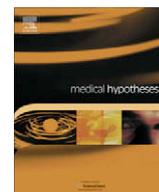


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# The gluten syndrome: A neurological disease

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### SUMMARY

**Hypothesis:** Gluten causes symptoms, in both celiac disease and non-celiac gluten-sensitivity, by its adverse actions on the nervous system.

Many celiac patients experience neurological symptoms, frequently associated with malfunction of the autonomic nervous system. These neurological symptoms can present in celiac patients who are well nourished. The crucial point, however, is that gluten-sensitivity can also be associated with neurological symptoms in patients who do not have any mucosal gut damage (that is, without celiac disease).

Gluten can cause neurological harm through a combination of cross reacting antibodies, immune complex disease and direct toxicity. These nervous system affects include: dysregulation of the autonomic nervous system, cerebella ataxia, hypotonia, developmental delay, learning disorders, depression, migraine, and headache.

If gluten is the putative harmful agent, then there is no requirement to invoke gut damage and nutritional deficiency to explain the myriad of the symptoms experienced by sufferers of celiac disease and gluten-sensitivity. This is called "The Gluten Syndrome".

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### Introduction – gluten causes an array of symptoms

Gluten grains (wheat, rye, and barley) have become staples in our diet. The quantity of gluten in our daily food intake has been steadily increasing with advances in food processing.

Gluten has been recognized as the instigator of celiac disease (also known as gluten-sensitive enteropathy), which affects one in every hundred people. The traditional concept is that celiac disease is a gastro-intestinal disease, and that symptoms are due to mucosal damage or malabsorption. It is defined as a gastro-intestinal disease, requiring histological evidence of mucosal damage to make the diagnosis [1,2].

But a host of symptoms "outside" the gut (so-called the "extra-intestinal symptoms") have been also been observed [3]. The bowel damage caused gluten toxicity cannot explain this wide array of symptoms. Consequently, there must be an alternative mechanism.

Importantly, evidence is accumulating that purports gluten to be responsible for significant ill health other than celiac disease: such as ataxia [4], eczema [5], and irritable bowel disease [6]. The name used for this group has been "non-celiac gluten-sensitivity". However, the term "The Gluten Syndrome" is proposed.

An explanation of the gluten disease mechanism must answer these questions. How can gluten cause such an array of symptoms? Why do people react so rapidly to tiny amounts of gluten? Why can celiac patients with extensive gut damage be asymptomatic?

The proposition that the fundamental problem is gluten's interference with the body's neural networks could be the answer.

### Hypothesis – gluten harms the nervous system

The hypothesis states: "Gluten causes symptoms, in both celiac disease and non-celiac gluten-sensitivity, by its action on the nervous system. This is called the gluten syndrome".

Occam's razor, the law of succinctness, states that an explanation should make as few assumptions as possible. Defining gluten-sensitivity as a neurological condition achieves this. It explains why there are such varied manifestations of gluten-sensitivity, while making a minimal number of assumptions.

The proposition is that gluten can, directly and indirectly, injure the nervous networks that control gut functions. This leads to the primary neurological symptoms found in gluten-sensitivity and celiac disease.

The smooth uninterrupted function of the body relies upon the autonomic nervous system. The sympathetic and parasympathetic pathways are driven by the respective neuro-transmitters. The regulation of the cardiovascular system, gut, bladder, uterus, and glands (pancreas, gall bladder, sweat, and saliva) all depends on this vast autonomic nerve network.

### Gluten the putative agent

Gluten is linked to neurological harm in patients, both with and without evidence of celiac disease. The first argument is that if

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gluten can affect nerve tissue, then there must be evidence that patients with celiac disease have neurological disorders.

#### *Neurological dysfunction and celiac disease*

Over 40 years ago, a report linked neurological disorders with adult celiac disease [7]. Their underlying argument stated that gut disease was a prerequisite for these neurological problems.

This was investigated further. Celiac patients completed a questionnaire regarding the presence of neurological symptoms [8]. Those reporting any neurological manifestations were compared with a control group: celiac patients had more neurological disorders (51.4%) in comparison with controls (19.9%). These conditions included: hypotonia, developmental delay, learning disorders, attention deficit hyperactivity disorder, migraine, headache, and cerebella ataxia. Epileptic disorders were marginally more common. When placed gluten-free, a therapeutic benefit was demonstrated in patients with transient infantile hypotonia and migraine headache. They concluded that the extent of neurological disorders that occurred in celiac disease was much broader than had been previously reported, with over a half affected. This concept has been well accepted [9].

A high prevalence of headache/migraine has also been found in celiac patients (46%) when compared with a control group (29%). Some had cerebral calcification when studied with head MRI scans, probably from long-standing disease [10].

Many celiac patients have gastro-intestinal motor abnormalities. About half get dyspeptic symptoms, suggestive of a gastro-intestinal motility disorder. Disturbed motility of the oesophagus, stomach, small intestine, gallbladder, and colon of untreated celiac patients has been documented [11]. Gastro-intestinal abnormalities from a malfunction of autonomic motility differ in different areas in the gut, such as: slower oesophageal transit (slow swallowing); delayed gastric emptying (full tummy for longer); impaired gallbladder emptying (fat digestion problems); slower oro-cecal transit time (bloating, constipation); and faster colonic transit (diarrhoea). These are all symptoms that are commonly reported in celiac disease and gluten-sensitivity.

