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Food hypersensitivity—immunologic (peripheral) or cognitive (central) sensitisation?

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Summary Patients with food hypersensitivity suffer poor quality of life and several unexplained health complaints, both abdominal and extra-abdominal. Part of the suffering is due to healthcare providers' neglect and poor insight, allowing a strong position for alternative medicine. Distinguishing food allergy from functional and organic disorders can be extremely difficult. We have found examination of faecal calprotectin and gut permeability to be useful for excluding organic disease, whilst conventional provocation tests for positive diagnosis of food hypersensitivity are cumbersome. Our new ultrasound provocation test has been promising, but we acknowledge that much work remains to be done before its sensitivity and specificity can be finally established. The majority of patients with self-reported food hypersensitivity have a non-allergic hypersensitivity disorder. We suggest that cognitive-emotional sensitisation at the brain level, and not peripheral (immunological) sensitisation, is a major pathogenetic mechanism by which the patients' various abdominal and extra-abdominal health complaints are generated. Extensive activation of cognitive networks might be triggered by peripheral sensory mechanisms, often misinterpreted as 'food allergy'. Clearly, the approach to patients with food hypersensitivity should be interdisciplinary.

Increasing public and medical interest have popularised claims that a variety of physical and psychological symptoms are the result of food hypersensitivity. In Western countries, the frequency of perceived food hypersensitivity in the general population is as high as around 25%. However, only 2% of the population have food allergy as medically defined. It is therefore important, and often a challenge, to find out whether the ingestion of suspected food items really causes the symptoms.

1. Definition of food hypersensitivity

Previously, adverse reactions to food were divided into two main categories, toxic and non-toxic reactions, the latter being subdivided into immune mediated (food allergy) and non-immune mediated,

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based on the pathogenic mechanisms involved. The non-immune mediated reactions might depend on enzymatic, pharmacological, chemical or psychosomatic mechanisms (Ortolani and Vighi, 1995). In 2001 the classification was revised (Johansson et al., 2001). Now the term hypersensitivity was used as the 'umbrella' to cover all kinds of adverse reactions to food, including reactions to food additives, side effects of drugs, psychological reactions, behavioural disorders, and others. The definition of hypersensitivity should be as follows: 'Hypersensitivity causes objectively reproducible symptoms or signs, initiated by exposure to a defined stimulus at a dose tolerated by normal subjects'. It was important that the hypersensitivity reaction should be reproducible in the sense that there was reasonable evidence from the patient's history or investigation of a link between the symptoms and the environmental factors to which the patients attributed their symptoms. The term 'food allergy', which sometimes was used unspecifically to include intolerances or psycho-emotional reactions, should be restricted to reactions mediated by classical immune mechanisms. Food allergy was divided into three groups, namely IgE-mediated food allergy (type-I), mixed IgE and non-IgE-mediated, and non-IgE-mediated food allergy. Non-IgE-mediated food allergy (type III or IV) involved cell-mediated immunologic reactions, immune complex formation or complement deposition. Immunologically sensitised lymphocytes play a major role. Non-IgE-mediated allergic reactions were therefore subdivided into those in which the reaction was initiated predominantly by mechanisms associated with allergen-specific antibodies other than IgE, and those in which a cellular response was predominant.

2. Subjective food hypersensitivity

Subjective food hypersensitivity is poorly defined. In practice, the diagnosis is based on the patients' subjective reports in the absence of indications of allergic and non-allergic hypersensitivity mechanisms and organic disease. Many patients with organic or functional gastrointestinal disorders claim that they are intolerant to various kinds of food. For instance, in a recent study from our department, 75% of the patients with *Helicobacter pylori* positive dyspepsia claimed intolerance for one or more food items. Eradication of the bacterium reduced the prevalence of food intolerance significantly, but 51% of the patients still reported food intolerance (Olafsson and Berstad, 2003). Likewise, patients with irritable bowel syndrome (IBS) commonly report various kinds of food hypersensitivity (Simren et al., 2001; Isolauri et al., 2004).

