
Cow's milk allergy: a new understanding from immunology

John Walker-Smith, MD, FRCP, FRACP, FRCPC

Background: Because of the high prevalence of cow's milk allergy as one of the most frequent clinical presentations of food allergy in infancy and early childhood, it is important to define the condition accurately. Allergy must be distinguished from the broader term *food intolerance*, which may be defined as a reproducible adverse reaction to the ingestion of a food or to any of its components, ie, proteins, carbohydrates, fats, and additives, and which includes toxic, metabolic, and allergic reactions. By contrast, food allergy may be defined as an adverse clinical reaction to a specific food component and that is immunologically mediated. The rapid increase in knowledge resulting from research in immunology in recent years has not only led to a better understanding of the basis for cow's milk allergy in infancy, but has also yielded considerable promise for improved diagnosis and management of the condition.

Objective: To review recent developments in immunology which demonstrate how they may lead to a better understanding of the clinical spectrum of cow's milk allergy in infants and children.

Data Sources: English language articles were selected from PubMed and selected abstracts that would have immediate, practical clinical implications. The review focuses on themes related to gastro-enterology, focusing upon the esophagus and small intestine.

Results: In cow's milk-sensitive esophagitis, there is dense infiltrate of eosinophils and increased T cell activation with upregulation of the chemokine eotaxin. In cow's milk-sensitive enteropathy, there is T cell activation, and it often results as a sequela of gastro-enteritis. Changing patterns in recent years suggests that sensitization occurs via mother's breastmilk to cow's milk and multiple food antigens. There is evidence of reduced Th₁ response in these children. This is related to associated IgA deficiency and low levels of cytokine transforming growth factor β .

Conclusions: The results of the present review demonstrate that the clinical manifestations of cow's milk allergy are very diverse, with differences between developing and developed countries. Understanding the immunologic mechanisms is of key importance in understanding this diversity.

Ann Allergy Asthma Immunol. 2003;90(Suppl 3):81–83.

INTRODUCTION

Cow's milk allergy is one of the most frequently encountered clinical syndromes of food allergy in infancy and early childhood. It is important to use accurate definitions. Allergy must be distinguished from the broader term *food intolerance*, which may be defined as a reproducible adverse reaction to the ingestion of food or to any of its components, ie, proteins, carbohydrates, fats, and additives. Such adverse reactions include toxic, metabolic, and allergic reactions. By contrast, food allergy may be defined as an adverse clinical reaction to food due to any type of abnormal immune response to a specific food component. Therefore, gastro-intestinal food allergy are those clinical syndromes of food allergy where gastro-intestinal symptoms follow food ingestion and the underlying mechanism is an immunologically mediated reaction within the gastro-intestinal tract. These symptoms may be accompanied by other manifestations outside the alimentary tract, such as in the skin or the respiratory tract.

From a clinical perspective gastro-intestinal allergy patients may be grouped into those with quick-onset allergy, ie, symptoms appear within 1 hour of food ingestion, and those with a slow onset, ie, symptoms appear after more than 1 hour after food ingestion, and finally those patients who have both quick and slow onset. When quick-onset symptoms occur, the child's mother is usually aware that food ingestion is related to the child's symptoms, whereas when the symptoms take longer to appear there may not be any such awareness.

ALLERGIC MECHANISMS

Recognition of the immunologic mechanisms involved in cow's milk allergy helps understanding. As a broad generalization when quick-onset reactions occur, these are IgE-mediated. This means mast cells are activated, and mediators, such as histamine and arachidonic acid metabolites, are released, and characteristically there is no structural damage within the gastro-intestinal tract. When slow-onset reactions occur, they are characteristically non—IgE-mediated. In the past some workers did not regard such reactions as allergic. However, it is now well accepted that non-IgE reactions do occur and that these may be T cell-mediated. Such reactions are characterized by cytokine release and attraction of macrophages to the lesions with release of lysosomal enzymes

University Department of Paediatric Gastroenterology, Royal Free Campus, Royal Free and University College Medical School, University College, London, United Kingdom.

Received for publication June 4, 2002.

Accepted for publication in revised form January 14, 2003.

and structural tissue damage within the gastro-intestinal tract. The severity of the lesion depends upon the ratio of Th₁ to Th₂ cells. More severe lesions are associated with Th₁ lesions.

