

Epidemiology and prevention of cow's milk allergy

Høst A, Halken S. Epidemiology and prevention of cow's milk allergy. Allergy 1998; 53 (Suppl 46): 111–113. © Munksgaard 1998.

A. Høst¹, S. Halken²

¹Department of Pediatrics, Odense University Hospital, Odense; ²Department of Pediatrics, Sønderborg Hospital, Sønderborg, Denmark

Key words: cow's milk protein; food allergy; incidence; prevention.

Arne Høst, MD, DSc
Department of Pediatrics
Odense University Hospital
DK 5000 Odense C
Denmark

Cow's milk protein allergy/intolerance (CMPA/CMPI), meaning reproducible adverse reactions to cow's milk proteins(s), may be due to the interaction between one or more milk proteins and one or more immune mechanisms, possibly any of the four basic types of hypersensitivity reactions. Immunologically mediated reactions are defined as CMPA. Mostly, CMPA is caused by IgE-mediated (type I) reactions, but evidence of type III (immune complex) reactions and type IV (cell-mediated reactions) has been demonstrated (1, 2). Non-immunologic reactions to cow's milk protein(s) are defined as CMPI. No single laboratory test is diagnostic of CMPA/CMPI, and differentiation between CMPA and CMPI cannot be based solely on clinical symptoms. The diagnosis has to be based on strict, well-defined elimination and milk challenge procedures (1, 3). Preferably, double-blind, placebo-controlled food challenges (DBPCFC) should be carried out in children older than 1–2 years. In infants, open, controlled challenges have been shown to be reliable when performed under professional observation in a hospital setting (4).

Incidence

CMPA/CMPI is the most common food-allergic disease in early childhood. Apparently, CMPA/CMPI was a rare disease before 1950. The reported increase of the incidence after 1960 may be at least in part caused by increased exposure to cow's milk-based infant formulas as a consequence of a decrease in the frequency of breast-feeding in developed countries. Prospective studies from the

last three decades on the incidence of CMPA/CMPI in industrialized countries have reported incidences of 1.8–7.5% (4–9). The variation of the incidence of CMPA/CMPI up to 1 year of age mainly reflects differences in diagnostic criteria, study design, composition of the materials, and perhaps also geography. In recent studies applying comparable prospective study designs, including controlled milk challenge procedures, the "true incidence" of CMPA/CMPI in infancy seems to be about 2–3%. If the diagnosis is mainly based on patient history and parents' reporting of the results of milk challenges, an overdiagnosis will occur. Symptoms suggestive of CMPA/CMPI are seen in about 5–15% of infants (1, 9), but in about 33% of these instances a cause-and-effect relationship between intake of cow's milk and symptomatology cannot be confirmed by controlled elimination/challenge (1). The yearly incidence of CMPA/CMPI in presumably exclusively breast-fed infants has been found to be about 0.4–0.5% (7, 10).

Etiologic and pathogenetic aspects

High-molecular-weight food proteins are absorbed through the intestinal mucosa, and formation of antibodies against cow's milk proteins is a normal physiologic response (1, 12). The development of CMPA/CMPI depends on several factors, especially genetic allergic predisposition, early cow's milk protein exposure, and cow's milk protein uptake and handling (1). A significant association between early neonatal exposure to cow's milk protein and subsequent development of CMPA/

Høst and Halken

CMPI has been documented (10, 13, 14). Prenatal sensitization may play a role in the pathogenesis of CMPA/CMPI in view of the finding of a very high frequency (76%) of specific IgE to individual cow's milk proteins in the cord blood of infants with later development of CMPA/CMPI (15). Recently, it has been shown that exposure to allergens, e.g., β -lactoglobulin, from 22 weeks of gestation may result in a primary immune response, leading to positive proliferative responses of stimulated mononuclear cells at birth (16). By sensitive methods, specific IgE antibodies to cow's milk proteins in cord blood have been demonstrated in 9–11% of neonates (17), and a recent study has reported a similar prevalence of 14% of cow's milk-specific IgE in the cord blood of babies with atopic predisposition (18). Thus, prenatal sensitization to cow's milk protein seems to be more common than previously described. However, the clinical relevance of prenatal sensitization remains to be further investigated. Does a weak intrauterine induction of a low IgE response need to be boosted neonatally in order to cause clinical disease? Nor can sensitization due to inhalation of food proteins be ruled out, considering the findings of significant amounts (equal to or higher than amounts in human milk) of potentially allergenic food proteins; e.g., β -lactoglobulin in house dust (19).

