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Psychological morbidity of celiac disease: a review of the literature

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Abstract

Background: Celiac disease has been linked to decreased quality of life and certain mood disorders. The effect of the gluten free diet on these psychological aspects of the disease is still unclear.

Objectives: To review the literature on psychological morbidity of celiac disease.

Methods: We performed a PubMed search for the time period from 1900 until June 1, 2014, to identify papers on psychological aspects of celiac disease looking specifically at quality of life, anxiety, depression and fatigue.

Results: Anxiety, depression and fatigue are common complaints in patients with untreated celiac disease and contribute to lower quality of life. Whilst aspects of these conditions may improve within a few months after starting a gluten free diet, some patients continue to suffer from significant psychological morbidity. Psychological symptoms may impact the quality of life and the dietary adherence.

Conclusion: Healthcare professionals need to be aware of the on-going psychological burden of celiac disease in order to support patients with this disease.

Introduction

Celiac disease (CD) is a chronic immune-mediated enteropathy (1) characterized by a large spectrum of symptoms and signs, which generally improve with good adherence to a gluten-free diet (GFD) (2).

In recent years, there has been an increased interest in how celiac patients perceive the impact of their disorder, how this perception relates to the clinical presentation of the disease and how their health is modified by treatment with a GFD. It has been recognized that the aspects of health which should be addressed go beyond the usual biological parameters and extend also to social functioning and psychological issues (3). Mood disorders such as anxiety, depression and fatigue are often linked to CD, before and after diagnosis, and therefore may influence the patient's quality of life (QoL) and adherence to GFD.

Methods

This work is part of a project initiated by the Oslo group and British Society of Gastroenterology on the clinical management of CD (2). We examined the literature on the QoL of celiac patients and some psychological aspects associated with CD (anxiety, depression and fatigue), asking how treatment with a GFD may modify them. A PubMed search identified papers on QoL, anxiety, depression and fatigue published between 1900 and 1 June 2014. Four authors (FZ, GLS, TRC, JCB) carried out the literature searches, the data collection and took the main responsibility for the writing of the paper. DS and JFL reviewed the paper, giving important feedback.

Results

Quality of life (QoL)

Several reports have described the difficulties of living with CD in adult subjects, in particular as regards the impact of this condition on physical, social, and emotional factors (4-23). Unfortunately, interest in the health perception of celiac patients has been affected by the lack of CD-specific QoL instruments allowing measurement of specific aspects of the disorder. Most studies exploring the QoL in CD patients used generic multi-item and multi-dimensional instruments developed for chronic disorders (24-27). The most widely used generic tools to estimate health-related QoL in CD were the Short Form Health Survey questionnaire (26) and the Psychological General Well-being index (28). It is only recently that CD specific questionnaires have been developed for pediatric (29, 30) and adult patients (31, 32) and translated in other languages (33-36). Although screen-detected (37, 38) and asymptomatic CD patients (39) seem to have a better QoL than symptom-detected patients at the time of diagnosis, the effect of the GFD on QoL of screen-detected and asymptomatic patients is still unclear. Mustalahti et al reported a positive effect of the GFD in both symptomatic and screen-detected patients (37), Johnston et al suggested the benefits were limited to those presenting with symptomatic disease (38), Vilppula et al (40) reported no change of the QoL in screen-detected patients on GFD and finally Ukkola et al described that the QoL improved in symptomatic and in screen-detected symptomatic patients but not in screen-detected asymptomatic patients (41) (Figure 1). Interestingly, a time-course assessment of the effect of treatment showed that, in symptomatic patients, the most significant quantitative improvement of most items is seen in the first three months after starting the GFD, with some additional improvement up to 1 year (39), (Figure 1). Compared to biological parameters,

