

FOOD ALLERGY: TWO COMMON TYPES AS SEEN IN BREAST AND FORMULA FED BABIES

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Cow's milk allergy can develop in both breast and formula fed babies. The allergy developing in breast fed babies is triggered by trace amounts of antigen, tends to cause severe reactions and may persist for several years. The allergy developing in formula fed babies is triggered by large amounts of antigen, is not associated with either positive prick tests or with anaphylactic reactions and often subsides spontaneously.

Introduction

COW'S MILK ALLERGY (CMA) has been the focus of attention and debate for a number of years. One of the early writers on the subject was Edwards A. Park,¹ at one time head of the Department of Pediatrics of Johns Hopkins Hospital. He described how his own son, who was being brought up on the breast, became drowsy and later vomited when at the age of six weeks he was first given 10 ml of diluted, boiled cow's milk. Four weeks later he was again given diluted, boiled cow's milk, this time only 5 ml. He collapsed and again vomited. Park had no doubt in his own mind that his son was highly allergic to cow's milk and in this respect differed, as he states, from the "considerable number of cases reported in the literature as examples of hypersensitiveness to cow's milk." He was sure that most children thought to be suffering from CMA were suffering "merely from ordinary forms of indigestion." There was obviously considerable debate, then as now, as to what actually constituted CMA. Some, like Park, included only those infants with severe anaphylactic reactions to cow's milk, others included infants with less severe symptoms. Clein,² when he described the symptoms which he recognised as being due to CMA, included those listed in Table I. He obviously included many that would have been excluded by Park.

Cow's Milk Allergy in Formula Fed Babies

In order to try to bring some semblance of order to the subject, Goldman and his colleagues³ studied a

group of 89 children with CMA. The only children studied were those who, when challenged on three separate occasions with cow's milk, reacted adversely, the reactions in any one baby being consistent. The symptoms of the babies included in Goldman's study are also listed in Table I. The distribution of symptoms in the two groups of children are very similar. Goldman included a few babies with more severe reactions and under the term asthma, we assume, included children who also had bronchitis. He did not mention a persistent rhinorrhea, constipation or a refusal to drink milk.

Goldman and his colleagues^{4,5} also carried out a number of studies, hoping to find a test other than oral challenge which might indicate that the baby had CMA. He concluded that the only reliable test was oral challenge. Although 59% of the babies with CMA, compared with 6% of controls, had positive skin tests to cow's milk proteins, skin tests were negative in 41% of cases and therefore could not be relied on to identify all the children with CMA. In his study he felt that three challenges with milk were necessary to prove the diagnosis. Bahna and Heiner⁶ consider that, in a typical case, one challenge is enough; we would concur.

The recognition of CMA is not difficult but many physicians are reluctant to make the diagnosis, with the result that many babies and infants are repeatedly ill and are often subjected to repeated courses of antibiotics which they might have been spared had the diagnosis been made soon after the baby first developed symptoms. CMA in formula fed babies should be suspected if, in the absence of any organic disease such as infantile pyloric stenosis, infectious gastroenteritis or cystic fibrosis of the pancreas, the child has recurrent symptoms involving the gastrointestinal tract (vomiting, diarrhea,

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Table I. Percentage of Children Manifesting the Various Symptoms of CMA in the Series Reported by Clein² and Goldman et al.³

	Clein n = 206	Goldman n = 89
Eczema	43	42
Vomiting	38	27
Colic	31	31
Diarrhea	23	40
Irritability	19	13
Bronchitis	17	
Rhinorrhea	13	
Asthma	15	31
Constipation	6	
Refusing milk	3	
Apathy, cyanosis and collapse	2	4
Urticaria and angioedema	2	8

colic and/or constipation), the respiratory tract (rhinorrhea, bronchitis or asthma), skin, (eczema or urticaria) and the central nervous system (irritability, restlessness and more rarely prolonged drowsiness). In most instances more than one system is involved, e.g., rhinorrhea and eczema or irritability and diarrhea.^{2,3,7} The prevalence of this type of CMA varies, depending on feeding habits, the persistence of the investigator and the symptoms thought by the investigator to be due to cow's milk.⁸⁻¹⁰

