Anxiety and depression in patients with self-reported food hypersensitivity

Kristine Lillestøl, M.D. a, b, *, Arnold Berstad, M.D., Ph.D. a, b, Ragna Lind, R.N., M.Sc. a, Erik Florvaag, M.D., Ph.D. a, c, Gülen Arslan Lied, M.D., Ph.D. a, b, Tone Tangen, M.D., Ph.D. d, e

a Institute of Medicine, University of Bergen, N-5021 Bergen, Norway
b Department of Medicine, Haukeland University Hospital, N-5021 Bergen, Norway
Laboratory of Clinical Biochemistry, Haukeland University Hospital, N-5021 Bergen, Norway
Institute of Clinical Medicine, University of Bergen, N-5021 Bergen, Norway
Department of Psychiatry, Haukeland University Hospital, N-5021 Bergen, Norway

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Abstract

Objective: Self-reported food hypersensitivity (SFH) is common. Psychological factors are assumed to be associated. We assessed anxiety and depression in SFH patients, using both questionnaires and interview.

Methods: Consecutive patients (n=130) and randomly selected healthy volunteers (n=75) completed the Hospital Anxiety and Depression Scale (HADS), the neuroticism scale of the Eysenck Personality Questionnaire (EPQ-N) and the General Health Questionnaire (GHQ). Seventy-six of the patients were also interviewed by use of the Mini International Neuropsychiatric Interview and the Montgomery–Aasberg Depression Rating Scale. All patients underwent extensive allergological, gastroenterological and dietary examinations.

Results: According to interviews, 57% of patients fulfilled the DSM-IV criteria for at least one psychiatric disorder. Anxiety disorders (34%) and depression (16%) predominated. According to questionnaires, patients scored significantly higher than controls on all psychometric scales except for depression (HADS). We also found an underreporting of depression in HADS compared with interviews (2.5% vs. 16%, P= .001). Food hypersensitivity was rarely confirmed by provocation tests (8%). Eighty-nine percent of the patients had irritable bowel syndrome.

Conclusions: Anxiety and depression are common in patients with IBS-like complaints self-attributed to food hypersensitivity. Anxiety disorders predominate. In this setting, depression may be underreported by HADS.

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1. Introduction

Self-reported food hypersensitivity (SFH) is common. In several Western countries, up to 20% of the general population claim adverse reactions to food [1]. However, the discrepancy between suspected and confirmed food hypersensitivity is considerable. According to current criteria, the term “food hypersensitivity” embraces IgE-mediated and non–IgE-mediated food allergy, as well as nonallergic reactions [2]. Common for most reactions is that the double-blind placebo-controlled food challenge (DBPCFC) is regarded as the “gold standard” diagnostic method [3], but only 1–2% are diagnosed with food allergy when this method is used [4,5]. In most cases, self-reported reactions to food remain unexplained.

Patients who attribute their symptoms to food hypersensitivity are often severely bothered and experience considerably impaired quality of life [6]. Their complaints are characterized by abdominal discomfort and pain, bloating...
and altered bowel functions, and patients commonly get a diagnosis of a functional gastrointestinal disorder, most often irritable bowel syndrome (IBS) [7]. In addition, they also often present with extra-intestinal symptoms such as headache, fatigue and musculoskeletal pain [8]. The coexistence of so many diverse unexplained health complaints suggests that the pathogenetic mechanisms are multifactorial and not confined to peripheral hypersensitivity reactions solely [9].

Emotional disturbances may play a role in the pathogenesis of SFH. Patients with psychiatric disorders such as anxiety and depression often present with somatic rather than emotional symptoms, a fact that often contributes to low recognition of these disorders in primary care [10,11]. It might therefore be hypothesized that for some of the patients who present with somatic symptoms self-attributed to food hypersensitivity, the complaints could be an expression of emotional problems like anxiety and depressive disorders [12]. Bodily symptoms of anxiety and depression may also be misinterpreted as allergic symptoms. Autonomic symptoms such as hyperventilation, sweating and heart palpitations frequently occur in anxiety disorders as well as in allergic and anaphylactoid reactions [13].

There are few studies of psychological factors in SFH [14]. Most of them are based on self-rating questionnaires, from which psychiatric diagnoses cannot be made, and the results are somewhat conflicting. One study reports that SFH is associated with neuroticism and general psychological distress [15]. Higher scores for anxiety, depression, shyness and defensiveness have also been reported [16,17], while others have not found an association between SFH and psychological problems [18,19].

