fed Nutramigen and 62 (Odense 44, Viborg 18) Profylac exclusively or in varying amounts as supplement to breastfeed-

Table 2. Sex and atopic predisposition in the exclusively breastfed, the Nutramigen and the Profylac group.

	Breast n=20	Nutramigen n=59	Profylac n=62
Boys	13 (65%)	35 (59%)	35 (56%)
Girls	7 (36%)	24 (41%)	27 (44%)
Biparental predisp.	19 (45%)	20 (34%)	23 (37%)
Single predisp. + CB IgE ≥ 0.5 KU/l	11 (55%)	39 (66%)	39 (63%)

Table 3. Exposure to possible confounding variables in the three study groups.

	Breast n=20	Nutramigen n=59	Profylac n=62
Smoking at home	5 (25%)*	28 (47%)	34 (55%)
Housing – flat	2 (10%)	10 (17%)	10 (16%)
detached house	18 (90%)	49 (83%)	52 (84%)
carpeted bedroom	10 (50%)	34 (58%)	44 (71%)
Household pets	8 (40%)	23 (39%)	19 (31%)
Daycare	11 (55%)	41 (69%)	45 (73%)

* (breast versus formula) $P < 0.05$.

ing. All mothers except one with CMPI had a normal daily intake of milk > 500 ml.

The three groups were identical as regards sex and atopic predisposition (Table 2). As shown in Table 3 significantly fewer of the infants who were breastfed exclusively were exposed to daily tobacco smoking at home compared with the infants who were fed formula exclusively or partly, but no difference was noted whether they had Nutramigen or Profylac. The three groups were identical as far as housing conditions, household pets and daycare outside home were concerned. All but one of the infants avoided introduction of solid foods until the age of 4 months and the majority avoided solid foods until the age of 5–6 months (Table 4). No difference was noted between the two formula groups but there was a tendency, though not significant, that the exclusively breastfed infants avoided solid foods for a longer period than formula-fed infants.

The infants in the two formula groups had amounts of formula varying from minor supplements (eventually only during the first few days of life) to exclusive formula feeding. Only 7 and 9 infants were fed Nutramigen or Profylac exclusively for 26 weeks. Fifteen and 11 infants only had minor amounts, and 48 and 53 had varying amounts of Nutramigen and Profylac respectively. Mean number of weeks in which the infants had Nutramigen or Profylac exclusively was 5.5 and 5.9 per child in respective groups. Corresponding figures in which the infants had Nutramigen or Profylac as a supplement to breastfeeding were 4.5 and 5.8 weeks per child. The two formula groups were

Table 4. Age for introduction of solid foods in the study groups.

Age	Breast n=20	Nutramigen n=59	Profylac n=62
3 months	0	0	1
4 months	3 (15%)	9 (15%)	15 (24%)
5 months	5 (25%)	25 (42%)	26 (43%)
≥ 6 months	12 (60%)	25 (42%)	20 (32%)

Table 5. Description of the infants with CMPA/CMPI.

Patients	1	2	3*	4	5
Breastfeeding (weeks)	0-26	0-18	0-72	0-72	0-72
Profylac (weeks)	0	18-79	0-1	0-1	0
Nutramigen (weeks)	0	0	0-1	0	0-1
CMP (weeks)	0	24	0	0	0
Age at debut (weeks)	1	24	2	3	10
Symptoms at intake of	MM	CMP	MM	MM	MM
Symptoms	AD,RW,E	AD,U	Vo,Co	Vo,Di,E	AD,Di,Rh
SPT (CMP) $\geq$ 3mm	+	+	0	0	0
Specific IgE (CMP, class)	0	1	0	2	3

MM = Mothers milk, CMP = Cow milk protein, AD = Atopic dermatitis, RW = Recurrent wheezing, E = Exanthema, U = Urticaria, Vo = Vomiting, Co = Colic, Di = Diarrhoea, Rh = Rhinitis

* The diagnosis never proved.

comparable with regard to amount and duration of formula feeding.

Follow-up rate at 6, 12 and 18 months was 100% (141), 99% (139) and 97% (137) with 0 drop-out in the breastfed group and 1 in each of the 2 formula groups at 12 and 18 months.

