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World J Gastroenterol 2007 July 7; 13(25): 3456-3465
World Journal of Gastroenterology ISSN 1007-9327

TOPIC HIGHLIGHT

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Psychological burden of food allergy

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Received: 2007-03-09 Accepted: 2007-03-12

Abstract

One fifth of the population report adverse reactions to food. Reasons for these symptoms are heterogeneous, varying from food allergy, food intolerance, irritable bowel syndrome to somatoform or other mental disorders. Literature reveals a large discrepancy between truly diagnosed food allergy and reports of food allergy symptoms by care seekers. In most studies currently available the characterization of patient groups is incomplete, because they did not distinguish between immunologic reactions and other kinds of food reactions. In analysing these adverse reactions, a thorough physical and psychological diagnostic approach is important. In our qualitative review, we present those diagnostic measures that are evidenced-based as well as clinically useful, and discuss the various psychological dimensions of adverse reactions to food. It is important to acknowledge the complex interplay between body and mind: Adults and children suffering from food allergy show impaired quality of life and a higher level of stress and anxiety. Pavlovian conditioning of adverse reactions plays an important role in maintaining symptoms. The role of personality, mood, or anxiety in food reactions is debatable. Somatoform disorders ought to be identified early to avoid lengthy and frustrating investigations. A future task will be to improve diagnostic algorithms, to describe psychological aspects in clearly characterised patient subgroups, and to develop strategies for an optimized management of the various types of adverse reactions to food.

Key words: Food allergy; Food reactions; Diagnostic measures; Psychological aspects; Quality of life

Teufel M, Biedermann T, Rapps N, Hausteiner C, Henningsen P, Enck P, Zipfel S. Psychological burden of food allergy. *World J Gastroenterol* 2007; 13(25): 3456-3465

http://www.wjgnet.com/1007-9327/13/3456.asp

INTRODUCTION

Adverse reactions to food are commonly expected to elicit a variety of symptoms, and several studies confirm that about 20% of the general population report symptoms related to food[1-4]. Some of these patients are characterized by an especially strong belief that food allergy is the underlying cause of their symptoms[1]. However, adverse reactions to food can have many causes. These include toxic reactions to food and non-toxic adverse reactions to food such as true food allergy and food intolerance as documented for responses to histamine or in patients with lactase deficiency.

Food allergy is characterized by the failure of the immune system to develop tolerance, or by the breakdown of tolerance, to food proteins. The absence of tolerance to food proteins can become evident primarily as classical immediate hypersensitivity responses (type I reactions) that are mediated by specific IgE antibodies to food proteins. Less common are food allergies by delayed type hypersensitivity responses (type IV reactions) mediated by T cells directed against food derived peptides, or by mixed IgE mediated immediate and late responses together with T cell-mediated reactions[5].

According to the underlying immunological mechanism, symptoms of allergic reactions may also vary depending on the level of sensitization, the food type and dose, as well as several possible co-factors. Type I reactions to food may present with initial local reactions to food proteins in the mouth and throat (so called oral allergy syndrome) resulting in pruritus, burning and tingling, erythemas, and swelling. Generalization of type I reactions to food proteins can involve several organs and lead to anaphylaxis. Typical cutaneous reactions are pruritus, urticaria, and angioedema. Gastrointestinal type I reactions to food include nausea, vomiting, and diarrhoea. Bronchial reactions are characterized by asthma and rarely, lung edema. When type I reactions lead to respiratory arrest and vessel dilatation together with a vascular leakage they may result in cardiovascular

shock and anaphylactic multiple organ failure[5-8]. Type VI or mixed reactions are often less well defined and characteristic; however, inflammatory responses involving the intestinal mucosa as in eosinophilic gastroenteritis and the skin as in atopic dermatitis or fixed food eruption have been clearly linked to delayed type hypersensitivity responses to food proteins[9,10].

The underlying cause of food intolerance may be an enzymatic defect or the effect of vasoactive substances present in food. The prototypic example of food intolerance due to an enzymatic defect leading to an adverse food reaction in the gastrointestinal tract is lactose intolerance caused by lactase deficiency. Food intolerance that follows a pharmacological-like elicitation pattern may be caused by vasoactive amines or other substances present in foods. In most of these cases, a dose-dependent effect can be observed such as for histamine in food. In addition, there is evidence for food induced adverse reactions that apparently cannot be explained by either one of these pathways indicating the existence of unknown activation pathways in food intolerance[11]. In all cases, but especially in these with undefined activation pathways, provocation tests with food are an important tool of the diagnostic measures. Moreover, it is necessary to collect and characterize patients with yet undefined food intolerance in order to identify new entities and better characterize e.g. psychosomatic food reactions. These psychosomatic reactions, which are not extensively discussed here, are assumed to originate from psychological rather than physiological dysfunction. The largest group represent somatoform disorders, characterized by various unexplained symptoms and an impaired functioning[11,12]. Modern conceptualizations of somatoform disorders emphasize their position as "interface" diagnoses between mental and organic illness. Accordingly, somatization is no longer understood as a purely mental, but a complex biopsychosocial event[13].

