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Review Article

Exploring Non-Coeliac Gluten Sensitivity: A Neuropsychiatric Disorder?

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Abstract

Gluten is the main storage protein of wheat grains. There is a large spectrum of disorders associated with dietary gluten intake. The evidence assessing the effects of gluten as a trigger of gastrointestinal symptoms, extra-intestinal sensations and mental state outside of coeliac disease and wheat allergy requires careful dissecting. Case reports and retrospective questionnaires highlight a potential link between gluten and mental health effects, however mechanisms will only be established with carefully conducted double-blind placebo-controlled cross-over designs which reveal reproducible findings.

Key words: Gluten, wheat, food intolerance, mental state

Introduction

Non-Coeliac Gluten Sensitivity (NCGS) is a syndrome diagnosed in patients with symptoms that improve by removal of gluten from the diet, after coeliac disease and wheat allergy have been excluded. Reported symptoms range from gastrointestinal complaints including abdominal pain, bloating and bowel habit abnormalities to systemic manifestations including disorders of the neuropsychiatric area such as “foggy mind”, depression, headache, fatigue, and leg or arm numbness [1]. There is confounding evidence supporting the prevalence, diagnosis and mechanisms of NCGS, especially given the absence of reliable biomarkers. This review aims to assess the current understanding of NCGS and highlight the potential role for gluten on mental state and not necessarily only on gastrointestinal symptoms.

What is Gluten?

To understand gluten related disorders, it is important to first understand what gluten is and acknowledge that wheat has long been considered as a common factor inducing gut symptoms [2]. Gluten is the main storage protein contained within the germ of wheat grains, where related water-soluble proteins exist in wheat, rye and barley. The term gluten encompasses a broad group of prolamins (gliadins and glutenins) found in wheat. The soluble gliadin fraction is largely resistant to degradation by gastric, pancreatic and intestinal brush-border membrane proteases in the human intestine and thus remain in the intestinal lumen after ingestion [3].

Furthermore, wheat contains many other non-gluten components including the non-starch polysaccharides, metabolic proteins, starch, minerals and vitamins, which may play a role in the development of symptoms. The carbohydrate component of wheat called fructans, has increasing evidence for inducing symptoms in many patients with irritable bowel syndrome.Fructans form part of the FODMAP (Fermentable Oligo-, Di-, Mono-saccharides and Polyols) group, who’s physiological effects include osmotic activity and rapid fermentation by virtue of their poor absorption in the small intestine, both inducing luminal distension and consequently gastrointestinal symptoms [4].The non-gluten proteins, α-amylase/trypsin inhibitors have recently been suggested to induce intestinal inflammation [5]. A variety of allergic (wheat allergy), autoimmune (coeliac disease, dermatitis herpetiformis and gluten ataxia) and non-immune-mediated (non-coeliac gluten sensitivity) conditions encompass the spectrum of disorders believed to be related to gluten exposure.

Gastrointestinal Disorders and Mental Health

Coeliac disease

Coeliac disease - Gluten is established as the causative agent

of coeliac disease, an immune mediated disease elicited by exposure to gluten in the diet of genetically susceptible patients. It is characterised by small intestinal injury and immunological activation and the only possible treatment is a lifelong avoidance of dietary gluten.

Depressive symptoms have previously been identified as a feature of coeliac disease [6] and exist in patients with food hypersensitivity [7], but the mechanisms remain to be determined. Changes in mood have also been described in coeliac disease [6,8] and in particular, symptoms of anxiety and depression have been shown to be related to gut symptoms [9].Changes in the gut-to-brain signalling pathway may play a role, given the associations with prolonged alterations in the autonomic nervous system, which in turn is related with altered emotional states such as depression [10].

Irritable Bowel Syndrome

Irritable Bowel Syndrome (IBS) is best regarded as a complex of symptoms without a single cause, including disordered gut motility, visceral hypersensitivity, and intestinal inflammation. It has also been reported that chronic life stress may predict the intensity of bowel symptoms [11]. IBS patients have high rates of 'abnormal' behaviour patterns including anxiety, depression and somatisation (conversion of an emotional, mental, or psychosocial problem to a physical complaint) [12]. An increased generalised anxiety and depressive symptomology may lead to patients being more concerned about their symptoms [13].

The above mentioned symptoms of IBS are a complex response to both biological, environmental and psychosocial factors, demonstrating that dysregulation of the gut-brain axis, a bidirectional, neurohumoral communication pathway between the central and enteric nervous systems, is involved in symptom development [14]. This involvement of the gut-brain axis, with physical and psychological components, further implies there is emphasis on the'perception of symptoms' and their impact rather than on the symptoms themselves [10].

