

An eye witness perspective of the changing patterns of food allergy

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Food allergy may affect the gastrointestinal tract of children and adults too, albeit less commonly. The changing clinico-pathological expression of such food allergy in children over a 30 year period is related, from the eye witness perspective of a paediatric gastroenterologist in London. Tissue diagnosis by biopsy, related to dietary elimination and challenge has been the basis for the first clinico-pathological descriptions and accurate clinical diagnosis of these syndromes as they affect the gastrointestinal tract. In the 1970s cow's milk sensitive enteropathy presenting as chronic diarrhoea and failure to thrive in infancy often after infective gastroenteritis, especially with enteropathogenic *Escherichia coli*, was an important problem. By the late 1990s such presentations had become most uncommon in developed communities but they continue to occur in developing communities. By contrast in more recent times, multiple food allergy associated with minor small intestinal enteropathy and gastro-oesophageal reflux in older children has become an important clinical problem in children seen in developed communities. Accompanying these changes has been a dramatic fall in the number of children with clinically severe gastroenteritis with severe dehydration requiring hospital admission. Furthermore, the

widespread diagnostic use of endoscopy of the upper and lower gastrointestinal tract in children with multiple biopsies has expanded gastroenterological diagnosis in children. This approach gives information about the oesophagus and ileo-colon not available in the earlier studies, which largely concentrated upon small intestinal biopsies, obtained by Crosby capsule biopsy. So, over this 30 year period clinico-pathological expression has altered but also the diagnostic approach has technically changed. *Eur J Gastroenterol Hepatol* 17:1313–1316 © 2005 Lippincott Williams & Wilkins.

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Introduction

The conception that food allergy may affect the gastrointestinal tract of both children and adults is now established, as this Review in depth makes clear. It was not ever so. This conception has been a source of much controversy amongst gastroenterologists, allergists and beyond. There is now an increasing recognition that food allergy does affect the gastrointestinal tract of man. This relates to two main facts. First, there is the recognition that the gastrointestinal tract has a major immunological role with the rapid expansion of knowledge of this role, as described by Teitelbaum and Walker [1]. Second, there is the increasing diagnostic use of both upper endoscopy (with biopsy of the oesophagus as well as the small intestine) and also ileo-colonoscopy (with multiple biopsies). The majority of clinico-pathological studies have been performed in children. Yet as Moneret-Vautrin [2] makes clear, chronic gastrointestinal food allergy in adults, whilst rare, does exist. The evidence for this is based upon a combination of endoscopy, biopsies and food challenges.

This personal review is written from the perspective of a paediatric gastroenterologist who has worked closely with adult gastroenterologists and allergists over a

number of years, as an eye witness concerning the changing patterns of gastrointestinal food allergy as seen in Britain. There has also been regular contact with children in the developing world. My first publication in the field was a review in 1975 [3] and the most recent in 2004 [4]. The latter paper reveals a large expansion in knowledge concerning the immunology of food allergy but the concerns of the first paper related in part to diagnostic criteria. Yet the problems of accurate clinical diagnosis, as applied for routine practice, still remain 30 years later, as Murch [5] makes clear. At present the best evidence for gastrointestinal food allergy relates to evidence of tissue abnormality which responds to dietary elimination, only to relapse upon food challenge, but this is not a simple approach. Hopefully, in the future non-invasive methods will be developed.

However, the pattern of disease as seen in children in developed communities has changed significantly during that period, as Murch [5] states. It is also clear that the pattern of disease is different between developed and developing communities. The pattern of food allergy formerly seen in developed communities is still seen in those that are developing.

Definitions

The first problem that arose concerning the recognition of food allergy was the issue of accurate definition. *Ab initio* it was seen to be important to distinguish conceptually between the broader term 'food intolerance' and the more specific term 'food allergy'. Cow's milk protein intolerance and cow's milk allergy were imprecisely treated as exchangeable terms in clinical practice, as reviewed in 1975 [3].

It was also seen to be important that definitions should be agreed between clinical allergists, gastroenterologists and scientists. So the British Society of Allergy and Clinical Immunology (BSACI) convened a working group made up of representatives of these three groups to draw up definitions of these terms [6]. These definitions are now widely agreed.

Food intolerance may be defined as a reproducible adverse reaction to ingestion of food or to any of its components, i.e., proteins, carbohydrates, fats and additives. Such adverse reactions include toxic, metabolic and allergic reactions.

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.

In children gastrointestinal food allergies are characterized by the onset of gastrointestinal symptoms following food ingestion, where the underlying mechanism is an immunologically mediated reaction within the gastrointestinal tract [7].

