

Natural history of cow's milk allergy. An eight-year follow-up study in 115 atopic children

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Abstract. – **Background.** Cow's milk allergy (CMA) is a disease of infancy and usually appears in the first few months of life. The evaluation of infants for possible CMA is one of the more common problems shared by pediatricians. The role of foods in determining and/or aggravating the clinical features of atopic dermatitis (AD) has been stressed in the last decades.

Objective. The aim of the present study was to investigate, in children with food related AD, the development of tolerance to the offending food(s), clinical or laboratory data to predict the development of food tolerance, and whether there are clinical or laboratory data to predict the onset of respiratory allergy.

Materials and Methods. In this prospective study we report on 115 babies, first examined at a median age of 6 months, and followed-up for 8 years. We have investigated several factors as predictive of the outcome, as follows: early onset; widespread or not-typical (reverse pattern) skin lesions, family history positive for atopy; persisting FA, high levels of total and specific IgE antibodies, association with CMA and asthma.

Results. All these parameters were significantly predictive of a long-term morbidity of AD children with CMA. The median age for tolerance to cow's milk was 7 years + 11 months, to egg 6 years + 6 months, and to wheat 7 years + 2 months. However a great number of both tolerant and intolerant children developed multiple sensitizations. Only 66 children (57%) acquired food tolerance, but there was the onset of asthma in 54% of cases.

Conclusion. The natural history of CMA is not well-known, since not many related studies have been done in children. The several predictive factors, all in a negative sense, may be the norm in atopic children. We suggest possible areas of intervention in children at risk due to parental atopy. Preventive measures may induce a dramatic improvement in children with food allergy, but we stress that the long-term prognosis is challenging, since asthma preva-

lence may increase up to 54% during a long follow-up. Therefore, the natural history of IgE-mediated AD in atopic children sensitized to several allergens may be less optimistic than generally reported.

Key Words:

Cow's milk allergy, Food allergy, Food tolerance, Natural history, Atopic dermatitis, Asthma, Children, Prognosis, Atopic march, Prevention.

Abbreviation list

AD = Atopic dermatitis
BM = Breast milk
CM = Cow's milk
CMA = Cow's milk allergy
FA = Food allergy
FH = Family history
GM = Geometric mean
MA = Median age
SCORAD = Severity scoring of atopic dermatitis
SD = Standard deviation
SPTs = Skin prick tests.

Introduction

The natural history of cow's milk allergy (CMA) in children is not well-known, since several widely discussed genetic and environmental factors can influence the development of atopic disease¹⁻⁵, also due to conflicting reports including different selection criteria, study design and data presentation, variations in patient selection. Differences may depend on whether the study group consists of in-

fants at risk or unselected children, their age when studied, or the study is prospective or retrospective⁶⁻³⁶.

We have explored the natural evolution of CMA, associated or not with atopic dermatitis (AD) in 88 children, a median age of 36 months, and a very high incidence of positive family history (FH). They were affected with food allergy (FA), as demonstrated by skin prick tests (SPTs) and/or RAST positive against the offending food(s) and positive responses to the elimination diets and challenge tests³. In this prospective study all children have been followed-up to evaluate the achievement of tolerance to the causative agent(s). At the final follow-up only 25/88 children (28%) tolerated the offending food, but 34/88 (38%) exhibited other sensitizations, including 10/15 children with CMA and 4/15 with egg allergy. Both tolerant and not tolerant children have developed additional sensitizations with significant statistical differences between the children who lost FA and those with persisting FA. Moreover, 15 children with CMA achieved the tolerance at an age significantly higher compared to children with allergy to other foods and 10/15 (67%) have exhibited more sensitizations, primarily asthma during the follow-up.

We can therefore affirm that CMA can be viewed as an unfavorable prognostic factor, and as a clue of a marked atopic predisposition. The persisting intolerance to the offending food was significantly associated with symptoms such as angioedema and AD singularly or variously associated³. The data are at variance with the common reports quoting that FA, in the majority of cases, improves or clears at a (very) young age^{14,17,18,31,33-35}. It is interesting to note that some foods, e.g. fish and nuts appear to induce more severe (as angioedema) and persisting clinical manifestations. This is not surprising since no child sensitive to these two foods lost food hypersensitivity³. As previously documented^{3,4}, other foods more often causing allergy are cow's milk (CM), egg, and wheat, which are among the most common foods consumed by children¹⁷, thus explaining why the AD outcome is not so optimistic as generally affirmed²⁻⁴.

In another prospective study⁷, AD was due to FA in 82% of children sensitized to CM and egg in 69% of cases, while 43% of children still had AD at the last follow-up. Tolerance to-

ward CM and egg was reached at age 4 years. In addition 54% of patients had bronchial asthma and/or allergic rhinitis (AR) during the follow-up.

The studies on AD natural history have selected numerous factors as predictive of the outcome, which partly confirm the above alluded to results, as follows: early^{34,35} or late AD onset after the 6th month of life^{7,19}; widespread or not-typical (reverse pattern) skin lesions^{7,14,15,18,19,32-35}, FH positive for atopy^{3,14,15,18,34,35}, male^{3,15} or female^{19,34,35} sex, persisting FA⁷, high levels of total and specific IgE³ directed against relevant foods¹⁷, association with CMA³⁶ a relationship between development of tolerance and symptoms and between tolerance and start of additional allergies, all with statistical significant differences^{3,7}. Positive SPTs and/or IgE antibodies to inhalant allergens at the first examination appeared to have a predictive value for the development of respiratory allergy ($p = 0.0007$)^{7,22,23}.