3. Double-blind placebo-controlled food challenge (DBPCFC)

The best method for diagnosing food allergy is still unknown. For many years, double-blind placebo-controlled food challenge (DBPCFC) was considered the 'gold standard', but recently that method has become disputed. The procedure is extremely labour-intensive and time-consuming, and the assessment is based on subjective symptoms such as abdominal discomfort and bloating, which makes the results more equivocal than generally thought. In practice, therefore, the diagnosis relies on a careful and standardised history, documentation of IgE-sensitisation by skin prick tests or serology, registration of food intake, elimination diets and open provocation tests, and DBPCFC is seldom performed. Other cumbersome methods such as endoscopic food allergen injection (Bischoff et al., 1997b), jejunal perfusion (Santos et al., 1999) and recording of the intestinal mucosal response by endosonography (Arslan et al., 2002) have been tried, but further documentation is required before these methods may be applicable in clinical routines. Therefore, it is desirable to define suitable objective measures which may include measurements of faecal characteristics, intestinal permeability, morphometry of mucosal biopsies and responses to provocation, which basically should be monitored objectively and not be too labour intensive and time consuming (Bischoff et al., 1997a; Arslan et al., 2004a).

4. A typical food allergic reaction

In an allergic rat, intestinal provocation with an allergen elicits mucosal swelling and leakage of plasma into the lumen lasting a couple of hours before the mucosa is again completely normal (Persson et al., 1993). The mucosal hyperaemia and exudation of plasma is regarded as a non-injurious defence mechanism. In man, the intestinal response to food allergens is less well characterised, but the consequences appear to be much the same (Santos et al., 1998). Massive luminal influx of fluid might be the cause of the symptoms, which usually are acute, short-lasting abdominal cramps and diarrhoea. A major problem in such IgE-mediated reactions is that all traces of an allergic reaction might have disappeared at

the time of investigation. A positive skin prick test and abnormal levels of total or specific IgE indicate an allergic predisposition, but do not prove that the complaints of the patients are in any way related to allergy. Therefore, a provocation test is often requested. In a previous study we applied endosonography to pick up the allergic response of the duodenal mucosa to provocation (Arslan et al., 2002). However, this test was also cumbersome and only the mucosal swelling, not the luminal fluid, was seen by endoluminal ultrasound. Therefore, we wanted to apply transabdominal two-dimensional (2D) ultrasound and focus both on GI-wall thickening, peristalsis and filling of the intestines with fluid after provocation with the suspected food item. The aim was to explore the feasibility of using ultrasound to monitor the response of the proximal intestine to direct luminal provocation.

5. New provocation tests with ultrasound

Patients with chronic abdominal complaints, self-attributed to food hypersensitivity, were challenged with the suspected food item through a nasoduodenal tube (Arslan et al., 2005). Using external ultrasound, the sonographic features (wall thickness and diameter of the duodenal bulb and jejunum, peristalsis activity, and luminal fluid) were recorded before and during 1 h after challenge (Fig. 1). Gastrointestinal symptoms were registered using a Visual Analogue Scale (VAS). Sonographic changes in response to challenge were observed in 14 (44%) of 32 patients. The sonographic response was significantly related to the response of the skin prick test ($p=0.008$) and of the DBPCFC ($p=0.03$). Apparently, the sonographic test was the most sensitive as it was positive in 14 patients, while the skin prick test was positive in 10 and the DBPCFC in four. However, the specificity of the new test is not yet known. Interestingly, the degree of provocation-induced symptoms was significantly correlated to the increase in intestinal wall thickness. Intra- and inter-observer variation of the tracing procedure revealed low values. Hence, we could conclude that responses of the proximal small intestines to direct provocation (swelling of the wall and exudation of fluid into the lumen) could be visualised by transabdominal ultrasound, and that this new provocation test may become helpful in the evaluation of patients with food hypersensitivity. However, we acknowledge that further validation studies are required (Arslan et al., 2005).

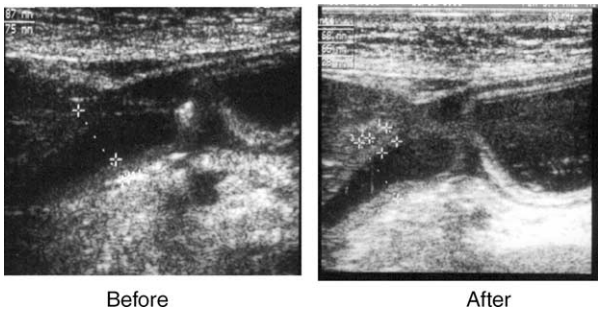

Figure 1 Ultrasonographic pictures of the distal gastric antrum, pylorus and duodenal bulb before and after provocation with an allergen through a nasojejunal tube in patients with food allergy. Note increased bulbus diameter and wall thickness after provocation (the two pictures are zoomed differently). Transabdominal ultrasonography performed with a 5.0 MHz curvilinear transducer. From Arslan et al. (2005).