Development of CMPA/CMPI

A total of 5 (3.6%) infants developed CMPA/CMPI during the first 18 months of life. One belonged to the group who were exclusively breastfed, 1 to the Nutramigen group and 3 to the Profylac group but one of the latter also had Nutramigen. None of these five patients had symptoms when ingesting Nutramigen or Profylac either before or after verification of the diagnosis. Table 5 shows data concerning nutrition and symptoms in these five infants. They all had onset of symptoms before the age of 6 months and 4 of them were diagnosed before 1 year of age. Patient 5 had a coincidental infection at the first milk challenge and therefore CMPA/CMPI was not diagnosed until she was 15 months old. Patient number 3 only had late reactions from the gastrointestinal tract with symptoms of exclusive breastfeeding. His mother reported identical symptoms at 3 challenges, but unfortunately we never succeeded in examining him when he had symptoms. The remaining 4 patients all underwent controlled challenges. Patient 1 was exclusively breastfed and had symptoms when breastfed. Patient 2 was exclusively breastfed until the age of 18 weeks when she started having supplements of Profylac without any problems. At the age of 5½ months she developed urticaria immediately after intake of a little ice cream, but tolerated Profylac and mother's milk, the latter without her mother being on a

Table 6. CMPA/CMPI in high risk (HR) infants with and without dietary preventive measures.

	Number of HR infants		
	Total	Follow up at 18 mo	No(%) with CMPA/CMPI
Non-prevention group			
Municipality of Odense 1985	75	75	15 (20%)
Prevention group			
Municipality of Odense 1988	72	72	4 (5.6%) $p>0.02$
Odense and Viborg 1988	141	137	5 (3.6%) $p>0.0005$

milkfree diet. Patient 3 had supplements of Profylac, as well as Nutramigen, during the first week of life but apart from this he was breastfed exclusively. During the first week of life Patients 4 and 5 had supplements of Profylac and Nutramigen, respectively; later on they were breastfed exclusively and had symptoms on breastfeeding when their mothers ingested cow milk proteins in the diet. Apart from Patient 3 the all had a positive skin prick test or specific IgE to cow milk indicating an IgE mediated reaction.

In the municipality of Odense 75 high-risk infants, defined as in the present study, were born in 1985 and of these infants 20% ($n=15$) developed CMPA/CMPI. None of these high-risk infants from 1985 were recommended any allergy preventive measures. Table 6 shows that significantly fewer, namely only 5.6% ($n=4$) of the subgroup, consisting of 72 identically defined high-risk infants from the same area, included in our prevention group from 1988, and strictly following the dietary measures, developed CMPA/CMPI compared with the non-prevention high-risk infants from 1985. Of the total prevention group from 1988, 3.6% developed CMPA/CMPI.

None of the infants in the prevention group developed reactions against other foods during 18 months follow-up. None of the infants who dropped out during the study developed CMPA/CMPI.

Table 7. Number of infants with non-food related atopic symptoms 0-18 months of age.

	Breast	Nutramigen	Profylac	Total
Total number	20	59	62	141
Follow-up at 18 mo	20	57	60	137
Any symptoms	3 (15%)	15 (26%)	20 (33%)*	38 (28%)
Recurrent wheezing	1 (5%)	6 (11%)	9 (15%)	16 (12%)
Atopic dermatitis	1 (5%)	4 (7%)	10 (16%)	15 (11%)
Abdominal colic	0	4 (7%)	5 (8%)	9 (7%)
Diarrhoea	1 (5%)	0	1 (2%)	2 (1%)

* Inclusive 3 infants who had both Nutramigen and Profylac.

Non-food-related atopic symptoms

Table 7 shows the cumulative incidences of other possible, but not food-related atopic symptoms during the first 18 months of life. A total of 38 (28%) infants had one or more of the symptoms: recurrent wheezing, atopic dermatitis, colic or diarrhoea. Food reactions were excluded by elimination/challenge procedures. No significant differences between the three groups were noted and in total 12% had recurrent wheezing, 11% atopic dermatitis and 7% infantile colic. Six of the infants in the Profylac group and 2 in the Nutramigen group had onset of atopic dermatitis before they ever had Profylac or Nutramigen. None had other possible atopic symptoms than the above mentioned.

Acceptance and side effects

Three infants refused ingestion of Nutramigen from the age of 4½ months, until then two of them were solely breastfed and never bottle-fed. Another three had problems with diarrhoea and another one had abdominal colic and diarrhoea due to Nutramigen, proven by elimination/challenge with Nutramigen. No symptoms at ingestion of Profylac.

One infant refused ingestion of Profylac at 24 weeks of age, until then she was exclusively breastfed and never tried to be bottle fed. Furthermore, one infant randomized to Profylac had both Profylac and Nutramigen during the first week of life due to misunderstandings when admitted to the department of pediatrics for a short period. During the study period all infants gained weight and increased length and head circumference normally according to Swedish growth charts (18).

Discussion

In prospective studies the effect of dietary allergy prevention has only been demonstrated in high-risk infants, i.e. infants with at least one first degree relative (parent or older sibling) with documented atopic disease. Breastfeeding in combination with avoidance of cow milk and solid foods for at least 4 months have resulted in a significant reduction of the incidence of atopic dermatitis and food allergy, especially CMPA/CMPI during the first 2–3 years of life (19–22). Generally, early introduction of solid foods in high-risk infants is associated with a higher incidence of atopic dermatitis in the first years of life (20–23). Some studies indicate that the preventive effect of breastfeeding on development of atopic dermatitis may be enhanced by maternal avoidance of potent food

allergens like cow milk, egg and fish during the lactation period (7, 24, 25).