In the present study we report that the natural history of IgE mediated FA is less favorable than previously observed^{14,17,18,31,33-35}.

Patients and Methods

Patients

To ascertain the natural history of CMA, we have prospectively studied and followed-up for 8 years 115 children, 66 males, 49 females, aged 4-12 months (median 6.5 months) attending the Division of Allergy and Immunology of the Department of Pediatrics of the Roma University "La Sapienza" because of suspected CMA and AD. In these children, at the first visit a 4-week diagnostic elimination diet was prescribed for diagnostic purposes. CM and dairy products were avoided if AD appeared when CM was the only feeding. If AD occurred when egg and wheat were also given, these foods were avoided. Further foods were eliminated following anamnestic data. Soy-milk (SOM1, Milupa), home-made, lamb-meat based-diet, and other nutritionally adequate food equivalents were employed. An open challenge test (OFC) was done when skin lesions cleared-up. If no immediate reaction ensued, food was fed in a normal way, and the skin accurately checked

by parents. At each visit the severity of skin lesions was evaluated. On the basis of OFCs results, a therapeutic elimination diet, excluding the offending foods, was given independently of IgE and/or SPTs responses. All patients were checked every year or more frequently if necessary.

We assessed whether the babies were "at risk" of atopic disease because of a positive FH of atopy since one or both parents and/or siblings suffered from asthma, or AD, or AR.

For each child a detailed clinical history was recorded with particular reference to the additional parameters: type of alimentation at birth, including the duration of breastfeeding (if it was the case), median age (MA) at the onset of clinical manifestations (AD), and at first CM feeding, presence of skin lesions and/or respiratory allergy. The diagnosis of atopic diseases in the children was done according the following criteria: clinical history, physical examination and positive SPTs and/or RAST to the most common inhalant and/or food allergens. Informed consent was obtained from parents of each child.

Skin Prick Test

Appropriate emergency equipment and medications were available on site. Skin testing was done at baseline by the prick method by a doctor trained in allergy with the co-operation of a qualified nurse. The skin was marked with a ballpoint pen for the allergens to be tested. The babies were then tested with: histamine hydrochloride (1 mg/ml) as a positive control and isotonic saline as a negative control. We continued with a battery of food allergens, including whole CM protein, casein, lactalbumin, egg, fish, wheat, soy, *Dermatophagoides pteronyssinus*, *Alternaria alternata*, *Lolium perenne*, *Olea europea* and *Parietaria officinalis* (SARM, Roma, Italy). The diagnostic extract of each individual allergen was placed on the volar surface of the forearm as drops through which the skin was superficially pricked with a straight pin for one second. A new pin was used for each prick test and then discarded, and the drop of the extract was then wiped off about one minute after the prick²⁴.

SPTs were read at 20 minutes and considered positive as follows:

+ when the wheal was the half of the histamine wheal;

++ when the wheal was equal to the histamine wheal;

+++ when the wheal was two-fold the histamine wheal;

++++ when the wheal was more than two-fold the histamine wheal²⁵.

We took for positive only children with a +++ or ++++ reaction, that is a wheal ≥ 3 mm with an area = 7 mm² (cut-off). So we considered as positive only the children with a mean wheal diameter of 3 mm or larger than the negative (saline) control. A positive (histamine) control was performed to ensure the absence of any antihistamine drug interference²⁶.

Total IgE

The determination of total serum IgE levels was done by paper radioimmunosorbent test (PRIST, Pharmacia Diagnostics AB, Sweden), and results were given in International Units (IU)/ml, usually expressed in geometric mean (GM) with one or two standard deviations (SD).

Specific IgE antibodies and determination of specific IgE levels were measured by radioallergosorbent test (Phadezym RAST, Pharmacia Diagnostics, Sweden).

RAST results are expressed in "RAST Units" (PRU = Phadebas Rast Unit) as follows:

1st class = IgE levels < 0,35 IU/ml,

2nd class = IgE levels > 0,35 IU/ml and less than 0,7 IU/ml,

3rd class = IgE levels between 0,7 IU/ml and 17 IU/ml,

4th class = IgE levels higher than 17 IU/ml.

Only RAST results > 0.35 IU/ml were considered positive.

The diagnosis of AD was made according to Hanifin and Rajka criteria²⁷. The severity score of AD was recorded according to the SCORAD index²⁸.

For the diagnosis of asthma, 3 episodes of wheezing without fever were required.

For the diagnosis of rhinitis, nasal discharge and/or blockage occurring continuously for at least 4 weeks plus the typical pale aspect of allergic mucosa on rhinoscopy, without any sign of infective rhinitis in other relatives was required.

For the diagnosis of FA, skin, gastrointestinal, and respiratory symptoms which occurred after OFC with the offending food.

Challenge Test

At the end of the 4-6 wk period, OFCs were performed in the hospital under observation in a unit staffed to undertake emergency equipment. CM or egg were administered as follows: a drop of CM (or of emulsified raw egg, or a bit of bread) was put upon the inner border of the lower lip, and a further 5 ml of CM (or 1 ml of emulsified raw egg, or 5 g of bread) were given after 5 minutes. One-hundred ml of CM or half-boiled egg, or 100 g of bread were given after 30 minutes. The reactions were defined as immediate if the first symptoms occurred within two hours of ingesting the food antigen, and delayed if the first symptoms occurred after two hours. If any symptoms secondary to the challenge test were observed, the challenge test in the hospital was terminated. After the last administration of the tested food the children were watched for at least four hours and then discharged.

Data were statistically analyzed using the Student t and the X^2 tests. The Fisher exact test was employed when possible.