EPIDEMIOLOGY

Epidemiologic data are only exact when the mechanisms behind the symptoms are clear. It is often difficult to distinguish between different forms of adverse reactions to food because pathways are not clear and psychological effects intermesh with them. As a result it is a difficult task to characterize the epidemiology of adverse reactions to food.

Epidemiologic research indicates that only approximately one third of perceived food reactions in children and 10% of those in adults are due to abnormal immunologic reaction to food[1,3,5,14,15]. True food allergy affects 6% to 8% of young children[16,17] and 1% to 4% in adults[3,18].

In up to 50% of care seekers, adverse reactions to food manifest primarily with GI symptoms. Therefore, many afflicted persons consult specialists in gastroenterology. Often they become classified as "functional" without defining the real problem[5,19,20]. In several population studies, 20%-45% of adults believe that they suffer from adverse reactions to food[1,21-23]. Such perceived adverse reactions may be caused by different mechanisms, and the majority of adverse food reactions are non-immunologic in origin, with lactose intolerance the most common adverse reaction world-wide[5].

One study noted a high prevalence of irritable bowel syndrome (IBS) and functional dyspepsia in patients with adverse reactions to food, indicating a link between IBS and adverse reactions to food[24]. Nevertheless, the role of food intolerance and food allergy in functional bowel disorders remains obscure. Many IBS patients give a history of food intolerance, but data from dietary elimination and re-challenge studies are inconclusive[25]. In a study by Jones *et al*[26] two thirds of a small sample of 21 patients with IBS showed non-immunologic food intolerance in double blind food challenge. The authors concluded that a certain type of food intolerance may play an important role in the pathogenesis of IBS. This study also emphasised the burden of psychological distress in these patients. Conversely, Bentley *et al*[27] found in their study that in only three of 19 IBS patients could the putative food mediated cause of adverse reactions be confirmed by double-blind food provocation. Importantly, however, the authors of this study found evidence of minor psychiatric disorder in 12 patients. In a larger study conducted with 189 IBS patients, 91 showed symptomatic improvement of their symptoms after three weeks of dietary exclusion. Seventy-three of these 91 responders were able to identify one or more food intolerances. Upon follow up, most of these responders continued to show fewer symptoms. In the group of nonresponders to dietary exclusion only very few were symptomatically well upon follow up[28]. A systematic review of these three and another four studies[29-32] found a positive response to an elimination diet ranging from 15% to 71%. Accordingly the authors concluded that whether adverse reactions to foods are a key factor in exacerbating IBS symptoms, whether dietary manipulation is a valid treatment option, and what role may be played by psychological factors, is unclear[33]. Even a recent review stated "no clear role for hypoallergenic diets in IBS"[5]. Although the studies note a high prevalence of IBS in patients with adverse reactions to food, the role of adverse physiologic reactions, such as lactose intolerance in IBS patients remains unclear[24,34,35].

MEASURES TO DIAGNOSE FOOD ALLERGY

Studies note a large discrepancy between truly diagnosed food allergy and reports of food allergy symptoms by care seekers. Two third of the symptoms reported by children and up to 90% of those reported by adults did not result from immunologic reactions[1,3,14,15]. In addition, several studies demonstrate that the history given by patients and their doctors concerning adverse reactions to food and food allergy are not reliable[36]. Beliefs about food allergy can even lead to severe dietary restrictions[37,38]. It is therefore important to take the right measures to diagnose or rule out food allergy prior to beginning a treatment regime.

The basis for all diagnostic measures is taking a detailed history of patient's complaints. This includes information on food tolerance as well as on putative adverse reactions

to food. It is also important to complete the history by exploring the possibility of atopic diseases and possible other putative allergic or adverse reactions. Details of the atopic disease history include reactions to aeroallergens such as birch pollen, pollen by ambrosia species, and house dust mites. When used with the techniques described in the following section, these data will help to identify possible allergic cross reactions to these aeroallergens. Especially diagnosing type I reactions to food also includes standardized questions regarding the organ systems that were affected during the adverse events. Practioners should inquire about and document symptoms of the oral allergy syndrome, gastrointestinal or cutaneous involvement, allergic asthma, and hypotension.