Confirmation of the diagnosis is made by demonstrating relief of symptoms with the avoidance of cow's milk, or other offending foods, and their recurrence with its reintroduction. Bahna and Heiner⁶ recommend avoidance of milk and dairy products for four weeks, followed by its cautious reintroduction. It is our custom to recommend avoidance of cow's milk and dairy products for seven to 10 days only, though avoidance for up to three weeks is occasionally required when the baby has respiratory symptoms. We then suggest that the baby be given as much milk as he was being given before he became ill. As soon as he reacts adversely, often after only one feeding, milk is withheld and he is once more given the food or formula which he tolerates. The challenge is difficult to implement if the baby is sensitive to many foods,⁷ as sometimes happens, and his symptoms do not clear with the simple elimination of cow's milk.

Cow's Milk Allergy in Breast Fed Babies

With the popularization of breast feeding we expected a fall in the prevalence of CMA, for Grulee¹¹ had shown that eczema, for example, was seven times as common in babies brought up on cow's milk as in those brought up on the breast, and Matthew and his colleagues¹² had shown that breast feeding, coupled with environmental control, reduced the incidence of eczema. Studies by others have been confirmatory.^{13,14} In spite of these findings Gordon and his colleagues¹⁵ have more recently found that, in allergic families, breast feeding does not protect the baby from the development of either atopic disease or high levels of IgE. This is not

surprising for babies can, unfortunately, be sensitized to foods being taken by the mother. This was first shown many years ago at a time when most babies were brought up on the breast.^{16,17} It has been confirmed more recently by Jakobsson and Lindberg¹⁸ and ourselves.¹⁹

We have records of 73 patients seen during the past 25 years who reacted adversely to foods being taken by the mother; 27 of the patients have been seen during the past two years. The reason for the recent increase in patients seen is probably due to the greater awareness of the problem by referring practitioners and by ourselves. It may also be due to the increase in the prevalence of breast feeding. The symptoms (Table II) manifested by babies sensitive to foods being taken by the mother are the same as those manifested by babies being brought up on a cow's milk formula but differ in this respect, that if the baby is actually given the food to which he is sensitive, he may have a severe, sometimes anaphylactic reaction.

The age at which symptoms were first noted in the 45 cases in which this information was recorded is given in Table III. In five infants symptoms seemed to date from the first feed or at least from the first week of life, suggesting that the baby may have been sensitized antenatally.

The foods which the mother had to avoid in order to bring relief to her baby are indicated in Table IV. A few babies were also sensitive to many other foods. The diagnosis was made in each instance by demonstrating relief of symptoms when the mother avoided the food to which her baby was sensitive and their return when she once more took the food. Prick skin tests were initially not carried out but more recently a few selected prick tests and RAST have been undertaken. Prick tests to foods to which the baby is sensitive are often positive and some have been strikingly so, in fact some of the strongest reactions to foods that we have seen have been in babies sensitive to foods being taken by the mother (Figure 1). This is in marked contrast to the negative prick tests to foods, cow's milk especially, seen in formula fed babies sensitive to cow's milk.

Allergies in Breast and Formula Fed Babies Contrasted

Although the symptoms manifested by formula fed babies sensitive to cow's milk and breast fed babies

Table II. Presenting Symptoms in 73 Babies Sensitive to Foods Being Taken by the Mother

Symptom	Number
Colic	28
Vomiting	17
Diarrhea	16
Rhinorrhea	16
Wheezy bronchitis	13
Eczema	11
Diaper dermatitis	3
Urticaria	2

sensitive to foods ingested by the mother are similar, there are several important and significant differences. The formula fed baby's symptoms are precipitated by relatively large amounts of antigen. The 7 kg infant

Table III. Age at Onset of Symptoms of CMA in Breast Fed Infants in 45 Instances in Which the Data was Recorded.

Age	Number
First week	5
2-4 weeks	15
2-4 months	17
5-12 months	8

Table IV. Foods Taken by the Mother which Precipitated Symptoms in Her Baby.