To our knowledge, psychiatric interviews have been used in only two studies of patients referred to hospital because of unexplained SFH [20-22]. Both studies were based on semistructured interviews. Pearson et al. [20,21] found that 18 of 19 patients had a psychiatric disorder, of which “depressive neurosis” was most common. Limitations of this study were a small patient sample and that the clinical investigations were limited to allergological and dietary assessments. Gastroenterological examinations were not performed. Vatn et al. [22] found that all of their patients fulfilled the diagnostic criteria of undifferentiated somatoform disorders, 24% were depressed and the majority reported current life stress or childhood trauma. These patients were well characterized in terms of allergological, dietary and gastroenterological assessment. However, the patient sample here was also small ($n=17$).

The main aim of the present study was to assess the prevalence of anxiety and depression in patients with gastrointestinal complaints self-attributed to food hypersensitivity who were also thoroughly examined with respect to allergological, gastroenterological and dietary factors. For this purpose, we wanted to use both self-rating scales and a structured psychiatric interview which is validated according to current diagnostic standards. We also wanted to assess self-rated general psychological distress, as well as neuroticism, which is suggested to be a vulnerability factor for the development of both anxiety and depression [23]. We hypothesized that anxiety, depression, general psychological distress and neuroticism would be more prevalent in patients than in a population-based control group.

2. Methods

2.1. Participants

Patients referred by general practitioners or specialist doctors to the Section for Clinical Allergology, Department for Occupational Medicine at Haukeland University Hospital (Bergen, Norway), because of gastrointestinal complaints self-attributed to food hypersensitivity, were considered eligible for inclusion in the study. Pregnant and lactating women were excluded, as well as patients with confirmed inflammatory bowel disease.

The patients went through a comprehensive clinical investigation program in the allergy and gastroenterology clinics, respectively. They were compared to a control group randomly selected from the general population, matched by age and sex (see below). The controls were not medically examined or interviewed, but they filled in questionnaires.

2.2. Somatic assessment

The allergological examinations included a complete medical history and skin prick tests using seven common food items and eight inhalants (ALK Abello, Hørsholm, Denmark). Levels of total and food-specific IgE in serum were also determined (ImmunoCAP-System, Phadia, Uppsala, Sweden). When indicated, trials with elimination diet, open provocation and DBPCFC were performed by a dietician, following procedures described elsewhere [7].

Patients also underwent the following gastrointestinal procedures: upper endoscopy with biopsies taken from the stomach and duodenum to diagnose Helicobacter pylori infection and celiac disease, respectively. Inflammatory bowel disease was excluded by measuring the intestinal permeability of $^{51}$Cr-labeled ethylenediaminetetraacetic acid and calprotectin in gut lavage fluid as previously described [24]. Microscopy and culture of stool samples were used to rule out gastrointestinal infections where indicated. A screening questionnaire based on the Rome II criteria was applied for the diagnosis of functional bowel disorders [25].

2.3. Psychiatric interview

We used the Norwegian version (5.0.0) of the Mini International Neuropsychiatric Interview (MINI) [26] with some additional modules from the MINI Plus. This version is validated according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) [27]. All interview sessions began with a brief
open interview with emphasis on main complaints and general psychosocial factors.

The severity of depressive symptoms was measured by the Montgomery–Aasberg Depression Rating Scale (MADRS) [28]. A score of 20 or more was assumed to indicate clinically significant depression.

The interviews were performed either by the last author or the first author, in the latter case with the last author as consultant. The investigation team was without a psychiatrist for some time during the recruitment phase; therefore only a subsample of the patient group underwent a structured interview.

2.4. Psychometric assessment

As a measure of general psychological distress, we used the 30-item version of the General Health Questionnaire (GHQ-30), a well-validated test which is frequently used to assess psychological well-being [29]. The sum score was calculated by the Likert method (0-1-2-3).

To assess the level of anxiety and depressive symptoms in patients and controls, we used the Hospital Anxiety and Depression Scale (HADS). HADS was originally constructed to detect anxiety and depression in nonpsychiatric medical patients [30]. It is later shown to be useful as a case finder also in other populations, and it is a well-validated questionnaire with good psychometric properties [31]. The scale consists of 14 items, seven relating to anxiety (HADS-A) and seven to depression (HADS-D). All items are scored on a four-point scale from 0 to 3. Cut-off scores can be used to identify cases with clinically significant anxiety and/or depression with reasonable certainty, and we defined case level as 8 or more on both subscales, as is done in the majority of studies [31]. The total HADS score is the sum of all 14 items.