Non-coeliac gluten sensitivity

Non-coeliac gluten sensitivity - Diagnosis of NCGS is currently based on the clinical response in intestinal and extra-intestinal symptoms to the gluten-free diet and to a gluten challenge [1]. The prevalence is not defined yet and is difficult to study given that the clinical presentation is multi-systemic and appears to be transient [15].Epidemiological studies show increasing numbers of the Western population believe themselves to have NCGS, ranging from 0.5% to 13% [16,17].

Evidence for Effects of Gluten Outside of Coeliac Disease

Gastrointestinal symptoms

Gastrointestinal symptoms - Several key studies now support gluten being able to induce gastrointestinal symptoms in patients without coeliac disease [18]. However, the trial designs and findings are variable and need to be considered carefully, as no or limited gluten-specificity [19-21] and a lack of reproducibility [19] have been found. Increasingly, evidence highlights potential methodology flaws and heterogeneity among the design of gluten challenge, where few patients show gluten-specific symptoms after a double-blind, placebo-controlled gluten challenge [22].

Extra-intestinal symptoms

Extra-intestinal symptoms - Previous studies of food hypersensitivity and coeliac disease have reported prevalence of extra-intestinal symptoms [23]. Multiple unexplained non-GI symptoms, including headache/migraine, musculoskeletal pain, heartburn, mood change, itchiness/rash, forgetfulness, are self-attributed to gluten by NCGS patientsasreported in surveys and during dietary trials [24].

Mental state

Mental state - In patients with functional gastrointestinal disorders, anxiety and depression are present, particularly as a personality trait [25]and may play a role in the genesis and/or the perception of symptoms. In one small study in patients with self-reported NCGS, 3-day exposure to 16g gluten per day increased depression scores compared to placebo [26]. Gluten did not specifically induce GI symptoms, nor activate cortisol secretion. The only measure of psychological wellbeing to alter was a significant increase in overall state depression score after the gluten challenge arm, indicating an increase in current feelings of depression with no effect on emotional disposition [26]. Other potential mechanisms were not investigated and a healthy control group was not included, warranting further mechanistic studies. The depressive symptoms demonstrated may lead to an increased concern about symptoms and an increased sensitivity in relation to visceral sensation. This finding of acute changes in the current emotional state only in the gluten-specific arm, with no effects on trait indices, provides a clue that the improvement reported by patients may be in the perception of their general well-being rather than in GI symptoms. Consequently, this might explain the basis for patients 'feeling better' on a gluten-free diet despite continuation of gastrointestinal symptoms, especially for 24% of self-reported NCGS who report uncontrolled symptoms despite gluten restriction [24]. It may also provide some insight into why the effect of gluten on gastrointestinal (and possibly extra-intestinal) symptoms appears to be random with limited specificity and reproducibility, taking into account the many influential variables inducing psychological dysfunction and other biological and psychosocial factors [10]. Since depression is a complex, multifaceted syndrome with a number of underlying dimensions that can lead to many behavioural and physical symptoms, the clinical significance of these findings

requires further research using additional measures of depression and emotional state.

NCGS has been related to the appearance of other neuropsychiatric disorders, including autism and schizophrenia [27-29]. A singular report of NCGS presenting with hallucinations has been described in an adult patient showing sensitivity to gluten with remission of longstanding hallucinations after gluten elimination and relapsing symptoms upon reintroduction of dietary gluten [30]. A paediatric case-report has also indicated psychosis as a possible manifestation of NCGS [31]. Furthermore, there is evidence for a role of gluten in bipolar disorder patients, where an increase of blood anti-gliadin deamidated antibodies (IgG) was found [32]. Although this has been studied to a much lesser extent, it hints towards associations of gluten and psychiatric related disorders.

The proposed mechanism for the effects of gluten outside of coeliac disease is based on an altered gut barrier function, resulting in an exaggerated increase in intestinal permeability. This leads to abnormal absorption of gluten peptides that can eventually reach the Central Nervous System (CNS) and stimulate the brain opioid receptors and/or causing neuro-inflammation. Gluten has been shown to increase the intestinal permeability [33], which allows for an increased absorption of undigested gluten peptides reaching the lamina propria, which cross into the circulation, and finally the blood-brain barrier. By interacting with opioid brain receptors, gluten peptides can affect the individual's behaviour or trigger activation of immune cells that migrate to the brain resulting in neuro inflammation [34]. These opioid peptides are referred to as gluten 'exorphins'[35], derived from partially digested food proteins including gluten and cross the blood-brain barrier interfering with CNS activity, as proposed in studies of autism [35,36].

