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Intolerance to hydrolysed cow's milk proteins in infants: clinical characteristics and dietary treatment

A. CARROCCIO*, F. CAVATAIO†, G. MONTALTO*, D. D'AMICO†, L. ALABRESE† and G. IACONO†

**Medicina Interna, Università di Palermo, †II Divisione di Paediatria, Ospedale 'Di Cristina', Palermo, Italy*

Summary

Background Multiple food intolerance in infants, including intolerance to extensively hydrolysed proteins (HP), is often difficult to treat. However, few data have been reported on clinical outcome and dietary treatment of these patients.

Aims To evaluate the clinical characteristics of patients with HP-intolerance and the long-term outcome of treatment with ass' milk.

Patients and Methods This study included 21 HP-intolerant infants (15 males, median age at diagnosis 2 months) treated with an ass' milk-based diet and 70 cow's milk (CM) intolerant infants (40 males, median age at diagnosis 3 months) treated with casein hydrolysate milk-based diet. All patients were followed-up for a median period of 4 years. Both HP-intolerance and intolerance to other foods were diagnosed according to the double-blind placebo-controlled procedure. Formal CM-challenges were conducted at yearly intervals until tolerance was demonstrated. At diagnosis and after one year of the respective diets, the following growth parameters were determined: relative weight for sex and age, relative weight for height and height z-score.

Results During the study period, multiple food intolerance was documented in 21/21 HP-intolerant infants (ass' milk group) and in 20/70 infants with CM-intolerance but tolerating HP (casein hydrolysate group) ($P < 0.0001$). In the ass' milk group, the more frequent food intolerances were toward soya, oranges, tomatoes and fish; goat's milk intolerance was demonstrated in five out of six patients receiving this food, and sheep's milk derivatives intolerance in four out of seven; these patients tolerated ass' milk. During the study period 3/21 patients in the ass' milk group became ass' milk intolerant; they showed vomiting (one cases) or diarrhoea (two cases). A lower percentage (52%) of patients in the ass' milk group became CM-tolerant during the study period than in the casein hydrolysate group (78%) ($P < 0.01$) and the age of the children at CM-tolerance was higher in the ass' milk than in the casein hydrolysate-treated children ($P < 0.05$). At diagnosis, a higher frequency of cases with elevated serum total IgE and specific IgE to CM antigens ($P < 0.01$) was observed in the ass' milk group. No difference was recorded between the two treatment groups in any of the growth parameters considered either at diagnosis or during the follow-up.

Conclusions HP-intolerant patients showed a higher frequency of persistent food intolerance and of multiple food intolerance than patients tolerating casein hydrolysate. Ass' milk feeding was confirmed as a safe and valid treatment of the most complicated cases of multiple food intolerance.

Keywords: Ass' milk, cow's milk protein intolerance, multiple food intolerance, soy, casein hydrolysate, growth

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Correspondence: A. Carroccio, via Coffaro 25, 90124 Palermo, Italy.

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Introduction

Cow's milk intolerance (CMI) is a very frequent problem in infants as it involves between 2% and 7.5% of the general population [1–3]; in these patients a cow's milk free (CM-free) diet often resolves symptoms, although some infants can present intolerance to the foods used instead of cow's milk [4–6]. These cases of multiple food intolerance are often difficult to treat because when the most common foods are eliminated from the diet, the infants may be at risk for malnutrition. In the present study we report the clinical characteristics of infants intolerant to extensively hydrolysed cow's milk protein and review our experience in the use of ass' milk in the treatment of multiple food intolerance [7].