Food	Number
Cow's milk	61
Egg	11
Citrus fruits	8
Wheat	6
Chocolate	2



Figure 1. Prick tests in a totally breast fed baby with eczema due to foods, and asthma due to animal danders. First column: H = histamine, 1:1000, C = control, HD = house dust, M = house dust mite. Second column: C = cat dander, D = dog dander, C = cattle dander, H = horse dander, F = feathers. Third column: M = cow's milk, E = egg, P = peanut.

sensitive to his/her formula is usually taking a 1 litre of his formula a day. This is equivalent to a 70 kg adult drinking 10 litres of milk a day. The breast fed baby, by contrast, is taking only trace amounts of the food to which he or she is sensitive for though the mother may herself be taking large amounts of the food, only trace amounts get through to her milk and into her baby. The reaction in the formula fed baby is usually associated with negative prick skin tests and is probably mediated by IgG or IgM antibodies or by immune complexes.^{20,21} The reaction in the breast fed baby is often associated with positive prick skin tests and RAST and is probably mediated by IgE antibodies. This is in keeping with the observation of Bjorksten and Saarinen²² that IgE specific antibodies to cow's milk proteins are detectable only in babies who have been breast fed.

Because the reaction in the two types of food allergy is mediated by different mechanisms the formula fed baby when given, for example eight ounces of the formula to which he is sensitive, has only a minor reaction (rhinorrhea, bronchitis, vomiting or diarrhea). He does not collapse. By contrast the breast fed baby who is sensitive to the trace amounts of cow's milk in his mother's milk may have a severe reaction if given only small amounts of cow's milk, as was well illustrated by Park's case report.¹ This reaction occurred even though the baby had been symptom free while on the breast.

We have noticed that the foods to which babies react are often those which the mother had taken in large amounts antenatally. We think that it is for this reason that cow's milk is so often incriminated. Ratner²³ made the same observation and gave 15 illustrative case histories in which the baby was found to be sensitive to foods (milk, egg, wheat and nuts) which the mother had consumed in excessive amounts when pregnant. That the reaction is IgE-mediated is in keeping with our knowledge of IgE-mediated reactions, for we know that they are triggered by trace or small amounts of antigen.²⁴ Sensitivities may, but do not always, persist for more than a few years.²⁵ The reaction of the formula fed baby, by contrast, is usually transient and if the baby is later given cow's milk he may not react adversely to it but if he is once more given cow's milk in large amounts on a daily basis his symptoms often return.²⁶

Discussion

Laboratory studies suggest that cow's milk antigens may trigger several different immune mechanisms.^{20,21,27,28} Our clinical observations suggest that there are at least two different types of CMA. The first, seen in the breast fed baby, is triggered by small amounts of antigen and is probably IgE-mediated. The second, seen characteristically in the formula fed baby, is triggered by large amounts of antigen and is probably not IgE-mediated. Firer and his colleagues²⁹ in Australia

have reached similar conclusions. We feel that it is important to make the distinction between these two types for several reasons. First, their management is different. As the child with IgE-mediated disease is on the breast, it is his mother's diet which has to be modified for if the baby is thought to be allergic to breast milk and is taken off the breast and placed on a cow's milk formula, his problems will almost certainly be compounded. He will probably be sensitive to cow's milk.^{18,19} When the formula fed baby develops CMA it is naturally his own formula that has to be changed. Second, the prognosis is different. When the breast fed baby is later given foods care will need to be taken to avoid those foods to which he is known to be sensitive; he may have to avoid cow's milk and dairy products for a number of years. By contrast, the child with disease not mediated by IgE may later be able to tolerate moderate amounts of cow's milk, particularly if it is given infrequently, without coming to any harm. With regards to antenatal advice, the physician counselling the mother of a baby with either form of the disease, but particularly with IgE mediated disease, will advise her when next pregnant to either avoid cow's milk and dairy products completely or to ingest them in limited amounts only.

