

The Role of Cow Milk Allergy in Increasing the Severity of Atopic Dermatitis

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ABSTRACT

Previous studies have shown that up to 33% of children with atopic dermatitis have experienced food hypersensitivity and among different kinds of food allergens Cow Milk (CM) has almost always been one of the most common food allergens in children. The aim of this study is to evaluate the cow milk allergy (CMA) as an increasing factor of severity of atopic dermatitis. One hundred and nineteen children (between 1.5 months and 12 years of age) with atopic dermatitis in the sense of Hanifin and Rajka's criteria entered this study and the severity of atopic dermatitis was identified via the SCORAD index. In order to make the diagnosis of cow milk allergy, a careful history, and a familial history of allergy was taken and the results of skin prick test (SPT) with CM and 4 other food allergen extracts, Radioallergosorbent test (RAST) with CM allergens and a food challenge test with cow milk (fresh or dried) were used. Also a total serum IgE determination and an eosinophil count (with a stool exam) were accomplished. The clinical manifestations of atopic dermatitis in patients was started from their first day of life up to 10 years of age. The family history in 83% of the patients was positive. Positive skin prick test and RAST with

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CM allergens were positive in 37.9% and 29.3% of cases respectively and the response to challenge test with cow milk was positive in 35 out of 40 patients and in total 44.5% had CMA according to a positive history of cow milk allergy and a positive outcome of the IgE tests (SPT and/or RAST) or a positive challenge test with CM allergens. The results showed that the most common food allergens in patients with atopic dermatitis are certainly cow milk allergens (44.5%) whereas other food allergens are tomato (29.41%), egg (28.57%), nuts (9.24%) and wheat (3.36%) according to the skin prick test. The mean total serum IgE was 307.11 ± 6.56 IU/ml (range = 6–5000) in children with CMA and 81.04 ± 5.97 IU/ml (range = 1–5000) in children without CMA while the mean eosinophil count was 569.52 ± 3.02 count/ml (range = 67–8500) and 314.22 ± 2.94 count/ml (range = 5–5000) respectively. The mean severity of atopic dermatitis according to the SCORAD index was 60.76 in children with CMA and 44.29 in children without CMA. The severity of atopic dermatitis in patients with CMA was significantly higher than patients without CMA ($p < 0.0001$). Also the mean total serum IgE and mean eosinophil counts in children with CMA were significantly higher than in children without CMA ($P < 0.01$ and $p < 0.0001$, respectively). It shows the important role of CM allergen proteins in the induction and in increasing the severity of AD in children.

Key Words: Cow milk allergy; Atopic dermatitis; Skin prick test; RAST; Open food challenge test.

INTRODUCTION

Atopic dermatitis(AD) is an intense pruritic chronic cutaneous inflammatory disease that usually occurs in children with a personal or family history of one or more of the atopic diseases (Hanifin, 1991).

AD affects 0.5–1 percent of the normal population but its prevalence in children is 5–10 percent (Adinoff and Clark, 1996) while it has either been reported to be in 10–15% in some reports (Hurwitz, 1993). This disease is a common ailment in childhood, affecting 10–12% of infants (Roehr et al., 2001). Although most of them gradually improve, 60% of the patients retain residual problems (Tofte and Hanifin, 2001).

Development of atopic disease seems to depend on both genetic factors and the exposure to several environmental factors (Isolaure et al., 1995). Increased exposure to various kinds of pollutants and indoor allergens and a decline in breast-feeding, along with an increased awareness of atopic dermatitis have been suggested as reasons for the increased frequency of atopic dermatitis (Boguniewicz and Leung, 1998). From recent studies it appears that the lifetime prevalence of AD in younger school children is 10% to 20% in NorthWestern Europe (Larsen, 2002).