Upper-gut motor abnormalities are also seen in people with celiac disease [12]. In 30 celiac patients, oesophageal motor abnormalities were detected in half of their patients: abnormal oesophageal acid studies (pH-probes) were abnormal in 30%; delayed gastric emptying was documented in 50%. In total, 75% were shown to have some sort of gastro-intestinal motility alterations. Tests of autonomic dysfunction were positive in 45% of these patients. This indicated that a gluten autonomic neuropathy was likely to play a role in their reflux.

#### *Neurological disorders in non-celiac gluten-sensitivity*

The second argument is that gluten has also been evidenced to cause illness independent of celiac disease. These disorders affect the gut, skin, and nerve tissue.

Irritable bowel is common, and now gluten-sensitivity is implicated in abdominal symptoms in the absence of villous atrophy. Celiac disease-associated serum antibodies are associated with diarrhoea-dominant irritable bowel syndrome patients and respond to gluten-free diet [6].

Dermatitis Herpetiformis is the best known skin disease associated with gluten ingestion. However, gluten intolerance gives rise to a variety of dermatological manifestations which may benefit from a gluten-free diet [5].

Gluten-sensitivity without histological gut damage, has been shown to provoke neurological dysfunction [13]. Neurologic/psychiatric manifestations in children with gluten-sensitivity are slightly higher than in controls [14].

A mechanism for such nerve damage might be through autoimmune damage [15]. A number of nerve and brain antibodies have been detected. Anti-ganglioside antibodies have been detected in 64% of patients with celiac disease who had also been troubled with some sort of neuropathy [16]. These auto-antibodies have been shown to bind to a number of critical nerve sites that will go on to damage the nerve.

#### **Audit of gluten sensitive children**

When gluten becomes the focus of interest, rather than mucosal damage, more attention will be taken of gluten antibody responses, especially the IgG-gliadin antibody level. Further, as gluten causes disorders in addition to celiac disease, then celiac disease is not a mandatory requirement for gluten-sensitivity. This concept changes the whole perspective of gluten harm.

An audit of 921 children from RF's gastroenterology and allergy clinic was carried out. They were investigated for celiac disease with IgG-gliadin antibody (Inova Diagnostics) and tissue transglutaminase (tTG); and 190 had a small bowel biopsy.

There were 724 with high IgG-gliadin levels (>14 units): mean age 5.3 years, s.d. 3.8. Importantly, all (whatever the biopsy appearance) were offered a gluten-free diet. There were three categories:

- (a) Definite celiac,  $n = 31$  (4.3%), with histology diagnosis. Calculated on intention to treat, 94% reported improvement on a gluten-free diet.
- (b) Possible celiac,  $n = 48$  (6.6%), with elevated tTG antibodies, but with normal gut histology: 75% reported improvement gluten-free.
- (c) Not-celiacs,  $n = 644$  (89.1%), with normal tTG antibodies and no evidence of gut damage: 53% reported improvement gluten-free.

Clinical features were similar across these three groups. In the respective groups, behaviour concerns (tiredness, lethargy, irritable, sleep disturbance) were reported in: 71%, 65%, and 51%; and gastric reflux in: 16%, 15%, and 24%. These are likely to be neurological symptoms generated by gluten-sensitivity.

These common symptoms have been noted in a recent study on the prevalence of celiac disease [17]. The parents of apparently "asymptomatic" children were interviewed as part of a population study to identify those with celiac disease. They found many children who had positive tests for gliadin antibodies also had irritability, lethargy, abdominal distension, gas, and poor weight gains.

A high proportion of children with gastro-intestinal, allergy, and neurological conditions have elevated IgG-gliadin antibodies. On a gluten-free diet, the majority report that they are better – they have the gluten syndrome. High IgG-gliadin levels can identify these children. The next step is testing this by a double blind study.

#### **Consequences of neurological harm by gluten**

Evidence points to the nervous system as the prime site of gluten damage. This theory is attractive because it gives a unifying answer that explains the following conundrums: the mechanism of the non-gut symptoms of celiac disease; the behaviour disturbances of gluten reactions; the psychiatric and personality disorders; the neurological symptoms; the autonomic system disturbances; why such small amounts of gluten can cause such major reactions by the amplification effect of the nervous system (not dependent on any gut damage); and why gluten can create such a diverse range of symptoms, because any agent that causes

widespread neurological harm (think of multiple sclerosis and Syphilis) can generate almost any array of symptoms.

Also, it can explain why celiac patients with extensive gut damage can be asymptomatic. The histological gut damage in celiac disease is not mediated through this neurologic system. It is caused by local toxicity to the bowel in susceptible people. If these people are not highly sensitised to gluten, then they may not experience any symptoms mediated through neural networks.

The implication of gluten causing neurologic network damage is immense. With estimates that at least one in 10 people are affected by gluten, the health impact is enormous. Understanding the gluten syndrome is important for the health of the global community.

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