Natural course of cow's milk allergy in childhood atopic eczema/dermatitis syndrome

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Objective: This review was undertaken to determine the role of adverse reactions to bovine proteins in atopic dermatitis, recently called atopic eczema/dermatitis syndrome (AEDS).

Data Sources: A PubMed literature search was conducted with use of the following phrases: atopic dermatitis and food allergy, atopic dermatitis and cow's milk, and cow's milk and eczema.

Study Selection: The authors' judgment and personal interest guided the literature selection.

Results: Food allergy has a role in at least 20% of the cases of AEDS in children younger than 4 years. Cow's milk is usually the first food given to an infant, and cow's milk hypersensitivity is often the first symptom of an atopic condition. Adverse reactions to cow's milk proteins are usually categorized as immunoglobulin (Ig)E-mediated or non–IgE-mediated cow's milk allergy and nonallergic hypersensitivity (intolerance); the symptoms do not allow differentiation of these entities. In patients with cow's milk allergy and AEDS, resolution occurs in 90% by the age of 4 years. Non–IgE-mediated cow's milk allergy often disappears before the age of 1 year. Associated reactions to other foods develop in approximately 45% of patients. Allergy to potential environmental inhalant allergens has been reported in up to 28% of patients by 3 years of age and up to 80% before puberty. After consumption of large amounts of cow's milk, 45% of 10-year-old children who had become tolerant of cow's milk, but also 15% of control subjects, still had gastrointestinal complaints. The presence of cow's milk allergy during infancy increases the risks for development of other food allergies, respiratory atopy, and persistence of AEDS.

Conclusion: Adverse reactions to bovine proteins have an important role in AEDS.

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INTRODUCTION

Atopic dermatitis (AD) or eczema is a chronic, inflammatory, primarily genetically determined skin disease that often manifests during the first 6 months of life. In new nomenclature recently proposed by the Nomenclature Task Force of the European Academy of Allergology and Clinical Immunology, AD was called the atopic eczema/dermatitis syndrome (AEDS).[1] Increasing evidence indicates that allergens, as major provocative factors, trigger AEDS or flare-ups of AEDS. During the first years of life, food allergens are the major triggers, although aeroallergens also have an important role, commonly after the age of 1 year. On the basis of our own observations, food allergy is involved in at least 20% of the children younger than 4 years who have AEDS. Other investigators have reported higher percentages of involvement of food allergy (40% or even more).[2] This finding may be attributable to a selection bias. In general, at least one-third of the young children with AEDS are thought to have food allergy.

The most important food allergens, accounting for 80% of all allergies in the United States and in most European countries, are cow's milk, hen's egg, and peanut.[1] In the Netherlands, cow's milk, hen's egg, and peanut are the most common allergens. In Spain, cow's milk is the third most frequent cause of food allergy (24.5% of the children with food allergy), after hen's egg (34.4%) and fish (30.4%).[3] The most common allergen inducing food allergy in AEDS is hen's egg (A.P.Oranje, unpublished data). Cow's milk allergy affects 2 to 8% of all infants (with and without AEDS).[4] In this article, we present an overview of published data and our personal opinion on the natural course of cow's milk allergy in children with AEDS.

METHODS

In the PubMed database, we used the following phrases to search the literature: *AD and food allergy* (760 hits, of which 22 articles were preselected and partially included in this analysis); *AD and cow's milk* (as a second search, omitting double selection; 369 hits, of which 13 articles were preselected and partially included in this report); and *cow's milk and eczema* (three additional articles were identified for inclusion). Other published sources were selected on the basis of personal interest. Closure of the data survey was on February 1, 2002.

SYMPTOMS OF FOOD ALLERGY

The diagnosis of food allergy is usually based on a combination of the interpretation of a "weighted" history, the results of serologic and skin tests, and elimination and reintroduction strategies.