TESTS IN TYPE Ⅰ ALLERGY TO FOOD

Prick tests and intracutaneous skin testing allow allergens to pass the epidermis and to localize close to dermal mast cells carrying putative allergen specific IgE antibodies. Consequently, cross linking of allergen specific IgE on mast cells can take place and a localized type I reaction with hives (urticae) and erythema is detectable after 15 to 20 min. Sensitivity and specificity of these skin test are high, and whenever possible, evaluated allergen extracts should be used. These standardized allergen preparations are available for more than 50 foods, alternatively food may also be tested by prick-to-prick tests (food-to-skin).

Total IgE can be detected in the serum of allergy patients, however, elevated total IgE rarely helps to establish a diagnosis. When testing indicates very high total IgE levels, the clinical significance of specific IgE values should be interpreted with caution. Today, standardized sets to measure specific IgE of more than 200 food allergens are available. Relevant selection of allergens together with measurements of specific IgE to pollen, latex, and house dust mite allergen are of great help to identify the relevant food eliciting type I responses. Alternatively, immunoblots or cellular activation tests may be performed to detect sensitizations especially to rare or unknown allergens.

TESTS FOR TYPE Ⅳ REACTIONS TO FOOD ALLERGENS

The relevance of allergic reactions to food allergens in children that include immediate type I IgE dependent reactions and/or delayed type Ⅳ T cell dependent cellular reactions is well established. These patients have a history of atopic dermatitis elicitation following the intake of certain food. Among other measures, atopy patch tests can help to establish the diagnosis in these patients. In atopy patch tests, a delayed type hypersensitivity response to, for example, pollen extracts, house dust mite extracts, or food is analyzed 48-72 h after applying extracts or food on the skin of the back[39]. No data is available for the use and significance of atopy patch tests for allergic delayed or mixed type responses at other organs than the skin. A localized delayed type hypersensitivity response on the skin is known as "fixed food eruption" and needs intralesional testing[10]. Delayed type hypersensitivity responses to food allergens were also investigated using peripheral blood mononuclear cells of atopic dermatitis patients. Significantly higher proliferative responses of the patients´ T cells were detected. However, the clinical significance of these findings is not clear. Therefore, this test system is still reserved for experimental use or for specific indications analyzed in specialized centers.

CONTROVERSIES IN DIAGNOSTIC MEASURES TO TEST FOR FOOD ALLERGY

Electroacupuncture, applied kinesiology, and bioresonance are sometimes used as putative test systems to detect food allergies or intolerance, frequently in attempt to explain and correlate symptoms with food intake. However, several scientific investigations indicate evidence that these methods are absolutely unreliable and unspecific and demonstrate that there is no indication for the use of such techniques[40].

In the search for suitable clinical food hypersensitivity markers, much attention has been paid to changes in non IgE immunoglobulines and their subclasses. Although some data suggests a possible role of IgA, IgG4 or total IgG, no correlation between the levels of these antibodies and the outcome of food provocation tests could be detected[41].

Detecting histamine in the serum or urine has also been used to diagnose acute anaphylactic reactions and today the measurement of serum tryptase seems most reliable, however, it requires a substantial clinical reaction in order to be positive. Therefore, histamine, histamine metabolites, and tryptase measurements are of little diagnostic value in the routine setting.

Other test systems have been explored for patients with suspected food allergy but have either failed to demonstrate correlation to the disease or have been shown to be unreliable. These systems include measurements of complement levels, immune complexes, serum cytokine levels, and particularly, measurement of white blood cell diameters and so called permeability tests. An immediate decrease of eosinophils in food sensitive children followed by an increase in serum levels of eosinophil cationic protein was demonstrated in single studies, however, further studies are required before use of these parameters can be recommended.

PROVOCATION TESTS IN PATIENTS WITH SUSPECTED FOOD ALLERGY

There are several significant arguments that food provocation tests are central to the diagnosis food allergy: (1) Only provocation tests allow differentiating in food allergy and food tolerance in sensitized patients. Especially atopic patients tend to develop sensitizations against several pollens, pollen related food antigens, and food antigens. However, the majority of these patients can tolerate the food in question. (2) Hypersensitivities to food may not be detectable by other diagnostic measures. (3) In some patients, we need to demonstrate that a certain food

was tolerated to avoid unnecessary dietary measures or behaviour.