Study Trial

The following parameters were studied at the 3-years, 5-years and at the last follow-up: age; AD severity score; development of food tolerance; duration of symptoms; respiratory allergy (asthma and/or rhinitis).

Results

The clinical characteristics of the 115 children at the first examination at a median age of 6 months are outlined in Table I, mean severity score of AD was 19 (8-81), and a typical disposition of skin lesion was present in 83 babies (72%).

Association With AD

AD was associated with CMA in 97/115 children (84.3%).

Family history FH of atopy was positive in 69 children (60%) and negative in 46 (40%) ($p = 0.0024$).

Sex

There were 66 males (57%) and 49 females (43%) ($p = 0.015$).

Age(s) (Figure 1)

The MA at AD onset (median age = 3.5 months, 5 days-150 days) was before 4 months of life in 66 babies (57%) between 4 and 6 months of life in 39 (34%) and after 6 months of life in 10 (9%) (Table I) ($p = 0.0001$).

Figure 2 shows the age of the first CM formula feeding. In 37 children (32%) CM formulas were given since birth, in 51 (44.5%) within the third month of life, and in 27 (23.5%) before the sixth month of life ($p = 0.0034$). As a consequence, 78 (68%) infants were fed breast milk (BM) at birth ($p < 0.0000$), and received BM for about 3 months.

SPTs and RAST

All children had positive SPTs. SPT positivity score was $> 2+$ in 92 children (80%) (p

Table I. Clinical characteristics of the 115 children with food-related atopic dermatitis (Follow-up 8 yrs) at the first examination.

	No.	(%)
Sex		
Males	66	(57)
Females	49	(43)
$p = 0.015$		
MA at AD onset in 115 children		
Before the 4 th mo of life	66	(57)
Between the 4 th and 6 th mo	39	(34)
After the 6 th mo	10	(9)
$p = 0.0001$		
Disposition of skin lesion		
Typical	83	(72)
Not typical (reverse pattern)	32	(28)
Age at the first feeding of a CM formula		
At birth	37	(32)
Before 3 months	51	(44.5)
Before 6 months	27	(23.5)
$p = 0.0034$		

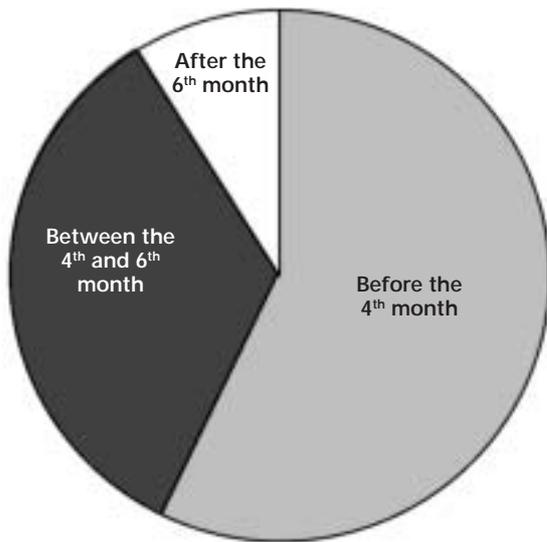


Figure 1. MA of AD onset in 115 children followed-up 8 years, $p = 0.0001$.

= 0.0001). In detail, SPTs were positive to CM in 98 infants (85.7%), to egg in 109 (95%) and to wheat in 11 (9.5%). Seven babies with no CMA and 6 with no egg allergy had positive SPTs to CM and egg, respectively. Moreover, 36 children (31%) were positive to inhalant allergens, and 24 (21%) had multiple sensitizations to food and inhalant allergens.

RAST results for CM/other foods were of second class in 11/115 (10%), third class in 21 (18%), fourth class in 69 (60%) and 14 (12%)

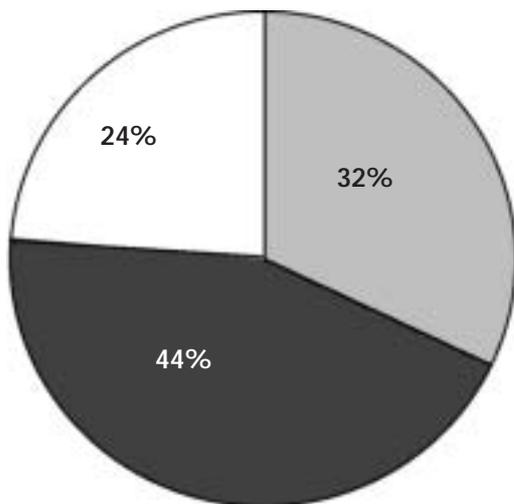


Figure 2. Age at the first feeding of a CM formula in 115 children followed-up 8 years, $p = 0.0034$.

had a negative/first class RAST at the first testing ($p = 0.0001$).

Total Serum IgE Levels

Total serum IgE levels were: GM 255 IU/ml, range 61-1110 IU/ml (2 SD).

Challenge Tests

Due to previous severe anaphylactic reactions the OFCs to egg was not done in 7 children and to CM in 3. Altogether, OFCs with CM were positive in 106/115 children (92.2%), with egg in 35 (30.4%) and with wheat in 8 (7%). Multiple sensitization was present in 43/115 (37.4%) children: to CM, egg and wheat in 27 cases, CM and wheat in 8, CM and egg in 8. The immediate allergic manifestations exhibited by the infants after the first ingestion of the offending foods and confirmed with the OFCs are outlined in Table II. In all children the allergic symptoms were immediate and appeared a few minutes after the ingestion of a small amount of the offending food.

Follow-up

At the last follow-up, the children were 8 years + 6 months-13 years + 2 months old (median age 9 years + 4 months).