The clinical manifestations of food allergy are variable. The reaction patterns can be categorized into immediate, late,

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and delayed types. Affected patients may have pulmonary symptoms, allergic gastroenteropathy, iron-losing enteropathy, colitis during infancy, persistent constipation, otitis media, or neonatal thrombocytopenia. Dermatologic symptoms are the most common and include urticaria, angioedema, circumoral lesions, morbilliform eruptions, eczema, perianal eruptions, and contact urticaria. Contact urticaria, including that induced by milk, is common in infants and toddlers with AD and food allergy. Cow's milk-induced contact urticaria is a wheal and flare reaction elicited after cutaneous exposure to cow's milk or cow's milk products such as cheese and yogurt.[5] Recently, Tan et al[6] reported cases in which urticaria occurred in a child after being kissed by the mother and during bathing after a few drops of cow's milk had been spilled into the bathwater by a brother. We described the occurrence of a serious episode of contact urticaria after a wheat-allergic child was bathed in water in which wheat-containing bath oil was used.[5]

FOOD ALLERGY AND ATOPIC DERMATITIS

An adverse food reaction is a general term that can be applied to a clinically abnormal response to an ingested food or food additive. Adverse food reactions may be attributable to food hypersensitivity (allergy) or food intolerance. Food intolerance is a general label describing an abnormal physiologic response to an ingested food, which has not been proven to be immunologic in nature. Hypersensitivity to cow's milk proteins (cow's milk allergy) can be subdivided into immunoglobulin (Ig)E-mediated cases or non–IgE-mediated cases of cow's milk allergy and nonallergic hypersensitivity (intolerance).[1]

Resano et al,[7] who studied etiologic factors in AEDS in 74 children of various ages, found that 64.9% of them had a food sensitization—to cow's milk (36.5%), hen's egg (35.1%), and fish (21.6%). These sensitizations to food were determined by means of skin tests, specific IgE studies, and antigen-specific histamine release tests.

Bohme et al[8] studied a community birth cohort of 2,256 children, including 221 consecutive children with AEDS; they underwent followup to 2 years of age, at which time they were reexamined and screened for atopic sensitization by skin prick test to foods and the Phadiatop test (Pharmacia & Upjohn, Uppsala, Sweden). During the first year of life, initial symptoms of AEDS were present in 88% of the children. Results of skin prick tests to common food allergens, including cow's milk, were positive in 27% of the cases, and the Phadiatop test was positive in 15%. In 67% of the children both test results were negative. The severity of the eczema did not differ between the children with and those without sensitization.

Recent data from a large longitudinal study (Early Treatment of the Atopic Child)[9] suggested an association between sensitization to cow's milk and the severity of AEDS in children. Further, the study group reported that the presence of sensitization to cow's milk indicates a worse outcome for patients with AEDS in terms of persistence and severity of the condition after 18 months of followup.

Dietary restrictions are indicated in selected patients and are especially useful in children 0 to 5 years of age who have AEDS. The younger the child, the more likely the possibility that an exclusion diet might be helpful in the management of AEDS. Little information is available from controlled studies, however, to prove the efficacy of an exclusion diet in a food-allergic infant.

COW'S MILK ALLERGY AND INTOLERANCE

Definition and Diagnosis

Cow's milk is usually the first food given to an infant. Cow's milk contains more than 25 proteins, of which the major allergens are β-lactoglobulin, caseins, α-lactalbumin, and serum albumin.[10] Most patients who are allergic to cow's milk are also allergic to the milk of goats or sheep, a finding ascribed to cross-reactivity.[11] Approximately 10% of the children with cow's milk allergy also have beef allergy.[12] Distinguishing between cow's milk allergy and cow's milk intolerance is difficult, especially in infants.

An adverse reaction to cow's milk is often the first symptom of an atopic condition in a child. Adverse reactions to cow's milk proteins are usually indicated as cow's milk allergy/intolerance because no distinction between the two entities is possible on the basis of symptoms. In addition, no completely reliable laboratory tests are available for the diagnosis of cow's milk allergy or cow's milk intolerance.[13]

AEDS is often associated with cow's milk allergy or cow's milk intolerance. In cow's milk intolerance, no clear underlying mechanism has been elucidated, and more than one abnormality may cause the symptoms in an individual patient. Approximately one-third of the children with AEDS have a diagnosis of cow's milk allergy or cow's milk intolerance, as determined by use of an elimination diet and challenges, and approximately 40 to 50% of children <1 year of age with cow's milk allergy or cow's milk intolerance have AEDS.[13] Hill et al[14] found AEDS in 57% of the children with IgE-mediated cow's milk allergy (at a median age of 3.7 years).