Thus, in many patients, open, single blinded or double blinded and placebo controlled food provocation tests are indispensable. Standardized procedures of blinding and of scoring the symptoms need to be established in order to deliver reliable and comparable test results. In general, patients are given increasing doses of the suspected food hidden in a standard preparation of oatmeal, rice gruel, or mashed-potatoes. In babies and very young children, food preparations are often offered in hypo-allergenic milk formulas. If possible, the type of putative immune reactions to food should be classified in advance of the provocation tests in order to adapt the provocation protocol and read out time. It is important to note that co-factors such as exercise or the intake of non-steroidal anti-inflammatory drugs (NSAIDs) like aspirin may be necessary to elicit food anaphylaxis (type I reaction). These co-factors need to be implemented into provocation protocols.

PSYCHOSOCIAL IMPLICATIONS OF ADVERSE REACTIONS TO FOOD

In clinical practice, physicians often show a lack of awareness of the psychological aspects of perceived adverse reactions to food and food allergy. It is important to assess with every patient the interplay between body and mind, and to explore whether psychological problems are contributing or determining the symptomatology. Psychological problems may lead to rather somatoform or hypochondriac disorders. In such cases any further somatic diagnostic measures may contribute to the formation of chronic symptoms. Individuals suffering from adverse reactions to food are faced with uncertainty and insecurity. The first symptom often occurs suddenly, and for the patient, threateningly. The patient's insecurity frequently persists during the often difficult diagnostical steps, steps that sometimes fail to result in a final diagnosis. Moreover, because treatments are limited to prevention of accidental ingestion and emergency management, once allergic reactions are truly diagnosed, the food-allergic persons must live with constant vigilance and fear[42-44].

Physicians are rarely faced with care seekers who show symptoms that are clearly the result of physical, rather than psychological factors. However, in most patients there is interplay between the physical and psychological, sometimes with one set of factors dominant over the other. Therefore, it is very important not only to apply laboratory measurement, but also psychosomatic diagnostic procedures. In daily care changes in food related symptoms according to mood, stress or life events should be assessed. It should be evaluated whether the patient exhibits enhanced depressive or anxious disposition or other tendencies of somatization. The approximate psychological burden within the patient could be easily measured by questionnaires like the patient health questionnaire[45].

PERSONALITY AND FOOD REACTIONS

More than twenty years ago Pearson et al asked "Food allergy: how much in the mind?". The group found a high incidence of psychiatric disorders (anxiety and depression) and a high suggestibility in patients whose belief that they had a food allergy could not be confirmed. They found that in subjects whose putative organic food hypersensitivity could not be confirmed, neurotic symptoms were attributed to allergy. This patient group was identical in psychiatric symptomatology with a group of psychiatric out-patient referrals[46,47]. A cross-sectional study among 490 students with self-reported illness from food and chemicals showed a correlation between food intolerance and depression, anxiety, and somatization[48] (Table 1).

In a small study, 13 of 17 patients with non IgE-mediated food intolerance reported major distress or trauma during childhood, including loss of parents, violence or major psychiatric illness. Only two patients had a stable childhood and were currently in a stable life situation. The authors supposed a multifactorial etiopathogenesis, balancing between immunologic, psychobiologic, and psychological factors[49].

These findings could not be confirmed in a community study of 273 adults who complained of food intolerance. Rather, this study demonstrated that subjects who were judged not to be allergic on clinical grounds did not manifest significant mood disturbance, impaired social adjustment, or other psychological symptoms. In this first occasion in which psychological variables were systematically assessed in a large group of subjects, it appeared that persons who attributed their symptoms to food allergy suffer less from mood disturbance than those who attributed their symptoms to stress or gastrointestinal disorder[50]. In another attempt to explore the psychological characteristics of people with perceived food intolerance, a community sample of 232 persons classified as food intolerant found no convincing data of a greater percentage of psychiatric involvement. The authors solely could conclude that perceived food intolerance is associated in women with psychological distress and in men and woman with slight neurotic symptoms[51].