6. The role of stress in the regulation of gastric motor function

Several studies by Taché and her group have documented that all kinds of stress (psychological, physical, chemical, visceral (i.e. abdominal surgery), immunological) lead to central release of corticotropin releasing hormone (CRH), which acts upon the central vagal motor nucleus to suppress efferent vagal activity (Taché et al., 2001). In rat models, such vagal suppression leads to gastroparesis and delayed gastric emptying. Studies by others have suggested that stress also impairs gastric accommodation, which means that not only gastric emptying but also the stomach's ability to adapt to a new volume without an increase in pressure is impaired. Gastric accommodation is an important (but largely neglected) reflex, which finely tunes the tone of the stomach wall so that it immediately adapts its volume during the ingestion of a meal without any increase in intragastric pressure. Impairment of the reflex might be one mechanism by which meal-related epigastric discomfort is generated in patients with functional gastrointestinal disorders and possibly also in patients with food hypersensitivity. However, the gastric accommodation reflex has not yet been investigated in patients with food hypersensitivity. Several CRH antagonists are already being tested in animal models. So far, no beneficial clinical effects have been reported.

7. The vicious cycle

We do not know where in the body functional dyspepsia starts, but emotional factors and stress

seem to play a central role (Pearson et al., 1983). We have proposed the following vicious cycle for its pathogenesis (Berstad, 2000). As a consequence of central release of CRH and its effect on the central vagal motor nucleus in the brainstem, stress and anxiety suppress vagal tone, which in turn causes impairment of gastric accommodation and generates symptoms like early fullness and epigastric discomfort after eating. Misinterpretation of perceptions from the stomach by a sensitive mind will generate more stress, and hence a vicious cycle. Similar mechanisms might be involved in the pathogenesis of food hypersensitivity.

8. Bowel gas

Patients with functional gastrointestinal disorders are hypersensitive to distension of the bowel when performed by an air-filled bag. Such visceral hypersensitivity is a characteristic feature of the majority of these patients. It is not known where on the afferent brain-gut axis the hypersensitivity is generated. It might be at the peripheral neurons, within the spinal cord, or at the brain level. It is tempting to speculate that impaired adaptive relaxation (for instance, impaired gastric accommodation) is involved in the pathogenesis of the hypersensitivity. Intestinal gas might have been swallowed or generated by intestinal bacteria during fermentation of heavily absorbable carbohydrates. Fermentation generates short fatty acids and gases like hydrogen, carbon dioxide and in some people, methane (Serra et al., 1998). The gases diffuse freely in the body and parts of them appear in expired air where they can be recovered and quantified by special techniques. Bacterial overgrowth in the small intestines is diagnosed when gas is generated too early (before 90 min) or in abnormal amounts after the ingestion of relatively resistant carbohydrates (Pimentel et al., 2000). Experimental distension of the small intestines generates contractions and pain. In contrast, distension of the large bowel generates adaptive relaxation and much less discomfort (Harder et al., 2003). Recent studies have indicated that patients with irritable bowel syndrome (IBS) have much more gas in their small intestines than healthy controls (Koide et al., 2000). Many patients with food hypersensitivity complain of abdominal gas with flatulence and the feeling of being bloated, especially after ingestion of fruit and fiber, which both contain heavily absorbable carbohydrate substrates for bacterial fermentation. The role of intestinal distension by fermentation generated gas in the pathogenesis of food hypersensitivity should be further investigated.

9. The role of fat

Long chain fatty acids in the duodenum release serotonin and cholecystokinin, which are neurotransmitters in the afferent vagus, conveying perceptions of satiety and neural reflexes regulating gastric emptying and accommodation (Barbera et al., 1995). The hormones are produced in mucosal enterochromaffin (EC) cells, which are 'open cells' facing the intestinal lumen with villi extending into the lumen, enabling the cells to 'taste' the intestinal content (Feinle et al., 2001a–c, 2002). Generally, fat in the intestines aggravates the abdominal discomfort in patients with functional gastrointestinal disorders (Accarino et al., 2001; Simren et al., 2003). Patients with food hypersensitivity often complain of fat intolerance. Similar mechanisms might be responsible for chemical hypersensitivity, which has been reported in patients with functional gastrointestinal disorders (Schmidt et al., 2004).