CLINICAL SPECTRUM OF COW'S MILK ALLERGY

Turning now to cow's milk allergy, which is the classical example of gastro-intestinal food allergy in childhood, several syndromes are recognized. Table 1 shows a schematic representation of the clinical spectrum of cow's milk allergy in infancy and childhood, grouped according to various clinical presentations as well as temporal rates of onset. It can be seen that these reactions range from those of quick onset such as acute cow's milk allergy, to those of slow onset such as cow's milk esophagitis, cow's milk-sensitive enteropathy, and cow's milk colitis. A third group with a varied presentation is seen as part of a multiple-food allergy.

DIAGNOSIS OF COW'S MILK ALLERGY

From a practical perspective diagnosis in gastro-enterologic practice is usually related to a clear response to food elimination evaluated clinically and in the laboratory. For organ-specific disorders, classically serial biopsies related to elimination and challenge were undertaken and for nonorgan-specific, double-blind, placebo-controlled challenge. In practice, food challenge is not used routinely; now the emphasis is on the recognition of characteristic pathology and its response to food elimination.

COW'S MILK-SENSITIVE ESOPHAGITIS

This syndrome has been well described by Cavataio et al.¹ Characteristically, there is a dense infiltrate with eosinophils within the esophageal mucosa but this is not a specific finding; in children with cow's milk sensitization, it responds to cow's milk elimination. However, in cow's milk sensitization, as opposed to reflux, there are more eosinophils in the lamina propria.² Butt et al³ have demonstrated that when children with this disorder are compared with those with primary reflux esophagitis there was an increase of the T cell activation marker CD-25 and HLA-DR expression providing evidence of T cell activation, but most strikingly there was upregulation of the chemokine eotaxin. Whilst it was suggested that lymphocytes homed from the gut to the esophagus, it was the expression of eotaxin in the esophagus recruiting eosinophils which produces the characteristic pathology. Thus, it

Table 1. Schematic Presentation of the Clinical Spectrum of Cow's Milk Allergy in Infancy and Childhood Grouped According to Clinical Presentation and Temporal Rates of Onset

Clinical presentation	Example
Quick-onset syndromes	Acute cow's milk allergy
Slow-onset syndromes	Cow's milk esophagitis Cow's milk-sensitive enteropathy Cow's milk colitis
Varied	Part of multiple food allergy

was suggested that there is a distinct epithelial chemokine distribution in infantile cow's milk-induced esophageal reflux. If this can be confirmed in larger numbers of children, eotaxin may be an attractive molecule as a potential target for specific immunotherapy.

Cow's milk-sensitive esophagitis can be diagnosed by demonstrating milk elimination and challenge responsive gastro-esophageal reflux. Histopathologically eosinophilic esophagitis may be indistinguishable from eosinophilic esophagitis, but such children neither respond to cow's milk elimination nor do they have associated gastro-esophageal reflux.

COW'S MILK-SENSITIVE ENTEROPATHY

This is a disorder characterized by an abnormal small intestinal mucosa when having cow's milk in the diet. The abnormality is reversed by a cow's milk-free diet only to recur once more on challenge. It is a temporary disorder of early infancy. There is a typical small intestinal enteropathy characterized by a thin mucosa and a patchy lesion. Classically, it was diagnosed by serial biopsies related to elimination and challenge. Nowadays, the findings of a typical enteropathy in a child with chronic diarrhea and failure to thrive combined with a rapid response to elimination of cow's milk are enough to make the diagnosis. Such children nearly always have malnutrition, which characteristically occurs as a sequel to gastro-intestinal infection.⁴ So this problem is declining in developed communities, but is still a common and important problem in developing communities.

Persistent small intestinal mucosal damage following gastro-enteritis may be attributable to persisting infection with a bacterial organism such as enteropathogenic *Escherichia coli*, a further insult with a new infectious agent, or to sensitization to a food antigen, most often cow's milk. The mechanism of the mucosal damage is related to T cell activation.