A study that compared patients with non IgE-mediated food hypersensitivity with two control groups (health care workers and volunteers from the general population) found significantly more subjective health complaints (most frequent tiredness, abdominal bloating, and headache) and significantly more worries about toxic interventions (especially concerning antibiotics, amalgam and additives in food) in the patient group. The reason for the patients' food intolerance, however, remained unexplained. The study authors suspected a sensitization phenomenon in their subjects in which "normal"complaints may transform into intolerable conditions[52]. Cognitive-emotional sensitization involves the central nervous system in complex neuronal networks. Above a certain level of activation, these networks lead to more and more perception of illness. Non IgE-mediated food sensitivity is supposed to be a sensitization disorder, not necessarily at a peripheral level, but more often at a brain level. Extensive activation of these cognitive networks, sometimes triggered by peripheral mechanisms, might be a crucial mechanism behind the many subjective health complaints[53,54], since

Table 1 Psychological aspects of adverse reactions to food

Author	Subjects	Examinations	Adverse reaction to food	Results
Pearson *et al*, 1983	8 males, 12 females; allergy clinic	Psychiatric clinical interview schedule Double blind placebo controlled food-challenge	Hypersensitivity was confirmed in 4 subjects	No psychological symptoms in subjects hypersensitivity was confirmed, high incidence of psychiatric disorder (neurotic depression, hysterical disorders) in subjects whose belief that they had a food allergy could not be confirmed
Rix *et al*, 1984	23 patients; allergy clinic	Psychiatric clinical intervie schedule Double blind placebo controlled food-challenge	Hypersensitivity was confirmed in 4 subjects	No evidence of psychiatric disorder in subjects hypersensitivity was confirmed, high incidence of psychiatric disorder (identical with a group of psychiatric out patient referrals) in patients whose belief that they had a food allergy could not be confirmed
Bell *et al*, 1993	490 young college students	Self-reported illness from several common foods and chemicals	Indefinite diagnosis	Correlation between perceived food intolerance and depression, anxiety, and somatization
Vatn *et al*, 1995	17 patients with food intolerance 34 healthy referents	Prospective placebo-controlled study General Health Questionnaire Double blind placebo controlled food-challenge	Non IgE-mediated food intolerance	13 of 17 patients reported major distress or trauma during childhood, including loss of parents and violence or major psychiatric illness. Psychological problems are frequent
Peveler *et al*, 1996	Community study in 273 adults	Blind food challenge test Clinical interview Several questionnaires Brief symptom inventory	Intolerance to test foods	Subjects that were judged not to be allergic on clinical grounds did not manifest significant mood disturbance or impaired social adjustment or other psychological symptoms
Knibb *et al*, 1999	Random mailing recruited 955 participants, of whom 232 perceived them-selves to be food intolerant	General Health Questionnaire-28 (GHQ-28) Eysenck Personality Questionnaire	Selfperception of food intolerance	It is concluded that perceived food intolerance is associated with psychological distress in women, and neurotic symptoms in both men and women, but there is no greater prevalence of psychiatric disorder among women or men
Lind *et al*, 2005	46 patients with food hypersensitivity 50 health car workers 70 volunteers	Subjective Health Complaints Inventory and Modern Health Worries Scale	Subjective food hypersensitivity No IgE-mediated allergy	Subjects with subjective food hypersensitivity reported more subjective health complaints and more worries An association between subjective food hypersensitivity and subjective health complaints was supposed

above a certain level of activation and arousal, normal physiological signs are interpreted as "symptoms".

LEARNING OF FOOD REACTIONS

Case reports have described multiple and severe allergy-like symptoms after the ingestion of peanuts that did not appear to be volitional and that could not have been provoked by the ingestion of peanuts. Only after a negative double-blind, placebo-controlled challenge the patient was able to consume peanuts without reaction. It has been proposed that Pavlovian (classical) conditioning may be an important mechanism in establishing the somatic reaction, initiated with an idiopathic allergic episode while eating peanuts[55].

While learning (e.g. Pavlovian conditioning) as the underlying mechanism of food aversions has not been experimentally proven in subjects with food intolerances, the learning of taste and food aversions has been shown to follow Pavlovian principles in other clinical cases: Conditioned taste aversion has been shown to occur with chemotherapy-induced nausea both in children[56] and adults[57], and is named "anticipatory nausea and vomiting" (ANV). The time-locked (contingent) presentation of the cytotoxic drug (unconditioned stimulus, US) with environmental cues in the hospital (conditions stimuli, CS) that result in ANV when these CS are presented alone, e.g. prior to injection for the second course of chemotherapy. Frequently, these CS are food stimuli ingested in the morning prior to hospitalization, and result in severe food avoidance and aversions afterwards[58]. The principles of Pavlovian conditioning in case of ANV have been shown to be effective[59], and they can also be used to prevent ANV to occur[60,61]. However, the incidence of ANV has significantly been reduced - though not eliminated - with modern antiemetic medication[62].