Clinical features and prognosis

CMPA/CMPI rarely develops in early infancy after 12 months of age. The onset of disease is in most cases closely related to the time of introduction of cow's milk-based formula, often within 1 week after introduction of cow's milk-based formula. A broad spectrum of symptoms in children may be caused by CMPA/CMPI. Many show cutaneous symptoms (about 60%) or gastrointestinal symptoms (about 50–60%), and about 20–30% show respiratory symptoms (1). Anaphylaxis has been reported in up to 9% (20). The symptoms may occur from a few minutes to 1 h after milk exposure ("immediate reactions") or after 1 h ("delayed reactions") and in some cases after days. By clinical and immunologic types of reaction, patients can be classified into three groups as immediate onset reactors, intermediate reactors, or late reactors (21–23). Most have symptoms from two or more organ systems (1, 20). In exclusively breast-fed infants with CMPA/CMPI, severe atopic eczema is a predominant symptom (1).

The overall prognosis of CMPA/CMPI in infancy is excellent, with a remission rate above 80% before 3 years of age. However, infants with IgE sensitization to cow's milk protein have an increased risk of persistent CMPA development

of allergy to other foods (about 50–60%), and development of inhalant allergy (up to 80% before the age of puberty) (1). The increased risk of development of other allergies seems to be confined to the group of infants with evidence of an early increased IgE response, perhaps due to genetic predisposition rather than to early exposure to cow's milk protein.

Prevention

There is evidence that the mode of early infant feeding influences the development of food allergy, especially in infants with hereditary atopic predisposition (physician's diagnosed atopic disease in first-degree relatives). For over 50 years, it has been debated whether breast-feeding can influence the risk of atopic diseases, and numerous studies have been conducted to test this hypothesis. Ideally, randomization to breast- or bottle-feeding should be done in such studies, but it seems unreasonable (and impossible) to allocate infants to bottle-feeding, if breast-feeding is possible. However, if breast-feeding is not established, randomization to different formulas can be done. No matter how careful such studies are planned and conducted, there will be a great risk of bias due to inevitable confounding factors such as social class, passive smoking, and other environmental factors. A possible protective effect of breast-feeding against the development of atopic diseases may be due to either avoidance of a "high dose" of cow's milk protein or a protective effect of human milk. Two common factors apparent in studies reporting benefit of breast-feeding were prolonged breast-feeding (at least 4–6 months) and delayed solid food introduction (after 4 months of age). Two factors common to the studies nonsupportive of an allergy-preventive effect of breast-feeding were a rather brief period of breast-feeding (less than 3–4 months) and early solid food introduction (1, 24). Recent prospective clinical trials in high-risk infants on the possible protective effect of breast-feeding in combination with avoidance of cow's milk and solid foods for at least 4 months have shown a significant reduction of the cumulative incidence of CMPA/CMPI (25–29). When breast milk is insufficient or lacking, a substitute formula is needed. Prospective studies show a preventive effect of an extensively hydrolyzed formula (eHF) in combination with avoidance of solid foods for at least 4 months in high-risk infants on the cumulative prevalence of CMPA/CMPI during the first years of life (24, 26, 30). Partially hydrolyzed formulas (pHF) may be effective in allergy prevention, but due to drawbacks of study design and lack of documentation, pHF cannot be

recommended at present. The protective effect against development of cow's milk allergy is a real prevention, and not only a postponement of the onset of symptoms (30). There is no documented beneficial effect of maternal diet during pregnancy. A few studies indicate a preventive effect of maternal avoidance of potential food allergens (milk, egg, fish) during the lactation period, but other studies do not confirm this finding (24, 30).