Patients and methods

This is a retrospective study including all the patients with hydrolysed protein intolerance treated by us with a CM-free, ass' milk based-diet and subsequently followed-up at our outpatients clinic for at least 1 year. The composition of ass' milk compared with human and cow's milk has been previously published [7]. Patients were recruited between January 1990 and December 1996 and CMI and subsequent multiple food intolerance were always diagnosed in our hospital, according to the double-blind placebo-controlled food challenge method in the majority of patients. Infants with disaccharide intolerance and breast-fed infants were not included. In this way, 21 infants (15 M, 6 F; age range 10 days-9 months, median 2 months) were included in the present study. After CMI diagnosis, all patients were treated with a casein hydrolysate (CH) formula (Nutramigen, Mead Johnson, Nijmegen, The Netherlands). As the patients subsequently showed intolerance to the new milk formula, they were put on an ass' milk-based diet. After commencement of this milk diet, the infants underwent outpatient visits every 2–3 months; visits included a complete physical examination, growth assessment (weight and height measurements) and accurate recording of the dietary habits of the patients. Furthermore, after 1 year of ass' milk-based diet, routine haematochemical analysis was performed in all children, including kidney and liver function tests, serum haemoglobin and albumin assays. The results of outpatient visits and laboratory data were recorded on individual clinical charts. All patients were followed for a median period of 4 years (range 1–8 years).

As controls we chose the data of the clinical charts of 70 patients with CMI, diagnosed in our hospital between 1990 and 1996, and treated with CH milk formula (Nutramigen). These patients were sex-age-matched with those on ass' milk diet and underwent a clinical follow-up with the same methods and frequency as described above.

Cow's milk and casein hydrolysate formula intolerance diagnosis

CMI was suspected if one or more of the following symptoms appeared on cow's milk diet and subsequently disappeared on CM-free diet: diarrhoea, bloody diarrhoea, vomiting, dermatitis, colic (fits of crying lasting more than 3 h/day, starting during or after feeding), regurgitation, food refusal of more than 50% of daily normal feeding, wheezing, constipation, failure to thrive, urticaria, shock. After we suspected CMI, cow's milk protein was excluded from the diet and a CH-milk formula was started. However, the onset of a new symptom or the persistent severity (or worsening) of one or more of the following symptoms, after 1–4 weeks of CH-milk diet, was considered indicative of CH-milk intolerance: bloody diarrhoea (10 cases), vomiting (10 cases), diarrhea (nine cases), atopic dermatitis (eight cases), food refusal with failure to thrive (six cases), regurgitation due to gastro-esophageal reflux (six cases), colic (five cases). In these cases, also CH-milk formula was suspended and an ass' milk-based diet was started. After 1 month of elimination diet, when the patients were well, in the majority of patients we performed a double-blind challenge in hospital, according to the method previously described [8–10]. In brief, the challenges were performed using ass' milk with added CH-milk powder or a placebo formula containing exclusively ass' milk. The challenge sequences were randomized by a computer generated method so that both parents and doctors were unaware of the nature of the challenge formula. The challenge was begun with an initial quantity of 5 mL and reached the total equivalent of a full feed in 3 h. If no reaction was observed, after 24 h the patients were discharged and continued the challenge at home, using several blinded feeds of milk coded A or B. The challenge period lasted 1 week for both the placebo and the CH-formula; during this period, the parents recorded any clinical symptoms. If a clinical reaction occurred, the challenge was stopped and the patients were re-examined in hospital. In the cases presenting CMI symptoms considered as not 'classical' — regurgitation owing to gastroesophagral reflux and colic — more than one diagnostic challenge was performed according to the procedures previously described [11,12].

Furthermore, one or more of the following laboratory examinations were positive at the diagnostic CM-challenge: increase in circulating polymorphonuclear leucocytes greater than 3,500/mm3 (6 h after CM-challenge), eosinophils in the faecal or nasal mucus, occult blood in stools. Microbiological examinations of the stools showed no pathogenic germs in the patients with diarrhoea. Finally, in some patients included in the present study [21/91] the CM-challenge was open and not placebo-controlled. In these cases, CMI diagnosis was confirmed by the histology

of the intestinal mucosa at the ligament of Treitz; in fact, the intestinal biopsy, performed according to the procedure previously described [13], was normal immediately before the challenge, whereas 24 h after the ingestion of cow's milk, the mucosa appeared damaged with a partial atrophy of the villi and a lymphocyte infiltration of the lamina propria.