But also without chemotherapy, humans may develop taste aversions in everyday life[63], e.g. when food ingestion is associated with the occurrence especially of digestive complaints (diarrhoea, bloating, crampy pain, nausea) that may not be provoked by the nutrients but may have occurred accidentally. On average, individuals may develop up to 10 aversions in their lifetime, and they may last many years[64]. Another specific sign of taste and food aversions is that they may occur after a single pairing of food with "neutral" stimuli (CS), a phenomenon that has been called "single-trial learning" and that is well characterized in animal experiments; this learning is thought to be specifically resistant to elimination (extinction)[65].

Conditioned taste or food aversions could be the underlying mechanism in subjects with lactose intolerance due to the lack of the enzyme lactase. These subjects are frequently unaware of their inability to digest lactose containing products, but avoid milk and other diary products because of their "disliking" of it.

IMPACT OF FOOD REACTIONS ON QUALITY OF LIFE

Subjective food hypersensitivity gives rise to negative consequences for daily life. A total of 300 subjects with perceived food intolerance were interviewed by Knibb

Table 2 Food allergy and quality of life

Author	Subjects	Examinations	Results
Primeau *et al*, 2000	153 peanut allergic children and 37 adults compared to 69 children and 42 adults with rheumatologic disease; furthermore their families	Impact on Family Questionnaire (IFQ)	Peanut allergic children have more disruption in their daily activities, more impairment in the familial-social dimension of the IFQ Adults with rheumatological disease reported more disruption in their family relations
Sicherer *et al*, 2001	253 children and adolescents with food allergy	Children's health questionnaire (CHQ-PF50) Allergy-related questionnaire	Worse scores for general health perception, parental distress and worries, and limitations in usual family activities compared to healthy controls. Family cohesion was greater in the food allergic group
Avery *et al*, 2003	20 children with peanut allergy and 20 children with insulin-dependent diabetes mellitus	Self-designed questionnaire Vespid Allergy Quality of life Questionnaire Cameras to record quality of life	Children with food allergy report more fear of an adverse event, more anxiety about eating, more restriction due to the illness
Marklund *et al*, 2004	1451 adolescents, thereof 19% "reactive" to food	Health Survey Short Form (SF-36)	Lower scores in seven of the eight scales (role functioning-physical, bodily pain, general health, vitality, social functioning, role functioning-emotional, mental health)
Lyons *et al* ,2004	162 young adults, of which 24 "reported" food allergy	Questionnaire, registering awareness and perceptions of food allergy, self-rated health State-Trait Anxiety Scale Perceived Health Competence Scale	Allergic subjects with high health competence reported great anxiety levels. They perceived that their allergy had less of an impact on their lives than others believed it would
Bollinger *et al*, 2006	87 families of food allergic children	Food allergy impact scale	All aspects of daily life are affected with most striking effects on family meal preparation and activities outside home

et al[51].They reported that patients took significantly more time off from work per year than did healthy controls. In 17% of the study group, physical activity and daily routine, such as participating in sports and travelling, were affected. A large questionnaire-based study among 1451 adolescents indicated that 19% of the participants reported that they perceived an adverse reaction to food, but their condition was not doctor-diagnosed. When compared to adolescents without such conditions, this kind of allergy-like condition, regardless of the underlying mechanisms, was associated with lower scores in seven of the eight scales in the Health survey short form (SF-36)[66]. Only the scale for "physical functioning" was not different between persons reactive to food and persons non-reactive to food. Unfortunately, the study did not distinguish between different forms of adverse reactions to food. Lind *et al*[52] found that patients with subjective food hypersensitivity have also more musculoskeletal and pseudoneurologic complaints.

Until the end of the last millennium no adequate studies with high evidence levels have been carried out about the psychological burden of truly diagnosed food allergy. The first well-designed study was published by Primeau *et al*[67] in 2000(Table 2). The group studied a sample of 301 patients and evaluated the quality of life and family relations of children and adults with peanut allergy, compared to that of children and adults with rheumatological disease. It was shown that the parents of allergic children believed that their children had difficulties in many areas. Their children had more impairment, especially in daily activities and in their familial social interactions, compared to children with a rheumatological disease. In contrast to the children in the study, adults with peanut allergy had comparable disruption in their quality of life but less disruption in family relations than adult rheumatological patients. In examining the various results, the authors emphasised the burden on parents of food-allergic children of being responsible in a potentially life-threatening incident.

Similar data show that the quality of life of peanut-allergic children seems to be more impaired than the quality of life experienced by children with insulin-dependent diabetes mellitus. In a population of 40 children with peanut allergy or diabetes, the children suffering from food allergy reported more fear of an adverse event, more anxiety about eating, and more restriction due to the illness. Both groups evidenced difficulties concerning food management and food restrictions. Peanut-allergic children, however, felt safe when carrying epinephrine kits[68]. It appears that an appropriate level of anxiety may be constructive in families coping with anaphylaxis in a child[67-69].