Food allergy (hypersensitivity) refers to an abnormal immunological response attributed to the exposure to a specific food but it is unrelated to any physiological effect of the food (Hoffman and Sampson, 1996). Clinical symptoms of patients with food-sensitive atopic dermatitis often improve with an increase in age (Iida et al., 1995). The concept that food hypersensitivity plays a pathogenic role in atopic dermatitis dates from several studies in the 1920's. A large number of reports implicating the role of foods in atopic dermatitis were also followed (Adinoff and



Clark, 1996; Oehling et al., 1997). AD is frequently associated with food allergies, which complicates the management in approximately 40% of these children (Li et al., 2001; Roehr et al., 2001) mean while in another study 33.8% (25 of 74) of the AD patients were diagnosed with food allergy (Eigenmann and Calza, 2000). Early recognition of food allergies is difficult and the patients are often missed because of the non-specificity of the symptoms (Majamaa et al., 1996). The most common food allergens are egg, cow milk (CM), and sesame in children (Dalal et al., 2002).

Approximately one third of AD children have a diagnosis of cow milk allergy according to the elimination diets and challenge tests, and about 40–50% of children < 1 year of age with cow milk allergy have AD (Novembre and Vierucci, 2001).

The prevalence of cow milk allergy is between 1.9% and 7.5% in population (Jarvinen and Suomalainen, 2001). Allergy to cow milk proteins (CMPs) occurs principally in the first half year of life, coinciding with its introduction to the infant's diet (Garcia-Ara et al., 2001; Sampson, 1996). Symptoms of CMA in 75–90% of patients appear within the first month of their life (Jarvinen and Suomalainen, 2001). Infants exclusively fed with hypoallergenic milk formula in the first 4 months of life have provided a protective effect in terms of not developing atopic dermatitis in the first 2 years of life, compared with infants fed with cow milk formula (Chan et al., 2002). The occurrence of atopic dermatitis in fully breast-fed children is due to hypersensitivity of the child to those foods; that are included in the maternal diet, namely chocolate, cow milk, egg, fish and/or oats (Restani et al., 2000).

The aim of this study is the evaluation of the role of cow milk allergy in increasing the severity of atopic dermatitis.

METHODS

One hundred and nineteen patients with definite diagnosis of atopic dermatitis who were referred to Allergy and Immunology Clinic in Children Hospital Medical Center—during 18 months—ranging in age from 1.5 months to 12 years old, entered this study. All patients fulfilled the criteria of Hanifin and Rajka in at least 3 major and 3 minor criteria (Adinoff and Clark, 1996; Boguniewicz and Leung, 1998; Hurwitz, 1993) for the diagnosis of atopic dermatitis, taking exact medical histories and questions about complaints and other allergic symptoms due to CMA.

The severity of atopic dermatitis was determined according to the Severity Scoring of Atopic Dermatitis (SCORAD) index, established by the European Task Force on Atopic Dermatitis from 0–100 and divided into 5 groups (0–19, 20–39, 40–59, 60–79 and 80–100) (Saurat, 1993).

Skin prick tests (SPT) with cow milk allergens and 4 other common food allergens (tomato, whole egg, nuts and wheat) (Pourpak and Farhoudi, 1997; Thompson et al., 2001) for 87 patients were performed (others were suffering from severe eczema) and their reagents were prepared from Dome Holister Stier–Canada. The skin prick test was performed with normal saline as a negative control and 1 mg/ml histamine as a positive control. Those who didn't have any responses to the negative control test and responded positive to histamine (wheal diameter over 5 mm) were tested with allergens. Wheal diameter over 3 mm (corresponding to wheal area of 7 mm²) and flare diameter more than 10 mm, were determined as positive tests (Demoly et al., 1997).



Radioallergosorbent tests (RAST), specific IgE to cow milk allergen (purchased from Kabi Pharmacia Diagnostic Uppsola, Sweden) for 62 patients were performed and evaluated on a 0–5 scale (we reported ≥ 2 + response of the tests) (Hoffman and Sampson, 1996), also total serum IgE with ELIZA kit (Diagnostic–USA) for 104 patients and eosinophil count for 85 patients were measured.