Diet treatment

After CMI or CH-intolerance diagnosis the unweaned infants were fed with ass' milk or CH-milk (in the respective groups) at a dose ranging between 210 and 250 mL/Kg/day. As previously reported [7], ass' milk was supplemented with MCTs at a daily dose of 40 mL/L of milk to increase its caloric value. After the age of 4 months, cereal flours, olive oil and lamb were carefully introduced into the diet. In infants with CMI diagnosed after weaning, cow's milk and its derivatives were excluded from the diet and ass' milk plus MCTs (or CH-based milk) were administered at the same daily amount as cow's milk had been previously. Together with CM, many other foods were initially excluded from the diet and the allowed foods were those thought to be less allergenic: lamb, rice, carrots, sugar, pears, apricots and, obviously, ass' milk. Other foods were subsequently introduced into the diet with great caution, according to the method described below. Both in the ass' milk and CH-milk groups, daily calorie intake ranged between 100 and 120 calories/kg body weight.

Adverse reaction to non-cow's milk food

In all the study patients new foods were introduced with great care. Each food was introduced singly, at least 15–20 days after the introduction of a previous new food. If after the introduction of a new food the parents observed symptoms, the infant was examined in hospital and the food excluded from the diet. If the symptoms disappeared during the elimination diet, a challenge was performed in hospital, using the method described for the CM-challenge, to confirm that the food in question had caused the intolerance.

Nutritional status evaluation

On diagnosis and after one year of ass' milk-based diet, the following anthropometric variables were determined: body weight, height and weight/height ratio. Relative weight for sex and age was used to monitor weight increases, i.e. percentage of the median weight for sex and exact age. Relative weight for height was the percentage of the median weight for sex and height. Linear regression between 1 year age points and 10-cm height intervals was used to obtain exact age and height reference points. Heights were standardized for sex and exact age in computing the height Z-score [= (observed height − mean height for sex and age/standard deviation for sex and age]. As previously described [14], Italian Regional Standards were used as reference values. Measurements were all made by the same author (F.C.) and the height of the patients was measured in a supine position, using the same procedure each time in the individual patients.

Routine chemical laboratory tests were performed using commercially available kits.

CM-tolerance evaluation

Formal challenges were conducted in our hospital at yearly intervals until tolerance was demonstrated. When there were no clinical reactions to the challenge, the patients were left on a free diet and followed up for one month with more frequent examinations to observe any eventual delayed manifestations. After a further 6 months of observation, patients who demonstrated CM-tolerance on challenge and were tolerant to all foods tested were discharged to the care of their family practitioner.

Laboratory examinations

A series of immunological tests were performed both at first diagnosis of CMI and at the end of the study. In particular, at diagnosis serum levels of total IgE were assayed and RASTs were performed to whole cow's milk, beta-lactoglobulin, alpha-lactoalbumin and casein. At the end of the study these tests were repeated and RASTs performed also for other food and environmental allergens. In addition, skin prick tests were carried out with food and environmental antigens.

Serum levels of total IgE were assayed using a commercial Kit (Phadebas IgE paper radio-immunosorbent test Kit, Pharmacia Diagnostics, Uppsala, Sweden); the upper normal limit for serum IgE varied according to age-dependent cut-offs (for each age class the cut-off was equal to the mean value + 2 SD observed in our laboratory in healthy infants of the same age range). IgE antibodies to specific antigens were measured with the Phadebas RAST assay (Pharmacia Diagnostic) and expressed as PRU/mL; values greater than 1.43 PRU/mL were considered positive. Skin prick tests (PRICKs) were performed using a commercial Kit (Lofarma Diagnostic, Milan, Italy); any weal diameter that exceeded that of the control and was more than one fourth the size of the histamine weal was regarded as positive (a planimeter was used to measure the area of the papule).