10. Release of histamine by stress

It has long been known that there are close anatomical and functional connections between the enteric nervous system and the mucosal mast cells. Electron microscopic examinations show that the two structures are in direct contact (Bienenstock et al., 1991). Using intestinal intubation and multilumen tubes allowing intestinal perfusion studies in man, Santos et al demonstrated release of histamine and tryptase from mucosal mast cells in response to stress (Santos et al., 1999). The stress model applied was repeated insertion of the left hand in ice water. In addition to mast cell mediator release, the response was characterised by oedema and marked increase in flow of liquid into the lumen (a well-known consequence of histamine-induced mucosal hyperaemia). Hence, the intestinal response to stress includes several of the characteristics of that provoked by allergens both in animals (Persson et al., 1993; Santos et al., 2001) and man (Santos et al., 1999). No wonder, therefore, that differentiating between allergy- and stress-induced intestinal problems in patients can be extremely difficult. We have found examination of mediators of allergy in gut lavage fluid to have limited value (Arslan et al., 2004a).

11. Clinical examinations

For the diagnosis of food allergy, accurate medical history and examination including skin prick tests and determination and IgEs in serum are mandatory (Sampson et al., 2001). Extensive clinical examination might be required in order to exclude organic diseases that can explain the complaints. Besides routine endoscopic examinations, we have found the 'intestinal function test' useful. In this test the patients are examined with whole gut lavage using intestinal perfusion through a nasoduodenal tube with 2 l of polyethylene glycol solution containing 50 μCi of ^{51}CrEDTA for 40 min and urine collection for 5 h (Berstad et al., 2000). The recovery of the marker in urine is a measure of intestinal permeability and the concentration of calprotectin in clear faecal evacuations is a measure of intestinal inflammation. Normal values of calprotectin and permeability indicate no (hidden) intestinal inflammatory condition. When in place, the tube is subsequently used for provocation tests and radiological examinations.

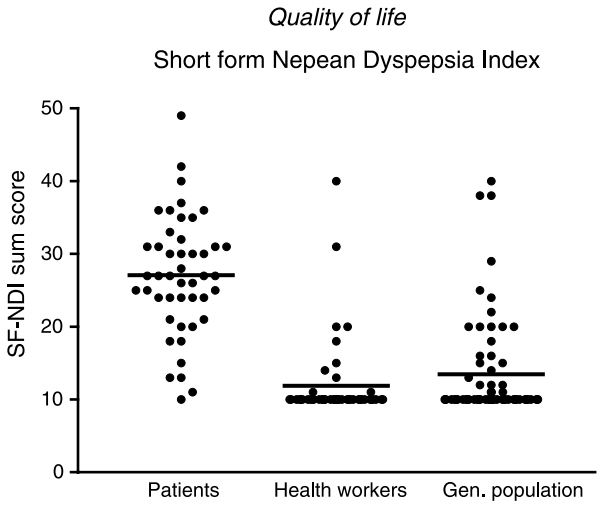

Figure 2 Quality of life in patients with abdominal complaints self-attributed to food allergy measured with short form of the nepean dyspepsia index. High scores indicate poor quality of life. The patients had significantly poorer quality of life compared to age and sex matched healthy health care workers or persons from the general population. From Arslan et al. (2004b).

12. Quality of life, subjective health complaints and modern health worries

Patients with food hypersensitivity often complain of lack of professional interest and help from healthcare workers who may not consider their illness to be serious enough. The question of how adverse reactions to food affect quality of life is therefore relevant. Previously, quality of life, subjective health complaints and modern health worries had not been investigated in these patients. We are the first group to study the topic and also the first to apply the 10-item short form Nepean Dyspepsia Index (SF-NDI) instrument for this purpose (Arslan et al., 2004b). The translation of the SF-NDI from English into Norwegian and back-translation to English showed that SF-NDI was understandable, easy to answer, relevant and meaningful. Psychometric properties (reliability, validity and responsiveness) tested over a 4 weeks interval were also satisfactory. The instrument revealed a considerably reduced quality of life in the patients on all subscales independent of the number of offending food items or presence of atopic disease (Fig. 2). Quality of life in the four patients with positive DBPCFC was similar to those with negative DBPCFC, indicating that patients with negative tests certainly deserve medical attention.