CHANGING PATTERNS

Gastro-intestinal infection, especially infection with enteropathogenic *E. coli*, has greatly diminished in developed communities. The latter has virtually disappeared in Britain, so the infants with severe small intestinal enteropathy attributable to cow's milk allergy rarely present with these symptoms nowadays. Yet in gastro-enterologic practice, children with less severe or even minor enteropathy still occur in developed communities, but these cases are often associated with immunodeficiency such as IgA deficiency. So in developed communities, children with the following features may be seen: namely, gastro-esophageal reflux, sleep disturbance, and colic with slow linear growth, but without the characteristic chronic diarrhea and malnutrition with severe failure to thrive associated with severe enteropathy, seen in the past associated with postenteritis syndrome. Such children may be intolerant to hydrolysates, a completely new phenomenon in recent years.

Murch⁵ has produced evidence that these infants may be sensitized via their mother's breastmilk; such cases have been seen increasingly in tertiary clinics in recent years. There may

be sensitization to multiple food antigens, although cow's milk is clinically usually the dominant feature. A family history is important in such children.⁶ Latcham et al⁶ studied 121 children with multiple-food allergy divided into those that had quick and slow reactions and those with slow reactions alone. They found that overall IgE was associated with quick-onset responses but not sensitization itself. They suggested that IgE may alter the type of response to food antigens, but actual sensitization to food antigens relates to immune dysregulation. The pattern in these children was consistent with a reduced systemic Th₁ response. Murch⁵ has suggested that a fundamental problem may be an inadequate response by cells of the innate immune system.

For some years it has been known that gastro-intestinal food allergy is associated IgA deficiency. Now transforming growth factor (TGF)- β is the major determinant of B-cell IgA production, and it is central in low-dose oral tolerance. Perez-Machado et al⁷ showed that there is inadequate production of the cytokine, TGF- β in children with cow's milk allergy alone or as part of multiple-food allergy. This has been shown by single cell cytokine production (CD8 lamina propria lymphocytes) and by immunohistochemistry. It seems probable that a major factor in accounting for sensitization in these children who are sensitized via the tiny amounts of antigen in breastmilk may be absence or deficiency of TGF- β by Th₃ cells.

CONCLUSION

The clinical manifestations of cow's milk allergy are very diverse and differ between developing and developed communities. Understanding the immunologic mechanisms involved is of key importance in understanding this diversity. A shift to Th₁ may be associated with tissue damage in the gastro-intestinal tract and gastro-intestinal infection, whereas a shift to Th₂ may be associated with only minor damage or

normal mucosa. Much more work is required to elucidate these mechanisms.

REFERENCES

1. Cavataio F, Iacono G, Montalto G, Soresi M, Tumminello M, Carroccio A. Clinical and pH-metric characteristics of gastro-oesophageal reflux secondary to cows' milk protein allergy. *Arch Dis Child*. 1996;75:51–56.
2. Furuta GT. Eosinophils in the esophagus: acid is not the only cause. *J Pediatr Gastroenterol Nutr*. 1998;26:468–471.
3. Butt AM, Murch SH, Ng CL, Kitching P, Montgomery SM, et al. Upregulated eotaxin expression and T cell infiltration in the basal and papillary epithelium in cow's milk associated reflux associated reflux oesophagitis. *Arch Dis Child*. 2002;87:124–131.
4. Walker-Smith JA, Murch SH. Gastrointestinal food allergy. In: *Diseases of the Small Intestine in Childhood*, 4th ed. Oxford, UK: Isis Medical Media, 1999:45–61.
5. Murch SH. The immunologic basis for intestinal food allergy. *Curr Opin Gastroenterol*. 2000;16:552–557.
6. Latcham F, Merino F, Lang A, Garvey J, Thomson MA, Walker-Smith JA, Davies SE. A pattern of minor immuno-deficiency and subtle enteropathy in children with multiple food allergy. *J Pediatr*. 2003 (in press).
7. Perez-Machado MA, Thomson MA, Walker-Smith JA, Murch SH. Constitutively decreased mucosal Th3 suppressor cells may allow low-dose sensitisation in infancy. *Immunol Lett*. 1999;69:101–102.

Requests for reprints should be addressed to:

John Walker-Smith, MD

The Wellcome Trust Centre for the History of Medicine at UCL

University College London

24 Eversholt Street

London NW1 1AD United Kingdom

E-mail: johnwalker_smith@hotmail.com