The infants' parents gave their informed consent to all the diagnostic and therapeutic procedures described in this study.

Table 1. Clinical characteristics of 21 casein hydrolysate intolerant-patients treated with ass' milk-based diet and of 70 CMI-patients treated with casein hydrolysate (CH)-milk-based diet

	Ass milk group	CH-milk group
Sex (M/F)	15/6	40/ 30
Age at CMI diagnosis (range and median)	10 days-9 months (2 months)	20 days-10 months (3 months)
Family history of atopy	9/21	20/70
Associated atopic diseases	5/21	7/70
Symptoms at CMI-diagnosis		
Diarrhoea	9	41
Vomiting	14	40
Colic	5	17
Regurgitation due to GER	6	20
Dermatitis	10	16
Bloody diarrhea	12†	16†
Failure to thrive	6	15
Number of patients becoming CM-tolerant	11*	55*
Age at achieving CM-tolerance (in years)	range 1–4, median 3**	range 1–4, median 1**

*$P < 0.01$ (Fisher test); †$P < 0.01$ (Fisher's test); **$P < 0.05$ (Mann–Whitney *U*-test).

Statistical analysis

Fisher's exact test was used to compare the frequencies. To compare anthropometric data, we first determined whether the distribution of values permitted the use of a parametric or nonparametric test using Shapiro's test; in the former case Student's *t*-test was used, in the latter the Mann–Whitney *U*-test (for intergroup comparison) or the Wilcoxon-rank sum test (for intragroup comparison).

Results

Table 1 shows the clinical characteristics of the patients in both groups. The two groups did not differ as regards sex and age at CMI diagnosis; family history of atopic disease in one of the first degree family members and the appearance of an associated atopic disease were more frequent in the patients included in the ass' milk group, but these differences were not significant. In particular, as regards atopic diseases, during the follow-up study period we observed four cases of bronchial asthma and one case of allergic rhinitis in ass' milk treated patients and four cases of asthma and three cases of rhinitis in CH-milk-treated patients. These patients had positive RASTs and PRICKs for one or more of the most common environmental allergens (eight cases for acari, seven cases for parietaria, four cases for cat's fur). As regards presenting symptoms at CMI diagnosis, only the frequency of bloody diarrhoea was significantly higher in ass' milk group than in CH-milk group ($P < 0.01$). Furthermore, in the ass' milk group we observed a lower number of subjects who became CM-tolerant during the study period than in the CH-milk group, and the age of the children at CM-tolerance was higher in the ass' milk-treated than in the CH-milk-treated children.

Table 2 shows the reported incidence of adverse reactions to foods in the patients of both groups. It is evident that multiple food intolerance was more frequent in the ass' milk

Table 2. Comparison of reported incidence of common adverse reactions to foods in ass' milk treated and casein hydrolysate (CH)-milk treated patients (total number of patients reacting to each food compared with total number exposed to food)

	Ass' milk	CH milk
CM alone	0/21	50/70
Eggs	8/21	4/65
Soy milk	16/16	10/32
Oranges	12/21	3/60
Wheat	6/21	6/70
Fish	13/18	4/60
Tomatoes	14/21	5/70
Casein hydrolysate	21/21	0/70
Peanuts	4/7	1/15
Beef	8/15	4/70
Chicken	10/22	2/70
Bananas	12/20	3/60
Cocoa	3/8	5/38
Goat's milk	5/6	6/15
Sheep's cheese	4/7	2/9
Ass' milk	3/21	0/0

Table 3. Immunological data at diagnosis and at the end of the study in 21 CMI infants intolerant to CH-formulas (ass' milk group) and in 70 CMI infants tolerant CH-formulas (CH-milk group)