Clinically, skin lesions cleared up in 66 (57%) children, whereas persisted in 49 (43%). As regards RAST changes, 16 (24%) of improved children were RAST-negative, 24 (36%) had a 2nd class RAST, 16 (24%) a 3rd class RAST, and 10 (15%) a 4th class RAST. Among the intolerant children, 8 (16%) had a 2nd class RAST, 9 (18%) a 3rd class RAST, and 31 (63%) a 4th class RAST, RAST was not repeated only in a not tolerant child.

Table II. Allergic manifestations triggered by OFCs in the 115 infants.

Symptoms triggered	No.	(%)
AD worsening	48	41.5
Gastrointestinal symptoms	19	16.5
Urticaria	14	12.5
Bronchospasm/wheezing	19	16.5
Anaphylactic shock	7	6
Angioedema alone or associated with AD, asthma, urticaria, vomiting, or diarrhea	8	7

Table III. Correlation between symptoms and development of tolerance during the follow-up in the 115 children.

Clinical features	60 tolerant		55 not tolerant	
	No	(%)	No	(%)
AD + FA	52	(60)	48	(55)
Asthma	18	(30)	28	(47)
Angioedema	2	(3)	4	(7)
Multiple sensitizations ($p = 0.0001$)	13	(22)	22	(40)

Natural History

Food tolerance was present in 66 children (57%). The MA for tolerance to CM was 7 years + 11 months, to egg 6 years + 6 months, and to wheat 7 years + 2 months. Therefore the children with CMA achieved tolerance at an age significantly higher than the children with egg or wheat allergy.

We then studied the correlation between symptoms and development of tolerance in the 115 children (Table III). During the follow-up there were significant differences between the 60 tolerant children and the 55 with persisting AD including either the symptoms manifested at the first examination, or the development of other sensitizations. Persistent intolerance to the offending food was found to be significantly associated with AD and angioedema ($p = 0.0001$). Moreover, a significant relationship was found between loss of FA and a high presence of asthma (30%) (Table IV) ($p = 0.022$). Among the improved children 18 (30%) developed allergy to inhalants (8 to *Lolium perenne*, 10 to Der p), and 28 (51%) of intolerant children developed respiratory allergy (9 to *Lolium perenne*, 19 to Der p). There was no difference in the MA of these 3 groups.

Table IV. Correlation between tolerance and development of asthma during the follow-up in the 115 children.

	Development of asthma	
	No	(%)
Tolerants	18/60	(30)
Not tolerant	28/55	(58)
$p = 0.022$		

The study of the correlation between sensitizing foods and development of additional allergies during the follow-up in the 115 children (Table V) revealed that 58/106 children with CMA developed several sensitizations during the follow-up ($p = 0.0047$).

At the follow-up after eight years (Table VI), when the children had a median age of 9 years + 4 months, it is true that six more children lost FA (57%) ($p = 0.003$), but 49 (43%) still had symptoms due to FA ($p = 0.0025$). Of these 49 children, 30 suffered from CMA and 19 from egg allergy ($p = 0.0263$), in addition they have developed more multiple sensitizations ($p = 0.035$). However a greater number of children, 62 (54%), suffered from asthma, an increase of 74% ($p = 0.0345$).

We then noted a significant relationship between the age of onset of AD and the outcome of skin lesions (Table VII). Among the improved children, 53 (80%) were less than 6 months old when AD first appeared, unlike 30 children (61%) with an onset of AD after 6 months ($p = 0.0001$).

Table V. Correlation between sensitizing food and development of additional food allergies during the follow-up in the 115 children.

Foods	Development of other allergies	
	No	(%)
CM	58/106	(55)
Egg	11/35	(31)
Wheat	1/8	(12)
Multiple sensitizations $p = 0.0047$	16/43	(37)

Table VI. Clinical course of 115 children with food-related AD (Follow-up 8 years).

Outcome	No.	(%)
Resolved	66	(57)
Persisting	49	(43)
Respiratory allergy	62	(54)

There was a significant relationship also between RAST results at the first examination and at the last follow-up. RAST classes are reported in Table VIII according to the outcome of children, with very significant differences.

Discussion

We have enrolled 115 highly atopic children (SPTs, RAST and OFC results), evaluating clinical features typical of CMA, either systemic such as anaphylaxis, or involving major shock organs including the gastrointestinal tract, skin, and respiratory tract, until the last follow-up. In this long-term, prospective study 115 infants were carefully followed-up with regular controls. As regards CMA incidence, a recent report found a mean of 2.16% in 15 studies in healthy and preterm infants, and of 14.72% in 3 studies in at risk babies²⁹.

The results of this study confirm that AD is a chronic, multifactorial disease, as shown by

Table VII. Age of onset of AD and outcome in 115 children with food-related AD according to the age of onset (Follow-up 8 years).

Outcome	Age of onset (months)			
	< 6		> 6	
	No	(%)	No	(%)
Resolved	53	(80)	13	(20)
Persisting	19	(39)	30	(61)
<i>p</i> = 0.0001				

all children suffering from FA, and by the elimination-provocation tests. Even if the children had a median age of 9 years + 4 months at the last follow-up, 58% of them were still affected with AD, moreover 54% of children developed respiratory allergy. These figures concur with the data reported by other investigators^{1,14,18,22,30,31,35}.