We also measured neuroticism, a personality trait defined as a general tendency to emotional overactivity or overresponsiveness [32]. For this purpose, a 23-item version of the neuroticism subscale of the Eysenck Personality Questionnaire (EPQ-N) was used, with a possible obtainable score ranging from 0 to 23 [33].

All patients completed their questionnaires at the gastroenterology clinic. The controls received their questionnaires by mail and filled them in at home. They were contacted after receiving permission from the Norwegian National Registry, using a randomized computer procedure. A sample of 520 persons was chosen among persons living in the city of Bergen, and they received a letter of information, a consent form, questionnaires and a pre-stamped envelope. Forty letters were returned due to change of addresses. Five were returned because the enquired person explicitly refused to participate. One hundred five (21.9%) of those who were enquired agreed to participate in the study.

The controls were not medically examined, but were asked to fill in a self-report form about food hypersensitivity. They received a list of various common food items, where they should answer the question, “Are you hypersensitive towards the following foods?” by either “yes,” “no” or “I don’t know” for each food item. An answer of “yes” to at least one food item was considered an exclusion criterion.

2.5. Statistics

Data were analyzed by SPSS version 15.0. Mean scores for each subscale were compared between patients and controls by unpaired t tests or by Mann–Whitney U test when subgroups were small. Levels of significance were set to P<0.05. Analyses were two tailed. Proportions were compared by chi-square statistics (Fisher’s exact tests).

There were no significant differences in mean scores between patients with confirmed food hypersensitivity and patients with unconfirmed food hypersensitivity. Patients were therefore treated as one group in the analyses.

Numbers of correctly completed questionnaires varied slightly between the different scales. When missing data were less than 20% in a questionnaire or a subscale, mean values were calculated based on the relevant correctly filled-in items and inserted where data were missing. When missing data were over 20%, the questionnaires or subscales were removed from the analysis.

2.6. Ethics

The study was approved by the Western Norway Regional Committee for Medical Research Ethics.

3. Results

3.1. Sample characteristics

A total of 178 consecutive patients were considered eligible for the study. Two patients were excluded because of pregnancy, two because of Crohn’s disease and 14 because of weak or no gastrointestinal complaints. Thirty patients dropped out because they found the investigation program too extensive or bothersome. The final number of patients included was 130 (107 women/23 men, 82.3%/17.7%), with mean age of 39.5 years (range 18–80 years).

Thirty (28.5%) of the 105 volunteers who were eligible as controls in the study reported hypersensitivity to at least one food item and were therefore excluded. The final number of controls included in the study was 75 (63 women/12 men, 84.0%/16.0%), with mean age of 41.0 years (range 20–76 years).

The self-administered questionnaires were completed by all patients and controls. Seventy-six (58.5%) of the patients were also interviewed. These patients were consecutively recruited during two periods, 28 patients were interviewed in 2001–2004 and 48 patients in 2006–2007. There was no significant difference in the distribution of age or sex between the interviewed and not-interviewed patient groups.
3.2. Somatic findings

Forty-seven patients (36.2% of the whole sample, \(n=130\)) had IgE antibodies to at least one food allergen, as verified serologically (food-specific IgE \(\geq 0.35\) kU/L) and/or by skin prick test. The most common food allergens were wheat (23.8%) and hazelnut (15.4%). Specific IgE antibodies towards inhalant allergens were present in 73 patients (56.2%).

Sixty (46.2%) of the 130 patients had positive elimination test result (symptom improvement by elimination of the food the patients supposed they did not tolerate). These were tested by open food challenge. Thirty-three patients (25.4%) had positive open food challenge test results and were then tested by the DBPCFC. The DBPCFC came out positive in 10 cases (7.7%). Four (3.1%) of these had IgE-mediated food allergy. The other six (4.6%) had non–IgE-mediated food allergy or nonallergic food hypersensitivity.

Abdominal symptoms satisfying the criteria of IBS were present in 115 (88.5%) of the patients. The majority (71.4%) had diarrhea-predominant IBS. Upper endoscopy was performed in all 130 patients and revealed indications of light reflux esophagitis in six patients (4.6%), while one had Candida esophagitis (0.8%). Four (3.1%) of these had IgE-mediated food allergy. The other six (4.6%) had non–IgE-mediated food allergy or nonallergic food hypersensitivity.