The diagnosis of cow's milk allergy/intolerance can be considered on two levels. The first level is the clinical history and symptoms. Elimination and reintroduction of cow's milk in the diet are required for the diagnosis of cow's milk allergy or intolerance in those patients with only delayed-type reactions. The second level consists of a serologic test measuring IgE antibodies, immediate skin tests, and atopy patch tests.[1,3,15] Final proof can be obtained by the oral provocation test in children 2 years of age or younger and by a double-blind, placebo-controlled oral challenge test in older children.[16]

Prognosis

The prognosis of patients with cow's milk allergy is good, with a recovery rate of approximately 50% at 1 year, approximately 70% at 2 years, and approximately 80% at 3 years of age.[17] A higher recovery rate was reported by Host and Halken,[18] who found that 87% of the children with cow's

milk allergy during infancy became tolerant before the age of 3 years. Bishop et al[19] reported a 78% recovery rate in children by the age of 6 years, whereas Sampson and Scanlon[20] found that only 33% of the children with AEDS, cow's milk allergy, and high specific IgE antibodies became tolerant by the age of 6 years. In our own patients with cow's milk allergy and AEDS, the recovery rate has been 90% by the age of 4 years. Cow's milk intolerance often disappears before the affected patients are 1 year old.

Associated adverse reactions to other foods, especially egg and peanut, develop in approximately 45% of patients. Allergy to potential environmental aeroallergens has been reported in up to 28% of patients by 3 years of age and up to 80% before the age of puberty.[17] In children who had had cow's milk allergy during infancy, Tikkanen et al[21] studied the followup status at 10 years of age. These authors reexamined 56 children with cow's milk allergy and compared the data with 204 age-matched control subjects. All but four children had become tolerant of at least small amounts of cow's milk protein. After consumption of large amounts of cow's milk, 45% of the children, but also 15% of the control subjects, had gastrointestinal complaints.

Complications and Associations

A study consisting of 16 patients who were 2 to 18 years of age and had histories of IgE-mediated anaphylaxis as well as 16 matched control subjects showed that the patients had a higher prevalence of other allergen sensitizations and persistent AEDS.[22] The patients also had more episodes of hospitalization and anaphylactic shock in comparison to the control subjects.

In a study of 100 consecutively examined children who were 1 to 17 months of age, Isolauri et al[23] noted a delay in growth of those children with cow's milk allergy. The aforementioned study by Tikkanen et al[21] showed that a considerable portion of the children with cow's milk allergy still had allergy-related complaints at the age of 10 years. In addition, these investigators found that the incidence figures for asthma, allergic rhinitis, otitis media, and AEDS were 3 to 4 times higher in the patients than in the control subjects.

AEDS complicated by allergy to food (in particular, cow's milk and hen's egg) results in a more prolonged course and an increased possibility of development of asthma.[9,24] Currently, however, no clear proof exists that the initial clinical manifestation of AEDS is strongly influenced by associated food allergy, such as cow's milk and hen's egg allergy.

CONCLUSION

The presence of a combination of AEDS and food allergy at the age of 1 year is a strong risk factor for the development of asthma by the age of 2 years.[9,24] Cow's milk allergens often precipitate the first allergic reactions in an atopic child. Clinically, allergy and intolerance are indistinguishable. Generally, cow's milk intolerance resolves before the age of 1 year, whereas cow's milk allergy resolves in most patients by the age of 4 years. Cow's milk allergy during infancy indicates a higher risk for development of other food allergies, respiratory atopy, and persistence of AEDS. Prospective double-blind, placebo-controlled randomized studies, including correct diagnosis of AEDS with use of definition, classification, and clinical severity scoring systems with sufficient statistical power, are necessary to ascertain the exact role of food allergy—in particular, cow's milk allergy or intolerance—in infants with AEDS.[25]