including serology, the time course for improvement of QoL measures seems to be earlier and faster (39). Paavola et al, analyzing CD patients on long-term GFD, reported that the QoL was unimpaired in screen-detected celiac patients and lower in symptom-detected patients, when compared to healthy controls (42). A recent randomized study showed that asymptomatic CD patients benefited from a GFD for anxiety and better health (based on the visual analogy scale), but not for social function, when compared to similar patients following a gluten-containing diet (43). Finally, Roos et al. showed similar psychological well-being in long-treated celiac patients and healthy controls (16). Poor dietary adherence was associated with a poor QoL (8, 10) but whether one causes the other remains unknown, and consequently it is unclear which is the cause and which the effect. A recent long-term longitudinal study suggested that subsequent deterioration in QoL was associated with a lack of dietary adherence (44). However, other studies (45, 46) reported no differences in QoL scores between patients with full adherence and patients with partial/non adherence to GFD, and Barratt et al found that perceived difficulty of adhering to a GFD may be associated with a decline in QoL (45). Several papers reported lower QoL in women with CD than in celiac men (9, 11-13, 18). Recently, Paarlahti et al. (47) reported that a long duration of symptoms before diagnosis, psychiatric, neurologic or gastrointestinal co-morbidities and persistent symptoms were predictors of a reduced QoL.

Anxiety

Anxiety has been widely described in CD patients, although a recent meta-analysis (48) concluded that anxiety is neither more common, nor more severe in adults with

CD compared to healthy adults. However, large studies are lacking (Table 1). Levels of anxiety appear to increase prior to CD diagnosis, although a diagnosis may be associated with feelings of relief (5). Cannings-John et al. (49) compared 68 adult celiac patients to 160 controls, celiac patients had an increased number of general practice consultations compared with controls in the 5 years prior to diagnosis and 3 clinical features were independently associated with subsequent diagnosis; these were depression and/or anxiety, diarrhoea and anaemia. An Italian study suggested an increased reactive 'state' anxiety in CD patients, but no increase in personality 'trait' anxiety (50) and a reduction in reactive anxiety after one year on a GFD (51). Among 441 German adult patients on a GFD, the levels of anxiety and risk of a probable anxiety disorder were greater than the general population (52). Interestingly, anxiety levels were greater in female CD patients compared to male patients, and living alone was associated with a reduced risk of anxiety disorder. The authors speculated that problems with buying and preparing food, plus the associated expense, within a family group may contribute to anxiety. In another study, social phobia, assessed by the Liebowitz Social Anxiety Scale, was found to be significantly greater in 40 celiac patients (53). Among these patients, social phobia levels were similar in newly diagnosed and treated individuals (53). In a study of 68 patients treated for a mean of 10 years, Hallert et al. (11) evaluated a 9-item Burden of illness protocol, assessing perceived worries, restrictions and subjective outcome. Whilst the importance of dietary adherence was ranked similarly high by men and women with CD, 10 years after diagnosis women expressed more concerns about the impact of the disease on socialising with friends and having to abstain from important things in life. A recent study (54) interviewed women with CD and looked at the impact of the condition on everyday living. They expressed a sense of

loneliness and invisibility, especially when socialising with others. In another large qualitative study of nearly 6000 Canadians with CD (17), women reported significantly greater emotional responses to a GFD but, with time, were more accepting of it than men. Frustration and isolation were the most common negative emotions.

Depression

Depression has been associated with CD (48). Morris et al. (55) and Hallert et al. (56) were among the first to describe this association. Though numerous papers have followed the causes of this association and the effect of a GFD on depression, these are still poorly defined (Table 1).

Using the modified Self-Rating Depression Scale, Addolorato et al. (51) described persistent depression after 1 year of GFD in celiac patients, Zingone et al. (57) and Siniscalchi et al. (58) showed that depression was present in CD at diagnosis, but that it persisted or even worsened in patients on a GFD. Nachman et al. (44), using The Beck Depression Inventory, showed that depressive symptoms were highly prevalent in untreated CD and there was a significant improvement in psychological symptoms after one year and four years of GFD (44). However, the Beck Depression Inventory score at 4 years showed a significant worsening compared to one year, though CD patients at the 4-years visit still had less depression than at CD diagnosis. A low adherence to GFD might be considered either a cause or a consequence of the persistent depression on GFD. This has been suggested in a 2004 study by Addolorato et al., which showed a beneficial effect of psychological support for CD patients on a GFD both in relation to psychological disorders and to