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3.3. Psychiatric disorders

Of the 76 interviewed patients, 43 (56.6%) fulfilled the criteria of having at least one psychiatric disorder according to the DSM-IV (Table 1). Thirteen patients met the diagnostic criteria of two or more different psychiatric disorders, making the total number of diagnoses 58. Anxiety disorders occurred most frequently and accounted for 56.9% of the total number of diagnoses. At least one anxiety disorder was present in 26 patients (34.2%), the most common being generalized anxiety disorder (\(n=11\)) and panic disorder (\(n=10\)). Depressive disorders were present in 12 patients (15.8%). The rates of depression as assessed by MADRS are presented in Table 2. Gastrointestinal symptoms and allergological findings did not differ between the patients who fulfilled the criteria for anxiety and/or depressive disorders and the patients who did not fulfill these criteria (Table 3). Likewise, there was no difference in prevalence of anxiety and/or depression between patients with confirmed food hypersensitivity and patients with unconfirmed food hypersensitivity.

3.4. Psychometric data

Psychometric data are shown in Table 4. The rates of adequately completed questionnaires varied from 92% to 99% in the different scales.
Mean score on EPQ-N in the 130 patients was significantly higher than in the control group (\(P=0.001\)). There was also a significantly higher mean score on GHQ-30 in patients compared to the control group (\(P=0.022\)), and mean scores on HADS-A and HADS-total were significantly higher in patients than in controls (\(P=0.013\) and \(P=0.021\), respectively). There was no significant difference in HADS-D between groups. Case-level HADS-A (HADS-A ≥8) was found in 23.5% of patients and in 12.5% of controls (not significant), while case-level HADS-D (HADS-D ≥8) was found in 2.5% of patients and in 8.3% of controls (not significant). The prevalence of case-level HADS-D was significantly lower than the prevalence of depression as measured by MINI (15.8%, \(P=0.001\)). The prevalence of case-level HADS-A was also lower than the prevalence of any anxiety disorder as measured by MINI (34.2%), but the difference was not statistically significant.

The difference in neuroticism between patients and controls was found in male as well as in female subgroups, while significant differences in GHQ and HADS were found in the female subgroups only. Mean scores did not differ significantly between the interviewed and not-interviewed patient groups on any of the scales.

### 4. Discussion

In the present setting of an allergy clinic, anxiety and depression were commonly associated with IBS-like symptoms self-attributed to food hypersensitivity. According to the interviews, the prevalence of any psychiatric disorder was 57%, of which anxiety disorders and depression predominated. According to the questionnaires, levels of anxiety, neuroticism and general psychological distress were significantly higher in patients than in healthy controls. However, we observed some significant discrepancies between interview and questionnaire results (see below).

The interview-based prevalences of depression (16%) and anxiety disorders, particularly generalized anxiety (15%) and panic disorders (13%), were considerably higher in our SFH patients than in the Norwegian general population (4–7%, 1–2% and 1–3%, respectively) [34,35]. This “diagnostic profile” of SFH patients resembles the findings of Pearson et al. [20,21]. Our findings of higher GHQ and EPQ-N scores in patients than in healthy controls are also consistent with previous results [15].

Several explanations can be given as to why anxiety and depression are prevalent in patients with SFH. The disorders may appear as a consequence of having chronic gastrointestinal symptoms. Being worried about, and bothered by bodily sensations and symptoms over time, may lead to or worsen mental illness [36]. On the other hand, psychological stress may modulate gastrointestinal function through the release of different hormones and peptides, such as mast cell mediators and corticotropin-releasing factor [37,38]. Anxiety is known to be associated with faster intestinal transit, while depressed persons tend to be constipated [39]. Additionally, patients with depression and anxiety often have a lower threshold for experiencing and reporting bodily symptoms [40].

SFH patients have a high number of subjective health complaints [8], which makes it likely that somatization mechanisms are involved in the pathogenesis and clinical presentation of this condition. The prevalence of somatiform disorders was 12% in our study, which is lower than what is usually found in studies of IBS [41]. This might be explained by the fact that we applied the MINI interview, which only covers the full DSM-IV criteria for somatiform disorders, and not the less strict criteria for undifferentiated somatoform disorder which is covered by the SCID-I interview [42].

Our patient sample had a high prevalence of IBS (89%), and the psychiatric disorders detected in the present study are similar to what is found in IBS studies [43]. Given also the extent of subjective extra-intestinal symptoms in SFH and in IBS [44], one might ask whether SFH actually is a distinct condition, or whether it is just another version of the so-called functional somatic syndrome(s) [45]. The main difference between our SFH patients and other IBS patients is that all SFH patients attributed their gastrointestinal symptoms to intake of specific food. In general, only about 60% of IBS patients report that their complaints are food related [46].