In several studies⁶⁻²¹ the reported rates of child improvement vary remarkably, ranging from 11%⁶ to 90%¹⁹, however seborrheic dermatitis was overrepresented in the latter study. Several reports have observed a favorable outcome in 40-50% of children at 13-15 years of follow-up^{14,16-18,30,31} while in others the consensus is not unanimous^{6,9,12,14}. In a Swedish study, children with AD retained their eczema as adults¹². We have found several parameters predicting a poorer outcome (Table IX), thus confirming the results of the above alluded to studies on AD natural histo-

Table VIII. RAST class at diagnosis and at last follow-up and according to the development of tolerance in the 115 children.

	RAST classes			
	Neg/1 st	2 nd	3 rd	4 th
No. of children				
At diagnosis:				
Tolerants	13	3 (5%)	10 (17%)	34 (57%)
Not tolerants	1	8 (15%)	11 (20%)	35 (64%)
Last follow-up:				
Tolerants	16	24 (36%)	16 (24%)	10 (15%)
Not tolerants	1	8 (16%)	9 (18%)	31 (63%)

At diagnosis: Tolerants vs not tolerants, *p* = 0.0001, Last follow-up: Tolerants vs not tolerants, *p* = 0.0001, not tolerants NS.

Table IX. Parameters predicting an unfavorable outcome.

Unfavorable factors	Statistics
Family history of atopy, positive vs negative	$p = 0.0024$
Male sex	$p = 0.015$
SPT results, positive vs negative	$p = 0.0001$
RAST results, positive vs negative	$p = 0.0001$
AD onset before the 4 th month of life	$p = 0.0001$
First feeding of a CM formula before the 3 rd month	$p = 0.0034$
Correlations between symptoms and development of tolerance	$p = 0.0001$
Between tolerance and development of asthma	$p = 0.022$
Between tolerance and development of additional allergies	$p = 0.0047$
Age of onset of AD and outcome	$p = 0.0001$
RAST Class at diagnosis and at last follow-up at diagnosis: Tolerants vs not tolerants	$p = 0.0001$
Last follow-up: Tolerants vs not tolerants	$p = 0.0001$

ry. These have selected numerous factors as negatively predicting the outcome as follows: positive FH for atopy, male sex, widespread or not typical (reverse pattern) skin lesions, early AD onset, male sex, association with CMA, while in a previous study positive FH for atopy, sex, but SPT responses, and severity of skin lesions had no predictive value⁷.

Several studies have emphasized the relationship between CM formula feeding and AD development^{39,40-42}. A prospective study¹⁵ showed that CM formula feeding was an unfavorable factor for AD development^{15,24,38,42}. We emphasize that 76.5% of the children of the present study were given CM formulas before the sixth month of life. Others stress that FA plays an important role in AD^{1,26,41,43,46-53}. Eighty percent of the children had serum total IgE levels higher than 2 SDs for age and 88% had positive IgE to food allergens. It was reported that 80% of AD is due to IgE-mediated allergy^{1,25,38}. Sampson et al⁵³ showed that such patients generally have elevated serum levels of IgE antibodies, and that such reactions are accompanied by increased amounts of circulating histamine⁵⁸. Atherton et al⁴⁴ suggest that the role of foods may be more critical in the beginning of the condition than later on.

In support of this unfavorable relationship between CM feeding and AD development, we report in this study 37 children (32%) that were fed CM at birth and 78 (68%) within or after the sixth month of life, as a complement or a substitute of BM feeding. Following an early exposure to CM formulas the allergic features appeared, hence significantly influ-

encing the atopy persistence ($p = 0.0021$). Furthermore, previous studies have enhanced the crucial role played by FA in AD pathogenesis^{1,17,23,42,43-53}. In this cohort, all children have shown SPTs and at least 101/115 RAST results positive for foods, allowing to conclude for an IgE-mediated AD. This finding represents an important contributing factor in 80% of children with IgE-mediated AD^{17,45}, in whom IgE antibodies are usually directed against the more relevant foods^{17,53}, accompanied by increased levels of circulating histamine⁵⁴.

As many as 16 children (13,9%) reacted to 2 and 27 (23.5%) to 3 foods, thus 88 (76.5%) reacted to 1 or 2 foods, and multiple sensitizations developed in 43 children (37.4%), in accordance with previous findings¹⁷. The management of CMA is based, whatever the clinical features, on a diet excluding both CM and closely related foods, following which the patients markedly improve⁴⁵. Therefore the elimination of offending foods represents the basal FA management, either because it can reverse the disease development, or can favor the revival of a complete tolerance possibly followed by a normal re-feeding. It is not yet completely known how food tolerance could be restored as a result of an appropriate, and carefully constructed diet. For example Jarrett⁵⁶ and Firer et al⁵⁷ have demonstrated that feeding a causative agent, such as CM, even in small doses, triggers an IgE-mediated response, thus altering the immune system, which could instead redress after a diet period. A controlled study has shown that the elimination of the offend-

ing food for one to two years, but also restricted to 3-6 months, can ameliorate the symptoms, even severe, related to the assumption of the offending food¹.

The MA for tolerance to CM was 7 years + 11 months, to egg 6 years + 6 months, and to wheat 7 years + 2 months. Therefore the children with CMA achieved tolerance at an age significantly higher than the children with egg or wheat allergy. At the last follow-up, the tolerance to CM and egg was achieved by 45% and 69% of children, respectively, however multiple sensitizations were frequent, despite ongoing pharmacological and dietetic management; thus stressing that AD is a multifactorial disease. However, CM is so a potent allergen that a drop posed on the lower lip may trigger anaphylaxis³⁶. The children with hypersensitivity to 2 or more foods achieved tolerance later to CM, egg or other foods, as already described^{7,17,31}. Sixty-six percent of the children with healing lost FA totally or partially, while 43% of the children with persisting AD were still sensitive to the offending foods ($p = 0.0001$). These data are in agreement with those of Sampson et al¹⁷.