Subjective health complaints (SHC) are defined as perception of illness in the absence of organic abnormalities that can explain the illness (Ursin and Eriksen, 2001; Eriksen and Ursin, 2002). Such complaints represent a significant health burden as they are the most frequent source of long-term sickness compensation and permanent inability to work (Wilhelmsen et al., 1995). Our patients with food hypersensitivity had considerably more subjective health complaints than controls. Compared with healthy controls, 65% of the patients and 14% of our sample from the general population scored abnormally high on subjective health complaints. The five most frequent complaints reported by the patients were tiredness (93%) followed by abdominal bloating (87%), headache (85%), diarrhoea (83%) and low back pain (70%) (Lind et al., in press). Reflux symptoms such as heartburn and acid regurgitation, which are prevalent in the general population (Agreus et al., 1994), had low scores in our patients, indicating that gastroesophageal reflux is not a major issue in food hypersensitivity. On the other hand, sleep dysfunction and rheumatic complaints got high scores, indicating that these patients have several extra-intestinal problems in addition to those from abdomen.

Scores on modern health worries showed increased worries for food additives, genetically modified food, antibiotics and use of amalgam in dental fillings. However, sum scores on modern health worries were similar among patients and controls. The results are interesting as they indicate that the patients attribute their

complaints to specific food culprits and not because of health worries in general. The result indicates a rather specific sensitisation mechanism. However, it may not necessarily be immunological.

In general, psychological factors should be taken into consideration when patients have symptoms from several organ systems in the absence of organic or biochemical findings that can explain the complaints. Symptoms from several organ systems without corresponding organic diseases are termed somatisation, which is typical for patients with functional GI disorders (Wilhelmsen, 2002). Hence, patients with IBS and patients with food hypersensitivity may share not only symptomatology and immunological findings, but also psychological features.

13. Cognitive (central) sensitisation

Our studies suggest that food hypersensitivity is a sensitisation disorder, however not necessarily via immunological mechanisms. Generally, sensitisation is caused by an increased efficiency in the synapse due to repeated use, in particular following irregular and extreme stimulation. It constitutes a feed-forward mechanism, helping the individual to react more efficiently in situations with increased probability of harm. Sensitised persons are continuously scanning the environment for offending agents. Our patients with food hypersensitivity spend a lot of time on this 'scanning'. They are also constantly worried about their condition and do their best to avoid foods to which they attribute their problems. Sometimes they hide their uncertainties and worries, and present their self-attribution to particular food items so strongly that the mere strength of their belief and the indisputable presentation suggests the involvement of some kind of psychopathology or cognitive bias. According to Brosschot, cognitive bias is a higher form of sensitisation, called cognitive-emotional sensitisation, or simply cognitive sensitisation (Brosschot, 2002). Such sensitisation is common in medically unexplained somatic complaints, and may even play a role in the aetiology of the complaints. Logically, behavioural therapy is more relevant for these patients than conventional advice about food elimination. Because perceiving or experiencing threat despite food elimination leads to the detection of even more threat, the patients get mixed up in (another) vicious cycle.

14. Conclusions

In general, patients with food hypersensitivity have a miserable life, their quality of life is clearly below normal and they have several unexplained health complaints, both abdominal and extra-abdominal. Distinguishing food allergy from functional and organic disorders is extremely difficult. The role of stress, fat and bacterial fermentation in the pathogenesis of food hypersensitivity should be further investigated. Examination of faecal calprotectin and gut permeability has been found useful for excluding organic disease, and a provocation test is mandatory for diagnosing hypersensitivity. Our new ultrasound provocation test is promising, but we acknowledge that much more work remains to be done before its sensitivity and specificity is finally established. The majority of the patients with self-reported food hypersensitivity have a non-allergic hypersensitivity disorder. We suggest that food hypersensitivity nevertheless is a sensitisation disorder, not necessarily at a peripheral (immunological) level, but more often at brain level, a phenomenon called cognitive-emotional sensitisation. Extensive activation of cognitive networks, sometimes triggered by peripheral mechanisms, might be a crucial mechanism behind the many subjective health complaints of these patients. Clearly, the approach to patients with food hypersensitivity should be interdisciplinary.

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