Parents of children with food allergy and adults with food allergy are offered the only reliable therapy, specifically, restriction or complete elimination of the responsible food allergen and emergency management of type I reactions, in case food allergen is accidentally ingested[18,70]. In particular, individuals with type I food allergy and their families must live with constant vigilance and fear, and they have to be concerned about potential exposures to relevant food allergens in a variety of settings, including restaurants, work and school environments, picnics and parties, and during travel. Anticipatory guidance measures such as reading food ingredient labels, concern for cross-contamination, exposure to relevant food allergens in a variety of social activities, are extremely important[71].

Against this background, Sicherer *et al*[72] conducted a study on the impact of childhood food allergy on quality of life among 253 patients ranging in age from 5 to 18 years. Scores in the food-allergic cohort were significantly lower for general health perception, parental distress and worry, and interruptions and limitations in usual family

activities, than in healthy controls. Scales were also lower in subjects with multiple food-allergies. Interestingly, the family cohesion scale was significantly greater in the food-allergic group. These findings have been affirmed recently in a sample of 87 families. Almost all aspects of daily life are affected, with most striking effects on family meal preparation and activities outside home[73]. Both studies found no significant effect on comorbid conditions such as asthma and atopic dermatitis.

There is only one recent similar study carried out in adults with food allergy. The study assessed young adults leaving home, and therefore taking full responsibility for their food intake. The authors examined a sample of 162 participants, of which 24 reported they were allergic to food, but in whom physicians had not confirmed the diagnosis. The study participants perceived that their allergy had significantly less of an impact on their lives than others believed it would. The subjects with allergy and with high health competence reported great anxiety levels[74].

DISCUSSION AND CONCLUSION

Twenty to forty-five percent of the general population report adverse reactions to food, often attributed to food allergy[1-4]. Literature reveals that the psychological burden concerning food allergy and adverse reactions to food is difficult to assess. The interplay between body and mind is often difficult to evaluate[8,71-73].

Many patients suffering from adverse reactions to food are not conclusively diagnosed even following placebo-controlled food challenge[5,15]. It remains uncertain whether this results from insufficient laboratory diagnostics or if such patients suffer from "psychological problems" like somatoform or hypochondriac disorders or adverse reactions that are not identifiable by diagnostic methods currently available. Studies tried to find psychological characteristics in patients with adverse reaction to food. Unfortunately, in most studies currently available, the characterization of patient groups is incomplete. The studies frequently did not distinguish between immunologic reactions and other kinds of food intolerance. Pearson and Rix[46,47] hypothesized that patients with non-confirmed food allergy had a higher incidence of psychiatric disorders, a conclusion that was confirmed in part by Bell[48]. Whether perceived food intolerance or depression/psychiatric disorder was the reason for the clinical picture, however, was not clear. Moreover, the first study that systematically assessed psychological symptoms in a large community study found no significant mood disturbance in persons with food allergy or food intolerance, and so could not confirm the former findings[50]. Perhaps these disparate findings can be rationalized by the theory of cognitive-emotional sensitization. After long-term activation of complex neuronal networks, normal complaints lead to a greater perception of illness[52-54]. One could postulate a higher vulnerability of neural networks in psychiatric disorders and other situations of chronic stress, such as adverse childhood. A sensitization phenomenon is also discussed with respect to the irritable bowel syndrome. In studies carried out with the aim to investigate allergic reactions to food, researchers often do not consider IBS.

Kelsay remarked that patients could be "more accurate about food allergies by flipping a coin than relying on symptoms"[8]. Literature reveals that many patients with diverse reactions to food do not see a doctor. Instead they make their diagnosis themselves. The misinterpretation of symptoms as allergies leads to restricted diets and malnutrition, and in case of childhood food allergy, even to failure to thrive[37,38]. Furthermore such misinterpretation leads to more worries and lower quality of life[66]. The interpretation of symptoms should be reserved to a physician to avoid uselessly restricting diets and malnourishment. Lyons *et al*[74] found that about 70% of young adults do not know what anaphylaxis means. Mandell *et al*[69] reported that sufficient information and concrete suggestions about avoidance and risk management help the patient and his family to develop good coping mechanisms. Allergic patients felt reassured by knowing other people had the same problems as them[68]. These facts underline the importance of information.