After two weeks of eliminating cow milk from patients diet for 10–15 days (Sampson, 1996), open food challenge test with cow milk for 40 patients was done (who didn't have any history of anaphylaxis, generalized urticaria or severe asthma with cow milk and all of them had shown positive response to elimination diet). All the challenges were performed in hospital in the morning when patients were fasting. They drank cow milk from serial dilution 1/5 to 1/1 with 30–40 minutes interval and were clinically controlled (about objective or subjective symptoms). All of these tests were performed in Allergy and Immunology Clinic of children Hospital Medical Center and during the tests, intensive safety measures were applied (Bahna, 1991; Bock et al., 1988).

Patients who had careful history of cow milk allergy and positive one of the IgE mediated tests (SPT and/or RAST) or positive challenge test with CM allergens were determined as cow milk allergic patients (Durham and Church, 2001; Hoffman and Sampson, 1996). Eventually, in order to determine the relationship between the severity of atopic dermatitis and cow milk allergy Kolmogorov–Smirnov test was done for normal distribution. It clarified that our data about IgE and eosinophil were showing abnormal distribution ($p < 0.05$), thus, all data were transformed to the natural logarithm ($\ln[X]$) for analysis. After all data were approached to normal distribution ($p > 0.05$). Differences in IgE and eosinophil logarithms and SCORAD means between two groups (children with CMA and without CMA) were analysed by the T-test. P-values of less than 0.05 were considered significant. In order to determine the correlation between SCORAD and IgE logarithm we applied Pearson Correlation Test. Also patients were divided into 3 age groups: 0–2, 2–6 and > 6 years of age, and analysed the age relationship with cow milk allergy, and the severity of the atopic dermatitis.

RESULTS

One hundred and nineteen patients with atopic dermatitis (1.5m–12y) participated in this investigation. The mean and median ages at the time of diagnosis were 3.4 and 1.9 years, respectively. The positive family history of allergic disease was identified in 83.6% (92 patients) of the children, in addition to that 33% of their parents were already engaged in familial marriages.

At the time of taking history there was considered to be 12 main chief complaints among patients, which could be related to drinking cow milk. The relative frequency of every complaint is shown in Table 1.

Skin prick tests and RAST were positive with cow milk allergen in 37.9% and 29.3% respectively and challenge tests with cow milk were positive in 87.5% (35/40). In the base of challenge test or careful history of severe allergy due to drinking cow milk with a positive IgE mediated diagnostic test (SPT and/or RAST) we determined sensitivity to cow milk (Majamaa et al., 1996) to be present in 53 patients (44.54%) of



Table 1. The relative frequency of chief complaints due to drinking cow milk in AD patients with cow milk allergy.

Complaint	R. frequency
Urticaria	16.66
Asthma	14.81
Nausea and vomiting	12.96
Diarrhea	12.96
Melena	11.11
Rhinitis	11.11
Cough	11.11
Colic pain	9.25
Conjunctivitis	9.25
Anaphylactic shock	7.40
Distention	5.55
Chronic constipation	5.55

119 patients with AD. Other common food allergens in the base of skin prick test were: tomato 29.41%, egg 28.57%, nuts 9.24%, wheat 3.36%. Patients were divided into 5 groups from 0 to 100 in scale of SCORAD scaling criteria. Then the frequency of cow milk allergy in every group was determined (Figure 1) and a comparison between severity of atopic dermatitis in children with cow milk allergy and those without CMA