The early age of onset of AD (< 6 months) was significantly associated with the lost of FA ($p = 0.0001$). According to several authors, both the age of onset of AD after the sixth month of life^{7,19} and the not typical or widespread skin lesions^{7,14-16,19,33} had a significant value in predicting the persistence of AD.

To our knowledge, several studies have reported an association with respiratory allergy, including this one^{5-10,12-15,18,20,21}, registering a 42.5% prevalence for asthma and of 48.3% for AR. Therefore, in children with AD appropriate strategies should prevent the development of respiratory allergy. Positive SPTs and/or IgE to inhalant allergens at the first examination appeared to have a predictive value for the development of respiratory allergy (asthma and/or rhinitis)⁷.

In addition, if there is a significant association of AD with CMA, or with egg allergy, the clinical improvement and food tolerance are attained 2-5 years later^{3,4,17,35}, whereas hypersensitivity to other foods, such as fish, cereals or nuts is lost even later^{3,17,37}. It is generally agreed that the AD outcome appears to be more favorable when the children leave CM hypersensitivity¹⁷, as particularly stressed by a

study where only one child out of 32 was still intolerant at the last follow-up³⁵, unlike the present study, and a previous one³. In keeping with our results, it is significant that 22% to 24% of tolerant children had low/negative specific IgE (SIgE) at the first visit and the last follow-up versus 2-11% of the children with persisting AD, which could be a predictive factor of tolerance. In our paper on the so-called BM allergy³⁸, at the last follow-up, a greater number of tolerant children were RAST-negative, versus those with persisting FA, compared to the first control where the ratio was specularly inverse ($p < 0.0001$). In the parallel study on the natural history of FA³, the proportion of negative RASTs increased by 82.2% in the tolerant and by 42.5% in the not tolerant children ($p = 0.0001$). Thus, in these studies, RAST turned negative in a significant part of tolerant children, enabling us to conclude that even the variations of RAST values can be predictive of tolerance.

In agreement with literature data, a high genetic risk for atopy existed in our cohort. We would like to stress that the above data do not strengthen the diffuse opinion of FA improving in a major part of children during the first years of life^{14,16-18,30,31}. However, 8 out of 21 children (38%) developed asthma during the follow-up³⁸. In this study 30% of children had asthma, which increased up to 54% during the long follow-up.

Above all the influence of foods can foreshadow a more remarkable risk of sensitization if they are administered more in the initiation of disease than after its induction⁴⁴. Some indirect support to this assumption could be provided by the observation that SPT reactivity to foods is particularly critical in very young babies with AD, subsequently fading gradually away⁵⁵.

We rather emphasize the importance of recommending to parents of neonates at risk for atopy a prolonged breastfeeding and a gradual weaning, which are frequently reported to be able to prevent or delay the development of atopic disease. Breastfeeding, if feasible, should be preserved or resumed, with the greatest care of prescribing a diet free of CM and related sources to the nursing mother. As previously alluded to, in BM exists a complete supply of nutritive and immune factors, nearly unappreciated until some time ago, whereas over the last few

years the study of the pertinent mechanisms is unfolding an always growing corpus of experimental results^{29,58-60}. Additional, possible areas of intervention in children at risk due to parental atopy would logically include avoidance also of cereals⁶¹, and egg⁶² as risk factor for an increasing incidence of AD, or a grass pollen asthma⁶³, the asthma risk is shared by the association of AD with FA within 24 months of age⁶⁴ and the sensitivity to CM and/or egg³. The avoidance of maternal smoke during and after pregnancy is advocated⁶⁵, as well as the reduction of exposure to relevant allergens, above all house dust mites in children at risk⁶¹ and cats in all children.

In conclusion, this study confirms that the natural history of IgE-mediated FA is less favorable than it is usually believed, especially in atopic children. These children may have CD137, notably involved in T-cell activation and differentiation, and expressed by blood and tissue eosinophils⁶⁶. Consequently, no firm evidence that FA is often "lost" over time⁶⁷ is in agreement with the study of these 115 children, where the CM allergens show that not much is necessary to set in motion the atopic march, and to maintain it, at least for eight years. This is not surprising because children with more severe courses are referred to our department by pediatricians and dermatologists for further investigations.