References

1. Høst A. Cow's milk protein allergy and intolerance in infancy. Some clinical, epidemiological and immunological aspects. *Pediatr Allergy Immunol* 1994;5 Suppl:5-36.
2. Bruijnzeel-Koomen CAFM, Ortolani C, Aas K, et al. Adverse reactions to food. Position paper. *Allergy* 1995; 50:623-36.
3. Niggemann B, Wahn U, Sampson HA. Proposals for standardization of oral food challenge tests in infants and children. *Pediatr Allergy Immunol* 1994;5:11-13.
4. Høst 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;45:587-96.
5. Halpern SR, Sellers WA, Johnson RB, Anderson DW, Saperstein S, Reisch JS. Development of childhood allergy in infants fed breast, soy or cow milk. *J Allergy Clin Immunol* 1973;51:139-51.
6. Gerrard JW, Mackenzie JWA, Goluboff N, Garson JZ, Naningas CS. Cow's milk allergy. Prevalence and manifestations in an unselected series of newborns. *Acta Paediatr Scand* 1997;234 Suppl:1-21.
7. Jakobsson O, Lindberg T. A prospective study of cow's milk protein intolerance in Swedish infants. *Acta Paediatr Scand* 1979;68:853-9.
8. Hide DW, Guyer BM. Cow's milk intolerance in Isle of Wight infants. *Br J Clin Pract* 1983;37:285-7.
9. Bock SA. Prospective appraisal of complaints of adverse reactions to foods in children during the first three years of life. *Pediatrics* 1987;79:683-8.
10. Høst A, Husby S, Østerballe O. A prospective study of cow's milk allergy in exclusively breast-fed infants. Incidence, pathogenic role of early inadvertent exposure to cow's milk formula, and characterization of bovine milk protein in human milk. *Acta Paediatr Scand* 1988;77:663-70.
11. Schrander JJP, Bogart JHP, Forget PP, Schrander-Stumpel CTRM, Kuiten RH, Krester ADM. Cow's milk protein intolerance in infants under 1 year of age: a prospective epidemiological study. *Eur J Pediatr* 1993;152:640-4.
12. Husby S. Dietary antigens. Uptake and humoral immunity in man [Thesis]. *APMIS* 1988;96 Suppl:1-40.
13. Buisseret PD. Common manifestations of cow's milk allergy in children. *Lancet* 1978;1:304-6.
14. Stintzing G, Zetterström R. Cow's milk allergy, incidence and pathogenic role of early exposure to cow's milk formula. *Acta Paediatr Scand* 1979;68:383-7.
15. Høst A, Husby S, Gjersing B, Larsen JN, Løwenstein H. Prospective estimation of IgG subclass and IgE antibodies to dietary proteins in infants with cow milk allergy. Levels of antibodies to whole milk proteins, BLG and ovalbumin in relation to repeated milk challenge and clinical course of cow milk allergy. *Allergy* 1992;47:219-29.
16. Jones AC, Miles EA, Warner JO, Colwell BM, Bryant TN, Warner JA. Fetal peripheral blood mononuclear cell proliferative responses to mitogenic and allergenic stimuli during gestation. *Pediatr Allergy Immunol* 1996;7:109-16.
17. Jacobsen HP, Halken S, Høst A, Bender L. Specific IgE antibodies against cow's milk protein in cord blood from newborns with and without atopic predisposition. *Pediatr Allergy Immunol* 1995;6 Suppl:98.
18. Oldæus G. Cow's milk hydrolysates. Prevention and treatment of cow's milk allergy. Linköping University Medical Dissertations No. 522. Linköping, Sweden, 1998.
19. Wittmann AM, von Leeuwen J, van der Zee JS, Aalberse RC. Food allergens in house dust. *Int Arch Allergy Immunol* 1995;107:566-8.
20. Goldman AS, Anderson DW Jr, Sellers WA, Saperstein S, Kniker WT, Halpern SR. Milk allergy. I. Oral challenge with milk and isolated milk proteins in allergic children. *Pediatrics* 1963;32:425-43.
21. Hill DJ, Ball G, Hoskings CS. Clinical manifestations of cow's milk allergy in childhood. I. Association with *in vitro* cellular immune responses. *Clin Allergy* 1988;18:469-79.
22. Hill DJ, Firer MA, Shelton MJ, Hosking CS. Manifestations of milk allergy in infancy: clinical and immunological findings. *J Pediatr* 1986;109:270-6.
23. Hill DJ, Ford RPK, Shelton MH, Hosking CS. A study of 100 infants and young children with cow's milk allergy. *Clin Rev Allergy* 1984;2:125-42.
24. Businco L, Dreborg S, Einarsson R, et al. Hydrolysed cow's milk formulae. Allergenicity and use in treatment and prevention. An ESPACI position paper. *Pediatr Allergy Immunol* 1993;4:101-11.
25. Halken S, Høst A, Hansen LG, Østerballe O. Effect of an allergy prevention programme on incidence of atopic symptoms in infancy. A prospective study of 159 high-risk infants. *Allergy* 1992;47:545-53.
26. Halken S, Høst A, Hansen LG, Østerballe O. Preventive effect of feeding high risk infants a casein hydrolysed formula or an ultrafiltrated whey hydrolysed formula. A prospective comparative clinical study. *Pediatr Allergy Immunol* 1993;4:173-81.
27. Lucas A, Brooke OG, Morley R, Cole TJ, Bamford MF. Early diet of preterm infants and development of allergic or atopic disease: randomized prospective study. *BMJ* 1990;300:837-40.
28. Vandenplas Y, Deneyr M, Sacre L, Loeb H. Preliminary data on a field study with a new hypoallergenic formula. *Eur J Pediatr* 1988;148:274-7.
29. Vandenplas Y, Hauser B, van den Borre C, Sacre L, Dab J. Effect of a whey hydrolysate prophylaxis of atopic disease. *Ann Allergy* 1992;68:419-24.
30. Halken S, Høst A. Prevention of allergic disease. Exposure to food allergens and dietetic intervention. *Pediatr Allergy Immunol* 1996;7 Suppl 9:102-7.