The third reason for making the distinction between the two types of CMA is that it is necessary to do this if an attempt is to be made to determine whether breast feeding does or does not play a role in the prevention of allergy, specifically to cow's milk. Clearly breast feeding can be expected to postpone the development of the type of CMA seen in formula fed babies and if the baby is never given cow's milk in the quantities that are given to most formula fed babies CMA may be prevented altogether. Breast feeding alone, however, cannot be expected to prevent the IgE-mediated CMA seen in the breast fed baby and though we do not think that this is nearly as common a problem as CMA in the formula fed baby, some of the most difficult cases to manage fall into this category. One breast feeding mother, for example, had a baby who reacted adversely to so many of the foods that she was eating that she said, were she to have another baby she would consider bringing him upon on formula rather than on breast milk, hoping that he might be sensitive to cow's milk only rather than to most of the foods that she herself was eating. The net result of breast feeding on the prevalence of CMA has still to be determined but it may not reduce it to the extent that might have been anticipated. It may be for this reason that infantile colic, while often relieved by the avoidance of cow's milk by the breast feeding mother¹⁸ and by the substitution of nutramigen for cow's milk formula in the formula fed baby,³¹ is as prevalent in the breast as in the formula fed baby.³²

That breast feeding is associated with the severer forms of CMA is also suggested by a review of Goldman's studies.³ He did not give details of the previous

feeding patterns of the babies in the study; we cannot tell, therefore, whether the babies who had positive skin tests to cow's milk had or had not been breast fed. However, two of the case histories, 5 and 6, presented because the babies had such severe reactions to cow's milk had, as we might have anticipated, both been breast fed. Case 5, who had been breast fed for three months, had an anaphylactic reaction when first given cow's milk at this time and was still very sensitive to cow's milk, as well as egg, at the age of two and a half years. Case 6 was also breast fed and when first given 120 ml of cow's milk at the age of three weeks developed seizures and diarrhea. He reacted in an identical manner when again given cow's milk on two subsequent occasions. These examples lend weight to our suggestion that when CMA occurs in breast fed babies it is usually of the severe form.

The fourth reason for making the distinction between the two types of CMA is that it may throw light on the biological importance of IgE. IgE is known to play an important role, probably as a gate opener, in the primary immune response, at least to viral antigens.^{33,34} To be effective in this role IgE must be produced in the very early stages of an infection, when antigenic exposure is minimal. Those who respond best to minimal, low dose stimulation can be expected to mount the most rapid and presumably effective immune response. That some babies, but not all, react to trace amounts of cow's milk and other food antigens encountered in breast milk indicates that some, presumably the most highly allergic, respond well to low dose stimulation. The inference is that the atopic individual is par excellence a low dose responder and can be expected to respond more briskly than the non-atopic to minimal antigenic stimulation. The more atopic the individual the broader his probable response to low dose stimulation. If this is so, this may well have given him a selective advantage in evolutionary history.

References

1. Park EA: A case of hypersensitiveness to cow's milk. *Am J Dis Child* 19: 46-54, 1920.
2. Clein NW: Cow's milk allergy in infants. *Pedia Clin No Am* 1: 949-962, 1954.
3. Goldman AS, Anderson DW, Sellers WA, Saperstein S, Kniker WT and Halpern SR: Milk allergy. I. Oral challenge with milk and isolated milk proteins in allergic children. *Pedia* 32: 425-443, 1963.
4. Goldman AS, Sellers WA, Halpern SR, Anderson DW, Furlow TE and Johnson CH: Milk allergy. II. Skin testing of allergic and normal children with purified milk proteins. *Pedia* 32: 572-579, 1963.
5. Saperstein S, Anderson DW, Goldman AS and Kniker WT: Milk allergy. III. Immunological studies with sera from allergic and normal children. *Pedia* 32: 580-587, 1963.
6. Bahna SL and Heiner DC: *Allergies to Milk*. New York: Grune and Stratton, 1980.
7. Gerrard JW, Lubos MC, Hardy LW, Holmlund BA and Webster D: Milk allergy: clinical picture and familial incidence. *Can Med Assoc J* 97: 780-785, 1967.
8. Gerrard JW, MacKenzie JWA, Goluboff N, Garson JZ and Maningas CS: Cow's milk allergy: prevalence and manifestations