References

- 1) BOCK SA. Natural history of severe reactions to foods in young children. *J Pediatr* 1985; 107: 676-680.
- 2) DANNAEUS A, JOHANSSON SGO. A follow-up study of infants with adverse reactions to cow's milk. *Acta Paediatr Scand* 1979; 68: 377-382.
- 3) CANTANI A, BELLIONI B, RAGNO V, et al. Epidemiologia e storia naturale dell'allergia alimentare: Follow-up di 88 bambini fino a 14 anni. *Aggiorn Pediatr* 1990; 41: 321-332.
- 4) DANNAEUS A, INGANÁS M. A follow-up study of children with food allergy. Clinical course in relation to serum IgE- and IgG-antibody levels to milk, egg and fish. *Clin Allergy* 1981; 11: 533-539.
- 5) ÅBERG N, ENGSTRÖM I. Natural history of allergic diseases in children. *Acta Paediatr Scand* 1990; 79: 206-211.
- 6) BARDARE M, ZANI G, MAGNOLFI C. Evoluzione della dermatite atopica ad insorgenza nei primi anni di vita. In: *Allergie alimentari*. Roma: Fisons Italcimici SpA 1992; 157-165.
- 7) BUSINCO L, ZIRUOLO MG, FERRARA M, et al. Natural history of atopic dermatitis in childhood. *Allergy* 1989; 44 (Suppl): 44-49.
- 8) FOUCARD T. Allergy and allergy-like symptoms in 1050 medical students. *Allergy* 1991; 46: 20-26.
- 9) GUILLET G, GUILLET M-H. Natural history of sensitizations in atopic dermatitis. *Arch Dermatol* 1992; 128: 187-192.
- 10) KISSLING S, WÜTHRICH B. Localization, manifestations, and micromanifestations of atopic dermatitis in young adults. Personal follow-up 20 years after diagnosis in childhood. *Hautarzt* 1994; 45: 368-371.
- 11) KISSLING S, WÜTHRICH B. Verlauf der atopischen Dermatitis nach Kleinkindesalter. *Hautarzt* 1993; 44: 569-573.
- 12) KJELLMAN B, HESSELMAR B. Prognosis of asthma: a cohort study into adulthood. *Acta Pædiatr* 1994; 83: 854-861.
- 13) LINNA O, KOKKONEN J, LAHTELA P, TAMMELA O. A 10-year prognosis for generalized infantile eczema. *Acta Paediatr* 1992; 81: 1013-1016.
- 14) MUSGROVE K, MORGAN JK. Infantile eczema. A long-term follow-up study. *Br J Dermatol* 1976; 95: 365-372.
- 15) QUEILLE-ROUSSEL C, RAYNAUD F, SAURAT J-H. A prospective computerized study of 500 cases of atopic dermatitis in childhood. *Acta Derm Venereol* 1985; Suppl 114: 87-92.
- 16) RYSTEDT I. Prognostic factors in atopic dermatitis. *Acta Dermatol Venereol* 1985; 65: 206-213.
- 17) SAMPSON HA, McCASKILL CC. Food hypersensitivity and atopic dermatitis: Evaluation of 113 patients. *J Pediatr* 1985; 107: 669-675.
- 18) VAN HECKE E, LEYS G. Evolution of atopic dermatitis. *Dermatologica* 1981; 163: 370-375.
- 19) VICKERS CFH. The natural history of atopic eczema. *Acta Dermatovener* 1980; Suppl 92: 113-115.
- 20) WÜTHRICH B, SCHADEL P. Die Neurodermitis atopica nach dem Kleinkindesalter. Eine katamnestische Untersuchung. *Z Hautkr* 1983; 58: 1013-1023.
- 21) WÜTHRICH B, OEHME J. The prognosis of atopic dermatitis after infancy. *Hexagon* 1984; 12: 1-8.
- 22) LUCENTI P, CANTANI A. Diagnosis and treatment of food allergy. *Eur Rev Med Pharmacol Sci* 1991; 13: 99-103.
- 23) BUSINCO L, CANTANI A, MONTELEONE AM, ZIRUOLO MG. Atopic dermatitis in children: an update. *Folia Allergol Immunol Clin* 1988; 35: 41-51.
- 24) PEPYS J. SKIN TESTING. *Br J Hosp Med* 1975; 14: 412-417.
- 25) DREBORG S, BACKMAN A, BASOMBA A, et al. Skin tests used in type I allergy testing. Position paper. *Allergy* 1989; 44 (Suppl 10): 1-59.
- 26) AAS K, BELIN L. Suggestions for biologic qualitative testing and standardization of allergen extracts. *Acta Allergol* 1974; 29: 238-240.