Other possibilities for how gluten may be related to depression and other mental health effects include abnormalities of serotonin production. Serotonin (5-HT) is a critical signalling molecule in the gut, shown to play a role in IBS symptom genesis [37] and dysfunctional serotonin neurotransmission has been implicated in depression [38]. As most serotonin is derived from the digestive tract [39], it may be possible that certain foods, such as gluten-containing ones, influence serotonin production. Furthermore, alteration in 5-HT signalling has shown to be associated with coeliac disease, where excess serotonin production was induced on exposure to a high-gluten, high-carbohydrate meal [40]. Another possibility could be that gluten may effect emotional state through purely interoceptive pathways. For example, it has been shown that other nutrients, such as fatty acids, can interfere with affective processes, both at the subjective and neural level, after subliminal (not consciously perceived) intragastric administration [41]. The mechanism remains unclear as to how gluten could be causally related to depression or neuro-psychiatric disorders.

Future Research Directions

A double-blind, placebo-controlled, cross-over gluten challenge has been advocated as the gold standard test to study NCGS [1]. However, a recent systematic review highlighted that this may not be the most valid way of verifying the existence of NCGS, given issues with high placebo and nocebo responses and heterogeneity of patients [16]. More than 80% of patients with suspected NCGS were not able to have their diagnosis confirmed after double-blind, placebo-controlled, cross-over gluten challenges [22]. Therefore, verification of NCGS in an individual is difficult and a single or even double short-term placebo-controlled challenge has doubtful validity. Reproducibility is a key feature of any clinical study and diagnostic pathway for food intolerance. Methodological considerations include patient selection (inclusion and exclusion criteria, methods of coeliac disease exclusion), methods of re-challenge (dose, type and delivery of gluten used), successful blinding (ensuring the gluten has not affected test foods taste and appearance), control of confounding dietary factors (especially background intake of FODMAPs) and endpoints (well defined cut-off points for determination of positive or negative response) [42]. Future research will need to assess ways to optimise diagnosis and approach to patients with suspected NCGS.

Depression is a complex, multifaceted syndrome with a number of underlying dimensions and can lead to many behavioural and physical symptoms, therefore the clinical significance of gluten's role in NCGS requires further research using additional measures of depression. Personality and emotional factors including levels of anxiety, anger, depression and curiosity are major indicators of psychological distress and well-being and require careful assessment. Dispositional and transitory emotions can be easily measured using various validated questionnaires such as the State-Trait Personality Inventory scale [43]. Determination of cortisol in serum and urine has long been used in the assessment of adrenocortical function and other disturbances in the hypothalamic-pituitary-adrenal axis and can therefore be used as an objective measurement [44]. Cortisol also serves in the diagnosis of depressive disorders [45] and is a frequently used marker for different kinds of stress-induced reactions [44]. Future research investigating NCGS will need to be careful in their psychological measurements.

Clinical Implications

In the clinical setting, the advocated diagnostic approach [1] for NCGS is fundamentally complex and time-consuming. Unfortunately, a more practical approach will only be possible with the development of biomarkers or other clinical predictors. Gluten may influence current feelings of depression, but has not shown any influence on depression as a personality trait [26]. The clinical significance of these findings requires further research using ad-

ditional measures of depression.The beginnings of such evidence, showing links between gluten and neuropsychiatric sensations, highlight that management options should be made on the basis of the patient's history of symptoms and personal preferences. As for many patients with IBS, additional therapeutic interventions may need to be instituted to optimise patient management. For example, one option could target the possible depressive effects of gluten [26]. Psychological treatments including dynamic psychotherapy, hypnotherapy, relaxation training, biofeedback, cognitive behaviour therapy and assertiveness training have all been suggested for use in the management of IBS. Although only some have been empirically evaluated [46], psychosocial treatments have shown some evidence for reductions in generalised anxiety and depressive symptomatology [47].

Conclusions

The results of this review highlight the complexity of the Non-Ccoeliac Gluten Sensitivity (NCGS). Although the role of gluten in coliac disease is well understood, the exact role in NCGS remains undefined, including the exact mechanism, diagnosis and identification of patients with NCGS. Although the data is scant, there are hints that gluten consumption by patients without coeliac disease may be related to current feelings of depression and may contribute to neuro-psychiatric disorders in some cases. Well-designed prospective studies are needed to establish these findings and to further elucidate whether depressive symptoms are a cause or consequence of NCGS, or whether they simply are parallel manifestations of an underlying disorder.

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