improved dietary adherence (59). However, most previous studies reported different results. A study of 154 patients found that a poor GFD compliance correlated with depression (60). Fera et al. (61), in a study of 100 patients treated for 8 years, found a high rate of depression, detected by the modified Self-Rating Depression Scale, which tended to improve with time, but which was not correlated with dietary compliance. Similarly, a 2013 cross-sectional study (62), reporting a self-reported depression prevalence of 39% among 2265 adult CD patients (based on the Major Depression Questionnaire), described that the long-term adherence to the GFD (>5 years) was associated with a reduced risk of depression, but they found no association between insufficient adherence and current depression symptoms. Finally, Hauser et al. (52) did not find any difference in depression between celiac patients on GFD and the general population. The authors reported no evidence that depression was predicted by diet adherence, years of GFD, presence of associated diseases, or delay in CD diagnosis. Finally, Barratt et al. (63) described that patients on a GFD, at risk of anxiety and depression according to the Hospital Anxiety Depression Scale, reported more symptoms in response to occasional dietary gluten exposure.

Mechanisms explaining anxiety and depression

As Table 2 shows, a number of mechanisms may explain the relationship between CD and psychological morbidities such as anxiety and depression, either before or after CD diagnosis. *Before diagnosis*, they may be a consequence of the disease symptoms with a decreased sensation of general well-being (64). Equally, they may be due to cerebral hypoperfusion in some brain regions (65), be a consequence of the reduction in brain monoamine metabolism related to malabsorption and malnutrition

(66), or of hyperhomocysteinemia and folate deficiency (67, 68). *On a GFD*, they may be particularly sustained by dietary restrictions and by compromised daily social relationships (21). Independently of GFD, psychological morbidities in CD may be also secondary to CD associated with autoimmune diseases. For example, Carta et al. in 2002 (69) showed that the association of CD with thyroid disease can represent a significant risk factor for depression and panic disorders. Some years later, Garud et al. (70) described a similar risk of depression in CD when compared with the general population but a markedly elevated risk of depression in patients with both CD and type I diabetes. A possible explanation of this increased risk may be that the cytokines produced by immune reactions may exercise an effect on the brain circuits responsible for mood regulation (71). However, a large Swedish population-based study (72) based on 13,776 CD patients found that CD patients were at an 80% increased risk of depression compared to controls and the adjustment for type I diabetes or thyroid disease did not affect the risk estimates (72). Finally, these psychological morbidities could be also a consequence of a chronic condition: in fact while Ciacci et al. found a higher prevalence of symptoms of depression in CD patients than in patients with chronic hepatitis (73), others have found no difference between depression in CD compared to patients with Irritable Bowel Syndrome (IBS) (70), and depression and anxiety compared to patients with type 2 diabetes (61). Finally, Hauser et al (52) described levels of anxiety greater in CD and in patients with inflammatory bowel diseases compared to controls and similar levels of depression among the 3 groups.

Depression and anxiety may be associated with other factors including an unsatisfactory sexual life (13), fatigue (58) and poor quality of sleep (57). Furthermore, symptoms due to reflux and/IBS are also associated with reduced QoL

and increase the likelihood of anxiety and depression in CD. Treating these co-morbidities may improve QOL and mood disorders in CD (74).