	Ass' milk group	CH-milk group	*P*-value
At diagnosis			
Number of cases with elevated serum IgE	13/21	20/70	0.02
Range and median IgE values (IU/mL)	8–213 (52)	6–191 (19)	0.008
Number of cases with RASTs positivity to CM antigens	14/21	21/70	0.006
Range and median RASTs values (PRU/mL)	0–26 (10.3)	0–18.3 (0)	0.009
At end study			
Number of cases with elevated serum IgE	6/21	8/70	0.11
Range and median IgE values (IU/mL)	4–204 (20)	6–171 (8)	0.17
Number of cases with RASTs positivity to CM antigens	5/21	6/70	0.13
Range and median RASTs values (PRU/mL)	0–22.4 (0)	0–20.4 (0)	0.31

These values were considered elevated: IgE (kallikrein units/L) age-dependent cut-offs (see 'method' section); RAST > 1.43 PRU/mL.

than in the CH-milk group (21/21 vs. 20/70; $P < 0.0001$). In particular, in the casein hydrolysate intolerant patients (ass' milk group), all the subjects who attempted to eat soy milk developed intolerance to this protein source; furthermore, in this group, five out of six patients showed intolerance to goat's milk and four out of seven showed intolerance to sheep's milk derivatives. Finally, 3/21 patients in the ass' milk group developed intolerance to ass' milk: one infant began to suffer from vomiting at the age of 9 months, and two showed diarrhoea at the age of 6 and 8 months, respectively. In these three cases a double-blind placebo-controlled challenge confirmed the diagnosis of ass' milk intolerance. They tolerated a diet based on rice, chicken and olive oil and symptoms disappeared on this diet treatment.

Table 3 shows immunological data of the study subjects at diagnosis and at the end of the study. At the diagnosis, IgE-associated CMI was more frequent in the casein hydrolysed intolerant patients (ass' milk group) than in the CH-milk group; this is also confirmed by the higher frequency of RASTs positivity for milk antigens; furthermore, serum IgE and RASTs values were significantly higher in the casein hydrolysed intolerant patients than in the CH-milk group (Mann–Whitney *U*-test). At the end of the study the frequency of positive serum IgE and RASTs for milk antigens was lower than that observed at CMI diagnosis in both groups; furthermore, in the casein hydrolysed intolerant patients the frequency of positive serum IgE and RAST for milk antigens remained higher than in CH-tolerants, but the difference was not statistically significant.

The skin prick tests for milk antigens, performed only at the end of the study, were positive in 5/21 CH-intolerant cases and in 7/70 CH-tolerant subjects (difference not significant; $P < 0.2$).

Table 4 shows growth data in the ass' milk-treated and CH milk-treated patients at diagnosis of CM-intolerance, after one year of the respective diets. No statistically significant difference was observed between the two group either at baseline or during the subsequent follow-up. However, intragroup comparison showed that after one year of the ass' milk diet period there was a highly significant increase in all the parameters considered. The same trend was observed in the CH-milk-treated group. Daily calory intake was similar in the two groups after one year of CM-free diet: mean (95% c.i.) kCal/kg body weight 115[100–132] in the ass' milk group and 112[102–140] kCal/kg b.w. in the CH-milk group.

Table 4. Relative body weight for age, relative weight for height (W/H) and height Z-score in the ass' milk and casein hydrolysate (CH) milk-treated patients, at CM intolerance diagnosis and after one year of CM-free diet

	At diagnosis	At 1 year
Ass' milk		
Weight range (%)	36–90*	70–150*
median	65	105
Height Z-score range	−3.21/+1.03*	−0.88/+1.74*
median	−0.65	+0.53
W/H range (%)	67–120**	92–107**
median	80	98
CH-milk		
Weight range (%)	40–96*	65–120*
median	63	90
Height Z-score range	−3.344/+1.18*	−1.05/+1.98*
median	−0.70	+0.39
W/H range (%)	61–103*	96–121*
median	78	105

*P-value < 0.0001; **P-value < 0.0005.

All haematochemical laboratory tests were within normal limits after 1 year in both groups.

