

# Clinical and Experimental Allergy

## The growing case for an immunological component to irritable bowel syndrome

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It is now generally accepted that irritable bowel syndrome (IBS) is a multifactorial condition with a variety of mechanisms being involved in its pathogenesis. In addition to psychological influences, which have probably been somewhat over-rated in the past, abnormalities of motility, visceral sensation as well as the central processing of noxious stimuli have been demonstrated [1]. The condition undoubtedly runs in families suggesting a genetic component and there is increasing evidence for the presence of low-grade inflammation in the gastrointestinal mucosa of at least a proportion of individuals. Dietary factors are also important and it is common for patients to complain that their symptoms are particularly troublesome following a meal. As a consequence they frequently conclude that they must have some form of dietary allergy, they certainly want to discuss the role of food in their condition and usually ask for a diet sheet. In addition, patients are now often seeking, finding and spending a lot of money on commercially available allergy tests of extremely questionable validity.

When trying to understand how the gut might react abnormally to food it is important to appreciate that one of the more consistent physiological abnormalities that can be demonstrated in many IBS patients is visceral hypersensitivity [2]. This results in an over-reactive gastrointestinal system, which can be perturbed by events that may not ordinarily be felt by a normal individual. Thus, the cephalic response to eating, whereby the colon is normally stimulated by activities such as smelling, tasting or chewing food irrespective of whether it is swallowed [3], can be exaggerated. From this it follows that the process of eating, rather than what is eaten, can have the potential for exacerbating the symptoms of IBS before food has reached the gastrointestinal mucosa. This makes it difficult to assess the mechanisms involved in a patient's reaction to food but it appears that, even after allowing for

any cephalic component, some IBS patients do appear to have specific food sensitivities but their identification is particularly challenging.

One of the first studies to investigate the role of food intolerance in IBS was reported by Jones et al. in 1982 [4]. Using a strict exclusion diet followed by the sequential re-introduction of individual food items they were able to demonstrate that a proportion of patients appeared to have a range of foods to which they were intolerant and this was confirmed by double-blind challenge. Although attempts to reproduce these results have met with variable success [5] these data lend support to the concept that food sensitivity contributes to the symptomatology of IBS. Unfortunately, patients find exclusion diets very difficult to follow and ideally they need to be supervised by a dietician. Thus an alternative way of identifying potentially 'harmful' foods is needed preferably in the form of a simple test, which would be far more appealing to both physician and sufferer alike.

If there is an immunological basis to some types of food sensitivity in IBS it is possible that the measurement of food antibodies or skin testing might provide a convenient method of identification. Because of the unequivocal relationship between some foods and immediate-type hypersensitivity reactions, such as peanut allergy, it is perhaps not surprising that IgE food antibodies and skin testing have been studied in IBS. However the results have not suggested any consistent relationship [6] except possibly in a small subgroup of patients with diarrhoea predominant IBS associated with atopic disease where a trial of oral sodium cromoglycate may be worth considering [7–10].

In contrast, IgG food antibodies have received little attention with respect to IBS. This is probably because these antibodies are far more controversial with some authorities dismissing them as just a normal physiological reaction to intercurrent changes in gastrointestinal permeability. This notion is supported by the fact that they can occur in apparently healthy individuals [11, 12] but with increasing evidence that there might be low-grade mucosal inflammation in some IBS patients [13, 14]

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coupled with the fact that the gut can also be hypersensitive it is possible such antibodies might contribute to the production of symptoms. In this issue of the journal Zuo *et al.* [15] have reported that, compared with controls, patients with IBS have higher titres of IgG antibodies to certain foods although there was no association with symptom severity. In addition, they confirmed previous observations that there was no relationship with IgE antibodies. These results are in accord with other recent studies suggesting IgG food antibodies are associated with IBS [16–18] and symptom improvement has also been reported when foods to which patients have antibodies are eliminated from the diet [17, 18]. In one study the number needed to treat in patients adhering to the diet was 2.5 which compares very favourably with other treatment approaches in this condition.

The number and type of foods to which IBS patients have had their circulating antibodies measured has varied considerably between studies but it is noteworthy that no consistent pattern of antibody profile has emerged. This may reflect the dietary preferences of the population under study and this concept is supported by the observation that shell fish antibodies were relatively common in the Zuo study which was undertaken in a coastal area where sea food is frequently consumed. Similarly cashew nut antibodies were relatively frequent in the Manchester study and by all accounts these nuts seem to be popular in this particular area.

A sizeable proportion of IBS patients date the onset of their symptoms to an episode of gastroenteritis – a phenomenon frequently referred to as post infective or post dysenteric IBS. It has been assumed that the inflammatory changes observed in some IBS patients might in some way be initiated by such an event [13, 14] especially as there is evidence that the anti-inflammatory response, especially with respect to cytokine production, may be suboptimal in a proportion of these individuals [19, 20]. However not all patients showing inflammatory changes report a previous episode of gastroenteritis and it is tempting to speculate that in such cases IgG food antibodies may have a role. Even when there is a history of gastroenteritis it is possible that the increased gut permeability associated with such an episode might lead to food antibody production rather than the infective episode necessarily being the cause of the continuing inflammation.

How could food antibodies lead to symptoms in IBS when they appear to cause no problems in other individuals? One possible explanation may reside in their effect on the phenomenon of visceral hypersensitivity, which is probably involved in the production of symptoms in these patients. Either a hypersensitive mucosa may be more easily perturbed by even a low-grade antigen–antibody reaction going on within the vicinity or such a reaction could lead to mucosal sensitization in an individual who

has a genetic predisposition to react in such a way. An alternative, but probably less likely mechanism, might be the cross reaction of certain food antigens with host antigens in genetically susceptible individuals.

In conclusion, there seems little doubt that some patients with IBS have evidence of low-grade inflammation in their gastrointestinal mucosa. There is also some preliminary data to suggest that this may in part be due to an impairment of an individual's ability to mount an adequate immune response. However, the role if any, of IgG food antibodies in all this is uncertain but certainly deserves further investigation.

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