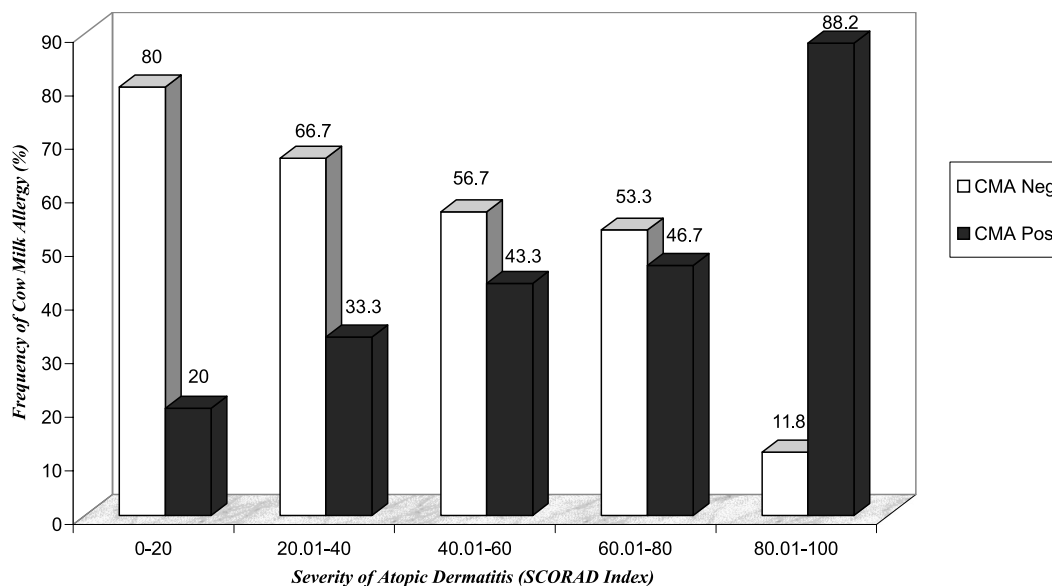
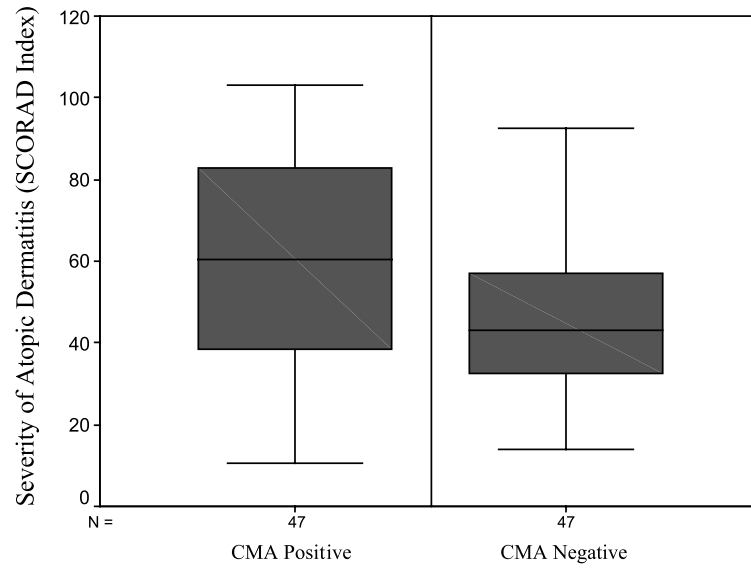


Figure 1. The relative frequency of cow milk allergy in patients with atopic dermatitis compared to the severity of dermatitis. (Black bars are patients with CMA and white bars are without CMA.)





AD Patients with and without Cow Milk Allergy

Figure 2. Comparison between the severity of atopic dermatitis in CMA positive children and CMA negative children. (Upper and lower lines show maximum and minimum of SCORAD, respectively and the box plot shows mean $\pm$ SD.)