In previous prospective randomized studies (6–9, 11–14, 26) on high-risk infants the use of hypoallergenic formula in combination with avoidance of solid foods for at least 4 months, showed a significant reduction of the incidence of atopic dermatitis and food allergy during 1–2 years of life. In one study (9, 26) the cumulative prevalence of food allergy remained significantly lower at 4 years due to a lower cumulative prevalence at 1 year and 2 years, since few children developed food allergies after 2 years. In the other studies the infants were followed up for 4 months (6), 6 months (8), 12 months (12, 14) and 18 months (7, 11, 13). These studies include 3 studies on a partially hydrolysed whey formula (6, 8, 13, 14) and 4 studies on extensively hydrolysed formulae, 2 on a casein hydrolysate (7, 9, 26), one on a casein hydrolysate or an ultrafiltrated whey hydrolysate (11) and one study on a hydrolysate of soy and beef collagen (12). In one of the latter studies (9, 26) the dietary intervention also included maternal avoidance of highly allergenic foods during the last trimester of pregnancy and during the first 1–2 years of life. In another study (12) dietary intervention also included maternal avoidance of highly allergenic foods during lactation, and infant avoidance of highly allergenic foods up to the age of 12 months.

To evaluate the possible allergy preventive effect of different preparations of hypoallergenic formula properly controlled, randomized and observer blinded studies of well-defined really high-risk infants should be conducted for a sufficient period, not only describing "atopic symptoms", but well-defined atopic disease, and in case of food allergy the diagnosis should be based on controlled elimination/challenge studies. Documentation for confoundings (e.g. introduction of solid foods and parental smoking) is mandatory.

Most studies of the effect of allergy prevention programmes deal with infants with single predisposition to allergic disease (3, 6–9, 13, 26). Two recent studies only included infants with allergic disease in at least two first-degree relatives (14) and/or one first-degree relative combined with cord blood IgE ≥ 0.5 kU/l (11, 12). Due to our definition of high-risk infants present study only included infants with a very high risk of developing atopic disease.

Diagnostic criteria differ considerably in the published studies. Some describe the development of possible atopic symptoms rather than specific atopic disease. The development of CMPA/CMPI has been evaluated in 4 studies based on elimination/challenge procedures (6, 9, 11, 14). In a previous study (11) we found a significant reduc-

tion in the cumulative incidences of atopic symptoms from 74% to 32% and food allergy/intolerance from 17% to 6% until 18 months of life. In the present study we found a significant lower cumulative incidence of CMPA/CMPI until 18 months at 3.6% compared to 20% in an identical defined birth cohort of high-risk infants born in the municipality of Odense during 1985. Also when comparing only infants from exactly the same area a significant reduction from 20% to 5.6% was found. In one boy the diagnosis was not verified sufficiently, but as he belonged to the prevention group we chose to include him in order not to underestimate the incidence in this group. In a previous controlled, randomized study (9) of 288 infants with single atopic predisposition a significant reduction was found in the cumulative prevalence of food associated atopic dermatitis, urticaria and/or gastrointestinal disease from 16.4% to 5.1% in a control group compared to a prevention group and in the latter group none developed CMPA/CMPI. In that study the prevention group was fed breastmilk and/or Nutramigen the first 12 months of life, solids foods were first introduced at 6 months and cow milk and other hyperallergenic foods were avoided the first 12 months of life. The two studies are not quite comparable but the results are concordant. In another recent prospective, randomized study of 67 infants with atopic predisposition in two first-degree relatives (14), feeding a partially hydrolysed whey hydrolysate (Nan-HA) compared with a conventional adapted formula for 6 months also reduced the incidence of CMPA/CMPI significantly from 42.8% (15/35) to 15.6% (5/32) at 12 months of age. These incidences seems rather high, and 2/5 with CMPA/CMPI in the prevention group had reactions against the partially hydrolysed whey formula Nan-HA whereas none of the infants on extensively hydrolysed formulae in previous (9, 11) or the present studies developed CMPA/CMPI against these products. Apparently, more high-risk infants seem to develop CMPA/CMPI on partially hydrolysed formula than on extensively hydrolysed formulae (9, 11). Although the definition of high-risk infants seems to be comparable in the mentioned studies, one should be cautious to compare these results, because of differing study designs and procedures.