A relatively high proportion (36%) of our patients had specific IgE antibodies to one or more food allergens. However, the role of allergic mechanisms in this population remains uncertain. Allergy was rarely confirmed by DBPCFC, and the high prevalence of IgE sensitization to food was mainly a consequence of cross-sensitization to pollen allergens. This observed discrepancy between self-reported and confirmed food hypersensitivity is a well-known clinical problem [4,5] and could partly result from limitations of current diagnostic standards for food hypersensitivity. However, it is also likely that bodily symptoms sometimes are misattributed to certain foods. In these cases, SFH reactions may be caused by central rather than peripheral (immunological) sensitization mechanisms [9,47], and a high level of anxiety and neuroticism may contribute to such central sensitization [48]. In SFH, avoidance of certain foods can be an adaptive response if it is limited to a few specific kinds of food, and the patients experience that their symptoms are relieved by doing so. For most of the patients, however, avoidance of food is not helpful, and a sustained avoidance of many kinds of foods, additives and chemicals may actually increase the abdominal complaints as patients become more focused and aware of their gastrointestinal reactions. Reinforcers such as medical investigations and treatments, and use of many kinds of alternative treatments, may make the patients more sensitive to their somatic sensations.

One strength of the present study is the use of structured psychiatric interview. The MINI covers the main diagnostic categories of the DSM-IV and has shown to be a good
instrument for the identification of psychopathology [26]. Interestingly, we found some discrepancies in results between the MINI interview and other instruments, particularly in the case of depression. Only 8% had a MADRS score of 20 or more, indicating clinically significant depression, while 16% had major depression according to MINI. The explanation for this inconsistency is that six patients had a MADRS score of 18 or 19 and thus scored lower than the threshold commonly used for depressive disorder. The discrepancy between MINI and HADS-D results was more pronounced. MINI yielded a significantly higher prevalence of depression than the HADS scale (16% vs. 2.5%, P=.001). The HADS has previously shown to be a useful case finder in both population studies and clinical samples [31]. However, it does not seem to perform well as a case finder for depression in our setting of referred patients with SFH. This may be due to the construct of HADS-D where there are no items covering somatic symptoms. The clinical presentation of depression may be predominantly somatic in patients with SFH, and the patients will therefore get a low score on HADS-D.

It is also suggested in an earlier study [22] that patients with SFH may have a tendency to underreport emotional distress when this is asked about in questionnaires. However, in an interview setting where the patients are asked about these symptoms by an interested and empathic clinician, they get more aware of their emotional symptoms and are more willing to express them. Pearson et al. [20] described that nonallergic patients who strongly attribute somatic complaints to food hypersensitivity may be reluctant to accept psychological explanations of their symptoms, and the patients may be worried about being labeled as mentally ill with no “real” disease. In our study, the psychometric assessment took place at an early stage of the investigation program, at the same time as the gastroenterological examinations. The focus then was that the symptoms had an organic explanation, and this may have influenced how the patients filled in the items on the psychometric questionnaires. The psychiatric interview took place at a later stage, when results from the allergological and gastrointestinal examinations were known to the patient. It might have been easier for the patients to be aware of and admit psychological symptoms when the possibilities of organic etiology had been thoroughly investigated and, in most cases, with negative result.

In this study, patients were recruited from an allergy clinic, and the validity of our results in other settings, such as primary care or general population, is uncertain. From IBS studies, it is known that patients who seek help in outpatient clinics report more severe gastrointestinal complaints and also more psychiatric comorbidity than nonconsulters and IBS patients in primary care [49,50]. In other studies, it is suggested that this “referral bias” also applies to patients with SFH [18,19]. Our choice of a control group from the general population might then not have been the most appropriate, since the patients were likely to be more ill than the controls in several ways, not only with respect to SFH. To get a better understanding of whether the high prevalence of anxiety and depression really is a characteristic feature of SFH, or whether it is merely one aspect of the patients’ illness behavior, it could have been interesting to compare our patient group with other outpatient groups suffering from related conditions, such as confirmed allergy, or some better understood gastrointestinal disorder. However, in a study from the general population, a high prevalence of depression as well as of anxiety disorders was found in individuals with SFH [51]. In this study, they applied a structured psychiatric interview. Hence, as we also found in the present study, selection of the psychometric instruments might be crucial when studying the role of psychological factors in SFH.

Our results suggest that assessment of depression and anxiety disorders may be a useful approach in the clinical investigation of patients with self-reported food hypersensitivity. Further studies are warranted, however, in particular on whether treatment of anxiety and depressive disorders may alleviate symptoms related to intake of food.

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