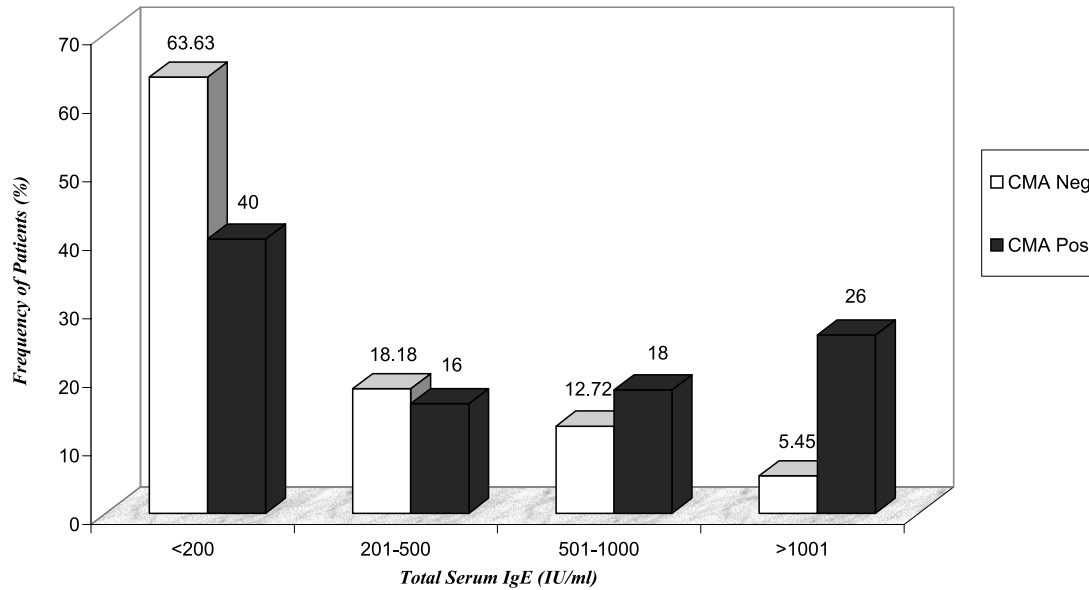


Figure 3. Comparison between total serum IgE in AD patients with or without cow milk allergy. (Black bars are patients with CMA and white bars are without CMA.)



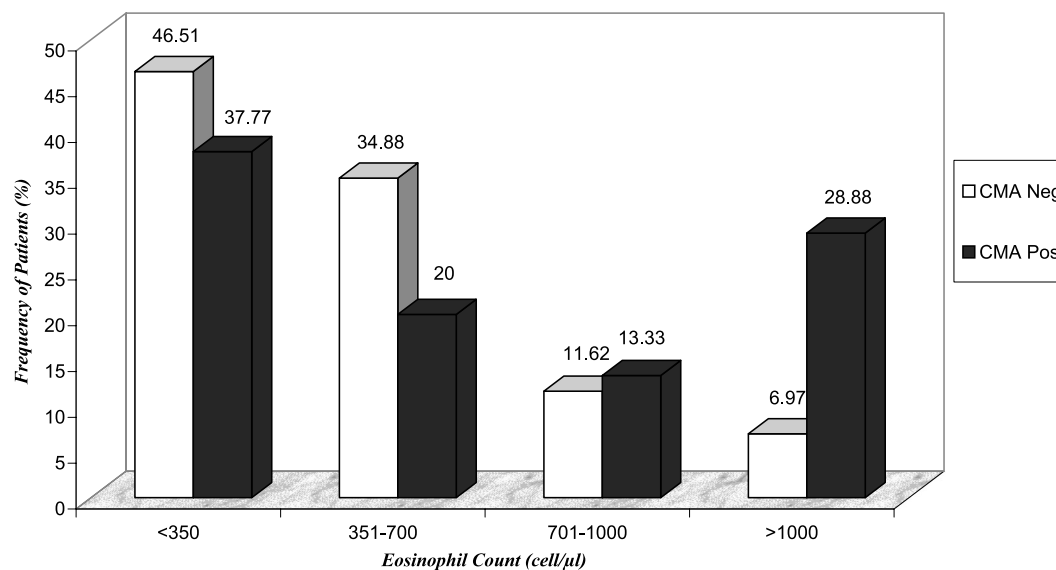


Figure 4. Comparison between eosinophil count in AD patients with or without cow milk allergy. (Black bars are patients with CMA and white bars are without CMA.)

was made which showed significant differences—that are shown in Figure 2. The mean severity of atopic dermatitis in the base of SCORAD index was 60.76 in children with CMA and 44.29 in children without CMA ($p < 0.0001$).

Patients were female 40% and male 60%. Male/female ratio in cow milk allergic patients was 2.31 and in non cow milk allergic patients was 1.53.

Total serum IgE levels in children with CMA in comparison with children without CMA are shown in Figure 3 and mean total serum IgE level was 307.11 ± 6.56 IU/ml (range = 6–5000) and 81.04 ± 5.97 IU/ml (range = 1–5000), respectively ($P < 0.01$). The Correlation Coefficient between SCORAD and IgE logarithm was 0.41 in children with CMA ($P < 0.004$) and 0.33 in children without CMA ($P < 0.02$).