Literature reveals a lack of well-designed studies describing the psychological burden of food allergy. Studies are scarce and are often carried out in a mixture of diagnoses, reflecting the difficult field of adverse reactions to food. Many of the studies that have been undertaken are limited because they rely only on questionnaires, and do not include examining the subject individually. The aim in further investigations should be to distinguish real food allergy from other kinds of adverse reactions to food, for example, food intolerance, irritable bowel syndrome, and somatoform or other mental disorders.

There are only a few studies carried out with type I food-allergic patients, and they are predominantly in paediatric patients. It seems, however, that there is increased interest in this area because most of the studies date from the last five years. It seems that children with food allergy suffer in a variety of areas related to quality of life. Surprisingly, they suffer more than children with other chronic diseases like rheumatologic disease or insulin-dependent diabetes mellitus[67,68]. This seems to be influenced by the real fear factor of possible anaphylaxis, implications on lifestyle, and by psychosocial activities and well-being. Patients, for example, have to trust labels on commercial food products and at restaurants. Treatments are limited to prevention of accidental ingestion and emergency management[42-44]. Yet, conditions in our society are such that accidental exposure to critical food allergens is common[75]. This becomes even more difficult considering, according to some investigations, that food allergy is the most common identifiable cause of anaphylaxis with fatal ending[7,76]. These facts represent a source of tremendous anxiety and stress for the patient and his family. In addition to the conclusion of Primeau[67] and Avery[68] that the high level of stress in families with a peanut allergic child may have beneficial effects on coping strategies, Mandell *et al*[69] reported that an appropriate level of anxiety might be constructive. A high level of anxiety motivated patients and parents to get information and concrete suggestion about avoidance and risk management. In most cases,

the high level of anxiety subsided and a high level of vigilance prevailed. In some cases, the authors found an extremely intense level of anxiety, which they described as maladaptive. Avery also attributed the low quality of life in allergic children to anxiety that can lead to mental health problems. One should be aware that anxiety might be unhelpful if the restrictions in lifestyle are unrealistic and unfounded. Deprivation due to restrictions in lifestyle can lead to social anxiety[73]. It could be hypothesised that patients with food allergy and similar maladaptive anxiety levels are likely to develop a comorbid anxiety disorder. In the available studies, anxiety often has been scored, but newer, reliable data regarding whether patients suffer from comorbid mental disorders (especially panic disorders with and without agoraphobia) according to ICD-10 or DSM-IV criteria, fail. Older data showed an association between panic disorder and type- I allergic reaction[77].

An extreme example of stress in patients with food allergy is anaphylaxis with nearly fatal ending. It is likely that post-traumatic stress disorder (PTSD) could be triggered by experiencing or witnessing such incidents[8]. PTSD is described in patients or family members with asthma[78]. Analogical studies in this area concerning food allergy are non-existent.

Many patients with adverse reactions to food show restricted diets. It could be speculated that these behaviours may lead to eating disorders. Pearson and Rix reported patients with total caloric intake less than 400 KCal a day, who existed on little more than boiled potatoes[46]. Case reports indicate an association[79,80] that should be systematically studied.

There are no studies carried out in adults with food allergy analyzing the impact on quality of life, especially concerning social aspects and partnership. Often disconcerting topics may be important and worth being studied. Intimacy and sexuality are constrained when a food-allergic person must continuously assess if there is a risk of transposition of critical allergens. Anecdotal evidence in a few cases indicates that kissing can induce food-allergy symptoms[81,82]. A survey among 1139 patients with self reported food hypersensitivity was carried out by Erikkson *et al*[83]. They found that 12% of the patients experienced allergic symptoms when being in close contact with a person who had eaten non-tolerated food prior to the contact.

Fortunately, investigations in this field have become more frequent in the last years, especially in children and their family. With respect to future study, emphasis should be laid on the psychological aspects of adults suffering from food allergy and their families, especially their partners. Studies should also focus on long-term consequences of food allergy and how childhood or adolescent food allergy influences psychological development and emotional wellbeing in adulthood. The relationship between mental disorders like posttraumatic stress disorder, anxiety disorders - especially the panic syndrome, and eating disorders should be probed[44].

Patients with adverse reactions to food demand not only an in-depth hunt for an allergen, but also prudent handling of psychological aspects attending somatic symptoms. The physician has to be aware that other comorbid mental disorders could present the need for professional treatment. To diagnose exactly means to examine the patient entirely - body and mind. Only where this occurs patients can receive the therapy they need, including strategies from avoidance and risk management of anaphylaxis to psychotherapy.

ACKNOWLEDGMENTS

We thank J Long for proofreading the article concerning grammar.

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