Changing clinical patterns of gastrointestinal food allergy in childhood

The 1975 review was triggered by the publication of clinico-pathological studies from Finland [8] and France [9], which described abnormal proximal small intestinal mucosa in children diagnosed as malabsorption with cow's milk intolerance or cow's milk protein allergy. From these and other observations it was natural to use the paediatric model developed to diagnose coeliac disease, defined as permanent gluten sensitive enteropathy [10]. This model required demonstration of a small intestinal enteropathy on biopsy, which responded to elimination of cow's milk from the child's diet by showing significant improvement – even complete healing – followed by relapse of the small intestinal lesion after challenge, as demonstrated by a third small intestinal biopsy. A single case report of serial biopsies using this approach was included in the 1975 review [3]. This observation was later extended [11] and described as cow's milk sensitive enteropathy. Changes in the density of intra-epithelial lymphocytes at diagnosis, after cow's milk elimination and after a positive challenge with cow's milk were also described [12].

These changes were similar to gluten related changes in coeliac disease. Clinically, this entity appeared to be a transient intolerance of cow's milk in children under the age of 2 years. So, unlike the permanent state of gluten intolerance in coeliac disease cow's milk allergy with enteropathy was temporary.

However, more recently in Finland significant cow's milk sensitive enteropathy (albeit very mild morphologically) has been observed in individuals in later life who had been thought to have outgrown cow's milk allergy [13]. The infants seen in Finland in the 1970s with chronic diarrhoea and failure to thrive who had cow's milk sensitive enteropathy have now vanished from the clinical scene there.

In London the children seen in the 1970s and 1980s with cow's milk sensitive enteropathy in a deprived community in east London, with many immigrants from the Indian sub-continent, commonly had a history of preceding gastroenteritis, often with enteropathogenic *Escherichia coli* [14,15]. Such children with chronic diarrhoea and failure to thrive have almost disappeared from current clinical practice in London. Gastrointestinal infection with enteropathogenic *E. coli* of the conventional serotypes has completely disappeared in local children. However, in developing communities it remains a very important problem and a significant cause of small intestinal mucosal enteropathy [16]. Gastroenteritis requiring hospital admission and intravenous fluids is also now uncommon. At Queen Elizabeth Hospital for Children gastroenteritis was so common that until the early 1990s there was a daily gastroenteritis clinic. Although rotavirus infection remains common its clinical expression with severe acute diarrhoea has declined. Persistent diarrhoea following rotavirus gastroenteritis with chronic diarrhoea and failure to thrive has become uncommon. A review of such cases as part of the post-enteritis syndrome showed they were often characterized by multiple viral infections, several hospital acquired, with no good evidence that the chronic diarrhoea followed directly from a single episode of infection with rotavirus [17].

It is the children with post-enteritis enteropathy related to infection with bacteria or multiple viral infections, followed by cow's milk allergy, that are relevant to the animal studies of Heyman [18], concerning increased intestinal permeability.

At the present time infants presenting with chronic diarrhoea and failure to thrive due to cow's milk sensitive enteropathy with a coeliac-like presentation have almost disappeared in Britain, just as they have in Finland. Furthermore, intractable diarrhoea in infancy has now become a rarity, only occurring in rare disorders such as

microvillous atrophy [19]. The previous prevalence of intractable diarrhoea in infancy was related to failure to make an accurate diagnosis due to lack of adequate gastrointestinal investigation, especially biopsy and so failure to establish effective therapy.

However, more recent studies of older children in Finland [20] using ileo-colonoscopy with multiple biopsies have established the presence of intestinal lympho-nodular hyperplasia in children with food allergies but not the severe proximal small intestinal enteropathy reported in the 1970s in infancy. This importance of ileal lympho-nodular hyperplasia as a gastrointestinal manifestation of food allergy in older children has been confirmed by others [21]. In children seen in London with food allergy in recent times, a subtle enteropathy may be present and there are immunological abnormalities in the biopsied mucosa, but not the severe enteropathies seen previously in infancy. However, subtle enteropathies were seen in the 1970s and 1980s as well as the severe lesions, e.g., patchy enteropathy [22] and a thin mucosa resulting from true villous shortening rather than marked hyperplasia [23]. The present situation appears to be that the severe lesions associated with cow's milk allergy are no longer seen but the milder or subtle lesions persist.