Discussion

CM-intolerant patients often show intolerance to other foods; in particular both soy milk [1,2,15] and casein hydrolysate-based milk [16–20] can be responsible for food intolerance. When multiple food intolerance is diagnosed, a period of total parenteral nutrition is often necessary and subsequently breast feeding is considered the safest method of realimentation [21]; however, if breast-feeding is not possible, alternative food sources must be found. In the rural centres of our country asses are still reared by farmers and this allowed us to attempt to re-feed the infants with multiple food intolerance using ass' milk and we had already reported that it was useful and safe [7].

In the present study, we reviewed the long-term outcome of the ass' milk-based diet, focusing our attention on its nutritional value. It is noteworthy that we evaluated the use of ass' milk in patients intolerant to an extensively hydrolysed protein formula. Intolerance to hydrolysed protein formulas, in fact, has been considered in the past years a very rare event but recent reports have hypothesized that it might not be uncommon [22]; however, very few data have been published about the natural history of CMI subjects also intolerant to hydrolysed protein milk formulas. In this respect, our retrospective study seems to demonstrate that the patients intolerant to extensively hydrolysed casein formula had a more severe clinical picture than the CMI-subjects successfully treated with CH-formulas. In fact, only 11/21 (52%) of the CH-intolerant patients included in this study achieved CM-tolerance at the end of the study, after a median follow-up period of 4 years, whereas 55/70 (78%) of CH-tolerant patients became CM-tolerant at the end of the study ($P < 0.01$). Furthermore, the CH-intolerants achieved CM-tolerance at a median age significantly older than the CH-tolerant patients. The higher hypereactivity of CH-intolerant subjects also seems to be confirmed by the higher frequency of multiple food intolerance that they exhibit compared with CH-tolerant patients. In general, we could hypothesize that the intolerance to extensively hydrolysed protein demonstrated in these patients is the sign of an elevated reactivity which is the basis of a more prolonged and severe food intolerance history. However, as we have reported data of a retrospective study involving a relatively small group of CH-intolerant infants, no definite conclusion can be reached and further prospective studies involving a large cohort of CH-intolerant patients are needed to confirm our observations.

The immunological data of our patients showed that at CMI diagnosis two thirds of the CH-intolerant patients had elevated levels of serum IgE. Furthermore, in these patients we observed a higher frequency and more elevated levels of total serum IgE and specific IgE to milk antigens than in the CH-tolerant subjects.

As regards the efficacy and the safety of ass' milk, we can note that in the subjects treated with this diet, weight and height were satisfactory and the more common haematochemical nutritional parameters were within normal limits after 1 year of CM-free diet. Furthermore, we did not observe any difference in growth parameters during the follow-up period between the ass' milk group and the CH-milk treated group; this result is very relevant as in the CH-milk group only 20/70 patients showed multiple food intolerance, whereas all infants treated with ass' milk had multiple food intolerance and this greatly limited food choice. As regards the foods involved in multiple food intolerance, the frequency of clinical reactions we observed is similar to that previously reported [9,20,23]; furthermore, we must underline that in patients tolerating ass' milk, we observed intolerance to goat's milk and sheep's milk derivatives; this confirms the possibility of lack of cross-sensitivity between natural milks of different origin and suggests that the ass' milk diet can be attempted also in cases intolerant to sheep or goat's milk [24]. Furthermore, this study demonstrates that ass' milk is a safe solution also in infants in whom hydrolysed-milk formulas had failed. For infants with this clinical condition, L-aminoacid-based formulas have been recently used with good results [25], also giving a satisfactory growth recovery [26]. However, we observed similar excellent nutritional results using a natural milk, ass' milk, which is certainly more palatable than the elemental formulas and is similar in composition to human milk. For the above reasons we strongly encourage ass-rearing and we are participating, as consulting physicians, in a Sicilian project to promote ass-rearing; studies on the long-term preservation of ass' milk are under way and, obviously, we will willingly give any aid to other physicians working in countries where it is not available.

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