- in an unselected series of newborns. *Acta Paedia Scand Supplementum* 234: 1-21, 1973.
9. Halpern SR, Sellers WA, Johnson RB, Anderson DW, Saperstein S and Reisch JS: Development of childhood allergy in infants fed breast, soy or cow's milk. *J. Allerg & Clin Immunol* 51: 139-151, 1973.
 10. Jakobsson I and Lindberg T: A prospective study of cow's milk protein intolerance in Swedish infants. *Acta Paedia Scand* 68: 853-859, 1979.
 11. Grulee CG and Sanford HN: The influence of breast and artificial feeding on infantile eczema. *J Pediatr* 8: 223-225, 1936.
 12. Matthew DJ, Taylor B, Norman AP, Turner MW and Soothil JF: Prevention of eczema. *Lancet* 1: 321-324, 1977.
 13. Saarinen UM, Kajosaari M, Backman A and Siimes MA: Prolonged breast feeding as prophylaxis for atopic disease. *Lancet* 2: 163-168, 1979.
 14. Chandra RK: Prospective studies on the effect of breast feeding on incidence of infection and allergy. *Acta Paedia Scand* 68: 691-694, 1979.
 15. Gordon RR, Ward AM, Noble DA and Allen R: Immunoglobulin E and the eczema-asthma syndrome in early childhood. *Lancet* 1: 72-74, 1982.
 16. Talbot FB: Eczema in childhood. *Med Clin No Am* 1: 985-996, 1918.
 17. O'Keefe ES: The relation of food to infantile eczema. *Boston Med Surg J* 183: 569, 1920.
 18. Jakobsson I and Lindberg T: Cow's milk as a cause of infantile colic in breast fed infants. *Lancet* 2: 437-439, 1978.
 19. Gerrard JW: Allergy in breast fed babies to ingredients in breast milk. *Ann Allerg* 42: 69-72, 1979.
 20. Lee SK, Kniker WT, Cook CD and Heiner DC: Cow's milk induced pulmonary disease in children. *Adv Pediatr* 25: 39-57, 1978.
 21. Minor JD, Tolbert SG and Frick OL: Leukocyte inhibition factor in delayed-onset food allergy. *J Allerg & Clin Immunol* 66: 314-321, 1980.
 22. Bjorksten F and Saarinen UM: IgE antibodies to cow's milk in infants fed breast milk and milk formulae. *Lancet* 2: 624, 1978.
 23. Ratner B: A possible causal factor of food allergy in certain infants. *Am J Dis Child* 36: 277-288, 1936.
 24. Jarret EEE: Activation of IgE regulatory mechanisms by trans-mucosal absorption of antigens. *Lancet* 2: 223-225, 1977.
 25. Kaplan MS and Solli NJ: IgE to cow's milk protein in breast fed atopic children. *J Allerg & Clin Immunol* 64: 122-126, 1979.
 26. Deamer WC, Gerrard JW and Speer F: Cow's milk allergy: a critical review. *J Fam Pract* 9: 223-232, 1979.
 27. Firer MA, Hosking CS and Hill DJ: Cow's milk allergy and eczema: patterns of antibody response to cow's milk in allergic skin disease. *Clin Allerg* 12: 385-390, 1982.
 28. Frick OL: B-lactoglobulin in immune complexes in milk sensitive children. *J Allerg & Clin Immunol* 69: 157, 1982.
 29. Firer MA, Hosking CS and Hill DJ: Effect of antigen load on development of milk antibodies in infants allergic to milk. *Brit Med J* 283: 693-696, 1981.
 30. Minor JD, Tolbert SG and Frick OL: Leukocyte inhibition factor in delayed-onset food allergy. *J Allerg & Clin Immunol* 66: 314-321, 1980.
 31. Lothe L, Lindberg T and Jakobsson I: Cow's milk formula as a cause of infantile colic: a double-blind study. *Pedia* 70: 7-10, 1982.
 32. Hide DW and Guyer BM: Prevalence of infantile colic. *Arch Dis Child* 57: 559-560, 1982.
 33. Bahna SL, Horwitz CA, Fiala M and Heiner DC: IgE response in heterophil-positive infectious mononucleosis. *J Allerg & Clin Immunol* 62: 167-173, 1978.
 34. Bahna SL, Horwitz CA and Heiner DC: IgE in cytomegalovirus mononucleosis (CMV Mono). *J Allerg & Clin Immunol* 61: 177, 1978.

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"A great deal of talent is lost in the world for the want of a little courage. Every day sends to their graves obscure men whom timidity prevented from making a first effort; who, if they could have been induced to begin would in all probability have gone great lengths in the career of fame. The fact is, that to do anything in the world worth doing, we must not stand back shivering and thinking of the cold and danger, but jump in and scramble through as well as we can."

Sydney Smith