London children seen during the last decade at a gastrointestinal food allergy clinic in an affluent area now more often are older children or, if infants, they often have multiple food allergies, i.e., to other foods as well as cow's milk [24]. Although such syndromes were seen in such clinics in the 1970s and 1980s, they were much less common. Quick onset symptoms (presumably IgE mediated) combined with slow onset (presumably T-cell mediated) are now a more common mode of presentation. These latter symptoms may be related to mild enteropathy, colitis and/or dysmotility. Full gastrointestinal investigation with upper and lower endoscopy with multiple biopsies is now current practice. As most of the children presenting to a gastroenterology clinic with gastrointestinal food allergy have non-IgE mediated allergy many cases will go unrecognized without appropriate referral for consideration of endoscopy and multiple biopsies, related to food elimination and challenge.

The transfer of the author's gastrointestinal food allergy clinic from a deprived socio-economic environment in east London (albeit improving from 1972 to 1995) to an affluent community in Hampstead, at the Royal Free Hospital (1995 onwards) was associated with a dramatic decline in children attending the clinic who were under 2 years of age with chronic diarrhoea and failure to thrive due to cow's milk allergy. This switch in population base diminishes the author's eyewitness account in the decline of this problem in east London but anecdotally there has now been a similar decline in children in east

London, presumably related to improvement in socio-economic conditions there.

At the Royal Free Clinic there was a rise in the numbers of children with multiple food allergy and often less obvious symptoms of food intolerance. Increasing numbers of children with reflux vomiting associated with cow's milk allergy were seen. Also, children were seen where mild cow's milk sensitive enteropathy was associated with gastro-oesophageal reflux [25].

There was also a change in diagnostic technique at that time. Suction small intestinal biopsy with the Crosby capsule was abandoned and upper endoscopy with multiple biopsies of the oesophagus, stomach and small intestine adopted. This meant that the oesophagus was routinely examined, not hitherto possible. The state of the oesophagus in earlier studies remains unknown.

The occasional case of infantile cow's milk colitis presenting as rectal bleeding in an otherwise well child was seen, but often with associated eczema, in the 1970s and 1980s [26]. More recently, children were seen with more severe ileo-colitis where there was intolerance to a wider range of foods.

Finally, in relation to the colon, in the 1990s came the surprising conception that constipation could be a manifestation of food allergy. In selected children with constipation, endoscopic biopsy of the large bowel mucosa is now recommended in investigation. More recently, this syndrome has been well described from Italy [27].

It is not the purpose of this article to speculate on the detailed reasons for these changes, as Murch [5] clearly outlines these. This account is limited to the observation of changes in the clinical patterns of children with food allergy attending a tertiary clinic in the period 1973 to 2000.

Historical context

The opportunities for accurate diagnosis and effective therapies improved dramatically following the advent of invasive diagnostic techniques to paediatric practice in chronic diarrhoeal syndromes other than coeliac disease from the 1970s onwards in order to provide tissue diagnosis. The European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) in 1992 emphasized the importance of tissue diagnosis by recommending mucosal biopsy in infants with chronic diarrhoea and failure to thrive in which food-sensitive intestinal enteropathy is possible and infants with rectal bleeding in which food allergy (colitis) is suspected [28]. More recently, the advent of ileo-colonoscopy with multiple biopsies, as used in Finland, and now in London,

has widened the gastrointestinal spectrum of food allergy. These multiple biopsy studies have greatly extended knowledge in this field. Lympho-nodular hyperplasia has become recognized as a characteristic albeit not a diagnostic feature.

At the same time, multiple food allergy and cow's milk associated reflux oesophagitis have formed an increasing part of tertiary clinical practice. More widely, acute infective gastroenteritis has declined in severity and severe dehydrating diarrhoea is uncommon in general paediatric practice.

Post-enteritis syndrome, defined as the persistence of symptoms beyond the expected period of spontaneous recovery, has almost disappeared in developed countries. However, it is being increasingly recognized in developing communities [29].

The changes in diagnostic approach to not only biopsy the small intestine but with the use of endoscopy to also biopsy the oesophagus and the ileo-colon have expanded the diagnosis of gastrointestinal food allergy in childhood. This broader approach does provide difficulties in directly comparing present studies with earlier more limited studies which concentrated on small intestinal biopsies. Nevertheless from the perspective of personal observation there have been obvious changes in the clinical features of children diagnosed as food allergy attending a tertiary clinic over 30 years.

The factors accounting for this change in pattern in developed communities include the decline in infectious disease, as well as a cleaner environment as outlined by Murch. Socio-economic factors always play a large part in paediatric disease.

The use of probiotics is one practical application of this, which is of therapeutic importance, as outlined by Laitinen and Isolauri [30]. This challenges the established approach of elimination of food as therapy for food allergy. They suggest that probiotics may have a more important role. This is a positive way forward but the greatest hope for the future must rest with greater immunological knowledge, to improve diagnosis and to provide better treatment.

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