Eosinophil count in children with CMA in comparison with children without CMA is shown in Figure 4. Mean eosinophil count was 569.52 ± 3.02 Count/ml (range = 67–8500) and 314.22 ± 2.94 Count/ml (range = 5–5000), respectively ($p < 0.0001$). The

Table 2. The age relationship with cow milk allergy in patients with atopic dermatitis.

Age (years)		Cow milk allergy		Total
		Positive	Negative	
0–2	Count (% within group)	35 (66.0%)	27 (42.9%)	62 (53.4%)
2–6	Count (% within group)	10 (18.9%)	20 (31.7%)	30 (25.9%)
>6	Count (% within group)	8 (15.1%)	16 (25.4%)	24 (20.7%)
Total	Count (% within group)	53 (100%)	63 (100%)	116 (100%)



Correlation Coefficient between SCORAD and eosinophil logarithm was 0.47 ($P < 0.001$) in children with CMA but this Correlation Coefficient was not significant in children without CMA.

The age relationship with cow milk allergy is shown in Table 2. It seems that cow milk allergy will outgrow with age and there is a significant difference between different age groups in prevalence of cow milk allergy ($P < 0.05$) but there was no significant difference in severity of atopic dermatitis in different age groups.

DISCUSSION

The patients who were considered to have positive milk allergy were about 53 patients (44.5%). As results showed positive familial history of allergy was 83.6%, this study confirms the finding that genetic predisposition to atopy plays a significant role in the development of AD. So it is suggested that a family with a positive atopic history eliminates cow milk from their new infant's diet for prevention of CMA and AD.

In this study male/female ratio in CMA patients was approximately two, that is the same as Businco's study (Belloni-Businco et al., 1999). Also in asthmatic patients it was shown that boys are affected more than twice as often as girls (Wright and Weiss, 2001), but it still needs more studies to establish a relation between sex dependent gene and asthma or cow milk allergy.

The relationship between the presence of cow milk allergy and the clinical severity of atopic dermatitis in children (SCORAD index) was another entity to be confirmed (Figure 1). Also the present results reveal major statistical differences in the severity of atopic dermatitis in cow milk allergic patients and other patients without CMA (Figure 2). It shows the role of CMA in induction of AD and these results show that cow milk allergens are one of the most important allergens in inducing and increasing the severity of AD in children. It is supposed that the first step in diagnosis and treatment of AD in infants and children could be the diagnosis of CMA and if it is positive, elimination of cow milk from either patients or their mothers diet (if breast fed) and replacement of hypoallergenic milk would be necessary.

Also cow milk allergy enhances total serum IgE (Figure 3) in children with atopic dermatitis. The difference between total serum IgE in children with CMA and without CMA was significant. ($P < 0.01$) This point recommends the above matter about the role of CM allergens in inducing and increasing AD. Also the relation between IgE and SCORAD in all patients with AD shows that IgE can be used as an severity index of AD in patients and this correlation is stronger in patients with CMA.

Numerous carefully controlled studies, both in experimentally induced allergic responses by allergen challenge and in clinical disease, have shown increased numbers of eosinophils and eosinophil granule proteins in tissue with a significant correlation between numbers of eosinophils and markers of severity (Church et al., 2001). Our studies showed that CMA enhances eosinophil count (Figure 4) in children with atopic dermatitis. Also the difference between mean eosinophil count in children with CMA and without CMA was significant ($P < 0.0001$), which is according to above-mentioned study (Church et al., 2001). As well, the relation between SCORAD and eosinophil



count in patients with CMA shows that eosinophil can be used as an severity index of AD in this patients but in patients without CMA it doesn't seem to be useful.

ABBREVIATIONS

AD	Atopic Dermatitis
CMA	Cow milk Allergy
CM	Cow milk
SCORAD	Severity Scoring of Atopic Dermatitis
SPT	Skin Prick Test
RAST	Radioallergosorbent test
IgE	Immunoglobulin E

ACKNOWLEDGMENTS

Thanks to all of our colleagues in Immunology, Asthma and Allergy Research Institute; in laboratory and clinics, and special thanks to Dr. Shahriar Faezei for his kind cooperation.

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