- 27) HANIFIN JM, RAJKA G. Diagnostic features of atopic dermatitis. *Acta Derm Venereol* 1980; 92 (Suppl): 44-47.
- 28) STALDER JF, TAIEB A, ATHERTON DJ, et al. Severity scoring of atopic dermatitis: the SCORAD index. *Dermatology* 1993; 186: 23-31.
- 29) CANTANI A. *Allergologia ed immunologia pediatrica: Dall'infanzia all'adolescenza*. Roma: Verduci Editore, 2000.
- 30) MEENAN FOC. Prognosis in infantile eczema. *Ir J Med Sci* 1959; 398: 79-83.
- 31) VOWLES M, WARIN RP, APLEY J. Infantile eczema: observations on natural history and prognosis. *Br J Dermatol* 1955; 67: 53-59.
- 32) STIFLER WC. A twenty-one-year follow-up of infantile eczema. *J Pediatr* 1965; 66: 166-167.
- 33) ROTH HL, KIERLAND RR. The natural history of atopic dermatitis. *Arch Dermatol* 1964; 95: 209-214.
- 34) RYSTEDT I. Long term follow-up in atopic dermatitis. *Acta Dermatol Venereol* 1985; 114 (Suppl): 117-120.
- 35) RYSTEDT I. Hand eczema and long term prognosis in atopic dermatitis. *Acta Dermatol Venereol* 1985; 114 (Suppl): 1-59.
- 36) CANTANI A, GAGLIESI D. Severe reactions to cow's milk in very young infants at risk of atopy. *Allergy Proc* 1996; 17: 205-208.
- 37) CANTANI A, MICERA M. Gli allergeni del latte vaccino favoriscono la marcia atopica: uno studio su 32 lattanti (2ª parte). *Aggiorn Pediatr* 1999; 2: 73-78.
- 38) CANTANI A, RAGNO V, BUSINCO L. Natural history of IgE-mediated food allergy in fully breast-fed babies: Report of twenty-one cases (Follow-up to 19 years). *Pediatr Allergy Immunol* 1991; 2: 131-134.
- 39) BUSINCO L, CANTANI A, BRUNO G. Results of dietary and environmental measures for the prevention of atopy in "at risk" babies. In: Chandra RK, ed. *Food Allergy*. St John's: Nutr Res Education Foundation 1987; 361-372.
- 40) BUSINCO L, CANTANI A, MEGLIO P, BRUNO G. Prevention of atopy: Results of a long-term (7 months to 8 years) follow-up. *Ann Allergy* 1987; 59/5 (Part 2): 183-186.
- 41) CHANDRA RK. Environmental engineering in the prevention of atopic disease: how early is early enough? In Chandra RK, ed. *Food Allergy*. St John's: Nutr Res Education Foundation 1987; 373-387.
- 42) SAARINEN UM. Prophylaxis for allergic disease: Role of infant feeding. *Clin Rev Allergy* 1984; 2: 151-167.
- 43) TALBOT FB. Eczema in childhood. *Med Clin North Am* 1918; 1: 985-996.
- 44) ATHERTON DJ, SEWELL M, SOOTHILL JF, WELLS RS, CHILVERS CED. A double-blind controlled crossover trial of an antigen-avoidance diet in atopic eczema. *Lancet* 1978; i: 401-403.
- 45) SAMPSON HA. Role of immediate food hypersensitivity in the pathogenesis of atopic dermatitis. *J Allergy Clin Immunol* 1983; 71: 473-480.
- 46) BROSTOFF J, CARINI C, WRAITH DG, JOHNS P. Production of IgE complexes by allergen challenge in atopic patients and the effect of sodium cromoglycate. *Lancet* 1979; i: 1268-1270.
- 47) GLASER J. The prophylaxis of allergic disease with special reference to the newborn infant. *NY State J Med* 1955; 55: 2599-2605.
- 48) GLASER J, JOHNSTONE DE. Prophylaxis of allergic disease in the newborn. *JAMA* 1953; 153: 620-622.
- 49) GRULEE CG, SANFORD HN. The influence of breast and artificial feeding on infantile eczema. *J Pediatr* 1936; 9: 223-225.
- 50) JACKSON PG, BAKER RWR, LESSOF MH, FERRETT J, MACDONALD DM. Intestinal permeability in patients with eczema and food allergy. *Lancet* 1981; i: 1285-1286.
- 51) RAJKA G. Atopic dermatitis. In: Rook A, ed. *Major problems in dermatology*, vol 3. London: WB Saunders Co 1975; 46-130.
- 52) RING J, SENTER T, CORNELL RC et al. Complement and immunoglobulin deposits in the skin of patients with atopic dermatitis. *Br J Dermatol* 1978; 99: 495-501.
- 53) SAMPSON HA, ALBERGO R. Comparison of results of skin tests, RAST, and double-blind, placebo-controlled food challenges in children with atopic dermatitis. *J Allergy Clin Immunol* 1984; 74: 26-33.
- 54) SAMPSON HA, JOLIE PL. Increased plasma histamine concentrations after food challenges in children with atopic dermatitis. *N Engl J Med* 1984; 311: 372-376.
- 55) VAN ASPEREN PP, KEMP AS, MELLIS CM. Skin test reactivity and clinical allergen sensitivity in infancy. *J Allergy Clin Immunol* 1984; 73: 381-386.
- 56) JARRETT EEE. Activation of IgE regulatory mechanisms by transmucosal absorption of antigen. *Lancet* 1977; ii: 223-225.
- 57) FIRER MA, HOSKING CS, HILL DJ. Effect of antigen load on development of milk antibodies in infants allergic to milk. *BMJ* 1981; 283: 693-696.
- 58) GOLDMAN AS. The immune system of human milk: antimicrobial, antiinflammatory and immunomodulating properties. *Pediatr Infect Dis* 1993; 12: 664-672.
- 59) HANSON LÅ. Breastfeeding provides passive and likely long-lasting active immunity. *Ann Allergy Asthma Immunol* 1998; 81: 523-527.
- 60) SLADE HB, SCHWARTZ SA. Mucosal immunity: The immunology of breast milk. *J Allergy Clin Immunol* 1987; 80: 348-358.
- 61) FERGUSSON DM, HORWOOD J. Early solid feeding and recurrent childhood eczema: A 10-year longi-

- tudinal study. *Pediatr Allergy Immunol* 1994; 5 (Suppl 6): 44-47.
- 62) HUANG J-L, CHEN C-C, KUO M-L, HSIEH K-H. Exposure to a high concentration of mite allergen in early infancy is a risk factor for developing atopic dermatitis. A 3-year follow-up study. *Pediatr Allergy Immunol* 2001; 12: 11-16.
- 63) ARMENTIA A, BAÑUELOS MI, ARRANZI V, et al. Early introduction of cereals into children's diets as a risk of grass pollen asthma. *Clin Exp Allergy* 2001; 31: 1250-1255.
- 64) LAAN MP, BAERT MRM, BIJLT AMH, et al. Markers for early sensitization and inflammation in relation to clinical manifestations of atopic disease up to 2 years of age in 133 high-risk children. *Clin Exp Allergy* 2000; 30: 944-953.
- 65) CANTANI A. Epidemiology of cigarette smoke in the homes of asthmatic children. *J Allergy Clin Immunol* 2000; 105: S35.
- 66) HEINISCH IV, BIZER C, VOLGGER W, SIMON HU. Functional CD137 receptors are expressed by eosinophils from patients with IgE-mediated allergic responses but not by eosinophils from patients with non-IgE-mediated eosinophilic disorders. *J Allergy Clin Immunol* 2001; 108: 21-28.
- 67) SAMPSON HA. Food allergy. Part 2: Diagnosis and management. *J Allergy Clin Immunol* 1999; 103: 981-989.