Fatigue

There is now good evidence to show not only that fatigue can be a symptom of CD, but also that it is a common clinical presentation (75-78). Serological screening for CD is now recommended in the work up of chronic fatigue (79). Case finding studies suggest a CD prevalence of about 3% among those presenting with chronic fatigue, i.e. similar to that in patients with IBS (77). Less is known about the prevalence of fatigue among those already on a GFD, or whether treatment of CD with a GFD successfully treats this symptom. In the last decade a small number of studies have more directly addressed these issues. Siniscalchi et al in 2005 demonstrated that celiac patients both at diagnosis and when on a GFD had higher levels of fatigue than healthy controls using a variety of validated scales (58). Perhaps more surprisingly, fatigue was not significantly different between newly diagnosed celiac patients and those on an established GFD. The same researchers from Naples have since shown that both treated and untreated celiac patients experience a worse quality of sleep than healthy volunteers (57) perhaps offering an explanation of the mechanisms behind this condition. Again, treated celiac patients did not show significantly different characteristics to their untreated counterparts. More recently, a large questionnaire study of 5912 Canadian celiac patients has suggested that "extreme weakness/tiredness" is reported by patients to improve over a prolonged period on GFD, such that of those on GFD for more than 5 years 72.4% reported this symptom had recovered (80). Interpretation of these findings is made more difficult by the fact that data originate from cross-sectional studies, rather than

from either randomised controlled trials of the effect of GFD, or cohort studies to permit examination of the alteration in state within individuals after establishment of a diet. It is therefore unwise to conclude too firmly that GFD either does, or does not alleviate fatigue in CD from the available evidence. One other potentially relevant finding is the suggestion that dietary supplementation with L-carnitine may treat fatigue in CD (81). Since carnitine is absorbed in the small intestine (82), it is tempting to assume that resolution of malabsorption should facilitate the intestinal uptake of carnitine. However, the range of gastroenterological and non-gastrointestinal conditions in which similar effects have been suggested indicates that mechanisms other than the correction of a deficiency may be operating (83, 84).

Summary

Our search of the available literature suggests that CD has a considerable psychological impact. Some elements of this may relate to the disease and its biochemical effects, but other aspects relate to the patient´s subjective perception of the disorder and of the GFD used to treat it. The treatment of CD results in a significant improvement in QoL for symptomatic patients, but patients with subclinical CD often report no such effect. However, a proportion of subclinical patients may report improvement in QoL parameters after commencing treatment. Overall, levels of anxiety and depression are greater in patients with CD (Table 1). However, the causes of this may vary at different stages (Table 2). Prior to CD diagnosis, patients may express concerns about unexplained symptoms and may feel frustrated about repeated consultations that offer no adequate explanation of their problems. At the time of diagnosis, there may be concerns about investigations and a

diagnosis of a long-term condition, although this may be accompanied by a feeling of relief that a diagnosis has finally been made. Whilst some psychological problems may lessen with time as knowledge of the condition improves and perhaps biochemical abnormalities are corrected, it appears that many patients have ongoing concerns about coping with the diet and do not adhere to the diet, particularly when going out and in social interaction. Fatigue is sometimes the unique symptom at CD presentation. Conversely, 3% of patients with chronic fatigue may be found to have CD. The available studies have not been able to show a consistent positive effect of the GFD in diminishing perception of fatigue.

Conclusion

The literature on the effect of treatment in the outcome of depression, anxiety, fatigue and QoL in CD is not consistent. However, it is important to consider that ongoing problems with anxiety and depression in particular may impact on dietary adherence and quality of life. Thus, healthcare professionals need to be aware of the ongoing psychological burden of CD in order to support their patients. The lack of clear evidence of improved QoL in asymptomatic CD after treatment makes mass screening, where a majority of patients may be subclinical or asymptomatic, controversial if the aim of screening is to improve QoL. Further studies are required to better understand this specific aspect.

Conflict of Interest

TC: Grant support: Coeliac UK: Crohn's and Colitis UK: Spouse is an employee of AstraZeneca.

DSS: has received an educational grant from Dr Schär (a gluten free food manufacturer) to undertake an investigator led research study on gluten sensitivity. Also has received an educational grant from both Biocard and Simtomax to undertake an investigator led research study on point of care tests

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Figure 1. Quality of life in screen-detected and symptom-detected celiac patients after 1 year of gluten free diet

Figure legend:

*the QoL improved in symptomatic screening detected patients.