REFERENCES

1. Johansson SG, Hourihane JO, Bousquet J, et al. A revised nomenclature for allergy. An EAACI position statement from the EAACI nomenclature task force. Allergy 2001;56:813–824.
2. Sampson HA. Eczema and food hypersensitivity. In: Metcalfe DD, Sampson HA, Simon RA, editors. Food Allergy: Adverse Reactions to Foods and Food Additives. Boston: Blackwell Science, 1997:193–209.
3. Martin Esteban M, Bone Calvo J, Martorell Aragones A, et al. Adverse reactions to cow's milk proteins. Allergol Immunopathol 1998;26:171–194.
4. Hill DJ. Clinical recognition of the child with food allergy. In: Harms HK, Wahn U, editors. Food Allergy in Infancy and Childhood. Berlin: Springer-Verlag, 1989:61–69.
5. Oranje AP, Aarsen RS, Mulder PG, Liefaard G. Immediate contact reactions to cow's milk and egg in atopic children. Acta Derm Venereol 1991;71:263–266.
6. Tan BM, Sher MR, Good RA, Bahna SL. Severe food allergies by skin contact. Ann Allergy Asthma Immunol 2001;86:583–586.
7. Resano A, Crespo E, Fernandez Benitez M, et al. Atopic dermatitis and food allergy. J Investig Allergol Clin Immunol 1998;8:271–276.
8. Bohme M, Svensson A, Kull I, et al. Clinical features of atopic dermatitis at two years of age: a prospective, population-based case-control study. Acta Derm Venereol 2001;81:193–197.
9. Wolkerstorfer A, Wahn U, Kjellman NI, et al. Natural course of sensitization to cow's milk and hen's egg in childhood atopic dermatitis: ETAC Study Group. Clin Exp Allergy 2002;32:70–73.
10. Yunginger JW. Food antigens. In: Metcalfe DD, Sampson HA, Simon RA, editors. Food Allergy: Adverse Reactions to Foods and Food Additives. Boston: Blackwell Science, 1997:49–63.
11. Savilathi E, Kuitunen M. Allergenicity of cow's milk proteins. J Pediatr 1992;121:S12–S20.
12. Werfel SJ, Cooke SK, Sampson HA. Clinical reactivity to beef in children allergic to cow's milk. J Allergy Clin Immunol 1997;99:293–300.
13. Novembre E, Vierucci A. Milk allergy/intolerance and atopic dermatitis in infancy and childhood. Allergy 2001;56(Suppl):105–108.
14. Hill DJ, Bannister DG, Hosking CS, Kemp AS. Cow milk allergy within the spectrum of atopic disorders. Clin Exp Allergy 1994;24:1137–1143.
15. Niggemann B. The role of the atopy patch test (APT) in diagnosis of food allergy in infants and children with atopic dermatitis. Pediatr Allergy Immunol 2001;12(Suppl):37–40.
16. Muraro MA. Diagnosis of food allergy: the oral provocation test. Pediatr Allergy Immunol 2001;12(Suppl):31–36.
17. Host A, Jacobsen HP, Halken S, Holmenlund D. The natural history of cow's milk protein allergy/intolerance. Eur J Clin Nutr 1995;49(Suppl):S13–S18.

18. Host A, Halken S. A prospective study of cow milk allergy in Danish infants during the first 3 years of life: clinical course in relation to clinical and immunological type of hypersensitivity reaction. Allergy 1990;45:587–596.
19. Bishop JM, Hill DJ, Hosking CS. Natural history of cow milk allergy: clinical outcome. J Pediatr 1990;116:862–867.
20. Sampson HA, Scanlon SM. Natural history of food hypersensitivity in children with atopic dermatitis. J Pediatr 1989;115:23–27.
21. Tikkanen S, Kokkonen J, Juntti H, Niinimaki A. Status of children with cow's milk allergy in infancy by 10 years of age. Acta Paediatr 2000;89:1174–1180.
22. Kaplan MS. Complications in children with a severe allergy to cow milk. Ann Allergy 1993;71:529–532.
23. Isolauri E, Sutas Y, Salo MK, et al. Elimination diet in cow's milk allergy: risk for impaired growth in young children. J Pediatr 1998;132:1004–1009.
24. Laan MP, Baert MR, Bijl AM, 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.
25. Oranje AP, de Waard-van der Spek FB. Atopic dermatitis and diet. J Eur Acad Dermatol Venereol 2000;14:437–438.

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