It is a disadvantage that our control group (from 1985) and prevention group (from 1988) were not from the same year, but due to ethical reasons (refusal by parents) it was not possible to allocate high-risk infants from 1988 to a cow milk formula fed control group. Consisting of 1 year birth cohorts of high-risk infants our prevention group and control group were comparable as regards season

of birth and environmental seasonal variations. No differences were noted concerning air pollution, heating of the houses (central heating in almost all houses) and pollen counts from 1985 to 1989. These factors may influence the development of allergy against inhalant allergens, but it is most unlikely that this difference should be the only explanation for the reduction in the incidence of CMPA/CMPI. During recent years most parents and doctors are getting more aware of atopic diseases and possible preventive measures. This might only cause a better compliance to an allergy prevention programme thus possibly enhancing the preventive effect of the programme. Moreover, this difference in year of birth seems to be a problem also in other studies as they include children over several years (9) or do not inform about the inclusion period (6–8). Apart from the year of birth and the allergy prevention programme the two high-risk groups were comparable as regards atopic predispositions, sex, season of birth, social status, daycare outside home, housing conditions, exposure to passive smoking at home and having pets at home or not. All the infants from both birth cohorts were identically defined and followed prospectively by the same pediatricians using the same diagnostic criteria.

Some previous studies compared the allergy preventive effect of different dietary regimens including breastfeeding (with and without maternal diet during pregnancy and/or lactation) and/or an extensively hydrolysed casein formula with soy formula (7, 8) and a partially hydrolysed whey formula with exclusively breastfeeding (6) and soy formula (13). Feeding soy formula showed no effect (7, 8, 13), but feeding an extensively hydrolysed soy and collagen product (12) also showed effectiveness in reducing the cumulative incidence of atopic symptoms including food related reactions during the first year of life. None of the existing studies compare the allergy preventive effect of the different preparations of hydrolysed, hypoallergenic formulae and the present knowledge does not allow any conclusion on the general preventive use of partially hydrolysed hypoallergenic formula.

The present study is a prospective, controlled and randomized, but not blind, study of a birth cohort of well-defined, high-risk infants using well-defined diagnostic criteria. The taste and appearance of Nutramigen and Profylac (and breastmilk) are rather different and the taste and appearance of Nutramigen were well known. It was impossible to avoid that the parents knew which of those two formulae they used and to avoid "leaks" of this information to the investigators. Thus, a reliable blinding of this study could hardly be performed. It

is not possible to randomize infants to breastfeeding, but the infants were at birth randomized to either Nutramigen or Profylac in case breastfeeding was insufficient or not possible. Not unexpectedly, the group of infants breastfed exclusively was less exposed to maternal tobacco smoking, but otherwise the three groups were comparable as regards sex, heredity, environmental factors and introduction of solid foods. A high proportion of the infants were breastfed, but only a minority were exclusively breastfed for 6 months or more. The majority of infants were partially breastfed with supplements of formula in varying amounts and only few infants were formula fed exclusively for 26 weeks. The infants in the two formula groups were fed formula exclusively or partly in an equal number of weeks. Few of these high-risk infants developed atopic symptoms and only 5 developed CMPA/CMPI. As one of these had both Nutramigen and Profylac they were distributed equally in the three groups. According to the results there does not seem to be reasonable risk of type 2 error as regards the Nutramigen group compared to the Profylac group. Due to the small number of exclusively breastfed infants there might be a risk of type 2 error when comparing this group with the formula groups. The infants developing CMPA/CMPI were all mainly breastfed and only had minor amounts of formula, 4 of them had symptoms on breastfeeding. Intake of cow milk protein was not registered in any these 4 infants before onset of symptoms, and it is noteworthy that they developed CMPA/CMPI at all. However, even a very small amount may be enough for sensitization (2) and they might have had cow milk protein without their parent's knowledge. In fact, one of the infants had onset of symptoms (urticaria) when she tasted her mother's icecream at 5½ months of age and it hardly can be totally excluded that she ever before tasted anything with cow milk proteins. Moreover, reactions to milk-contaminated "non-dairy" products in patients with CMPA/CMPI are described (27) and a possibility of inhalation of sensitizing milk proteins may exist. In contrast to another study on partially hydrolysed whey (14), none of the infants developed CMPA/CMPI when fed Nutramigen or Profylac, and none had reaction against these products. None of the infants developed CMPA/CMPI after the age of 6 months, and thus it seems that this diet period of 6 months is sufficient to prevent CMPA/CMPI as far as possible until the age of 18 months.

We conclude that feeding breastmilk, an extensively hydrolysed casein formula (Nutramigen) or an ultrafiltrated whey hydrolysate (Profylac) combined with avoidance of solid foods during the first 6 months of life in high-risk infants significantly

reduced the cumulative incidence of CMPA/CMPI during the first 18 months of life. No difference was noted whether the infants were fed breastmilk, Nutramigen or Profylac and a diet period of 6 months seems sufficient. Both formulae were well tolerated and accepted by the infants.

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