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Wheat - A Precious Nutrient That Can Become Harmful: Wheat/Gluten Related Disorders

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Abstract

Wheat grains have a complex structure which contains an organized distribution of nutrients. Cooking induces gluten formation. Celiac Disease and Wheat Allergy are well known wheat-related disorders, the first being a gluten-dependent autoimmune enteropathy, the latter a hypersensitivity IgE - mediated reaction.

The pathogenetic mechanism of non-celiac gluten sensitivity is still under investigation. The clinical diagnosis is: the presence, in relation to the ingestion of gluten containing foods, of intestinal and extra-intestinal symptoms in patients where celiac disease and wheat allergy have already been excluded. There is ongoing evidence that non-gluten derived proteins have an important pathogenetic role in non-celiac gluten sensitivity and probably also in celiac disease: Amylase Trypsin Inhibitors-ATIs are proteins that are also present in rye and barley; they are triggers of innate immune response in non-celiac gluten sensitivity. They may also exacerbate immunomediate inflammatory bowel diseases. Gluten-free diet is the only effective therapy both in celiac disease and non-celiac gluten sensitivity. Alternative therapeutic strategies are under investigation in Celiac Disease: -exogenous enzyme gluten digestion to obtain less toxic fragments; - molecules able to be remodeling enterocyte tight junctions which become permeable in celiac disease. Researches should be devoted to creating a less toxic grain, while to date grain has been genetically modified to increase gluten content. We advise a future for researches in agronomy. A role for functional and nutraceutical foods must be investigated.

Another emerging issue is due to the consciousness of wheat/gluten-microbiota-brain and mind interactions.

Keywords: Non-celiac gluten sensitivity; ATIs; Wheat and brain; Gluten-free diet

Introduction

Cereals constitute a major source of nutrients since the setting of farming during the so-called Neolithic revolution [1].

Wheat grains are mainly constituted by starch (90%), wheat germ with the highest nutritional value as it is rich in amino acids, fatty acids, polyunsaturated fats, Thiamin, Vit E, folic acid, Zinc, mineral salts, fibers. Both starch and wheat germ are lost in refined flours; endosperm contains the NaCl-water-soluble glutenins and the alcohol soluble gliadins, both representing the 80% of wheat proteins. Added water and mechanical strength give rise to the formation of gluten which gets the dough elastic and viscous. Wheat prolamines (gliadins) are the major endosperm storage proteins of grains. Gliadin is the most toxic fraction rich in glutamine and proline peptides, resulting from protease (pepsin and trypsin) [2].

The complex structure of wheat grains induces to expand the definition of gluten associated diseases to wheat-gluten associated diseases, a term which matches overall with Non-Celiac Gluten Sensitivity (NCGS) we will discuss later.

Wheat-Gluten Related Disorders

- Autoimmune, as Celiac Disease that may become clinically evident after months or years of gluten ingestion;
- Allergic, which starts from minutes to hours after gluten exposure;

- Innate immunity related, as Non-Celiac Gluten Sensitivity (NCGS) which starts from hours to days after gluten ingestion.

Celiac Disease (CD)

Celiac disease is the main known gluten related disorder; in fact, CD is an immune-mediated enteropathy induced by the ingestion of gluten and triggered by environmental factors in genetically predisposed subjects. CD causes malabsorption of nutrients resulting in systemic disorders; it is also associated with gastro-intestinal and extra-intestinal autoimmune diseases. The prevalence of CD is around 1% in the general population, but despite improved diagnostic tools, the disease remains undiagnosed in most affected people (9/10) [3,4].

In addition to serological markers, the diagnostic protocol for adults requires mucosal biopsies from the duodenal bulb and jejunum. The classical histopathological picture is the unmistakable pattern of villus atrophy, crypt hyperplasia and intraepithelial lymphocyte infiltration. CD diagnosis is confirmed by the repair of mucosal damage after a gluten-free diet.

Wheat allergy

Wheat allergy is a hypersensitivity response to wheat proteins, associated with the production of specific class of antibody IgE. Symptoms include: Atopic dermatitis, respiratory and gastrointestinal disorders occurring after wheat products ingestion. A contact allergy may also occur as urticaria; ω -gliadin is implicated in the onset of inhalation allergy, the so-called occupational asthma or baker asthma. Skin-prick tests are recommended for diagnosis.

Wheat-Dependent Exercise Induced Anaphylaxis (WDEIA)

The main causes are ingested food such as wheat and also crustaceans, followed by physical exercise. Japanese scientists

described two forms: WDEIA is the commonest one; sensitization occurs via the gastrointestinal tract (ω -5 gliadin); the second form recognizes a sensitization via the skin and/or mucosa by hydrolysed wheat proteins present in soap; the sensitizing agent is γ -gliadin; allergic reaction occurs after exposure to soap or after gluten ingestion [5].

The prevalence of wheat allergy ranges from 2% to 9% and from 0.4% to 0.5% in paediatric and adult western population respectively.

Non-celiac gluten sensitivity

From the 70s, many patients referred to our Center for the Study of Malabsorption Syndromes of S. Orsola Polyclinic - University of Bologna-Italy, also coming from other regions; at that time, only few serological tests for Celiac Disease were available. Some patients had symptoms consistent with CD, but the diagnosis was not confirmed by serological and genetic tests, as well as histopathological small intestine mucosa evaluation. In a few cases antibodies to gliadin IgG type were found and considered nonspecific. In the absence of a well-established diagnosis, patients themselves decided to start gluten-free diet getting immediate benefit. NCGS was described in a paper dated 1970 [6].

Since then scientific studies have increased exponentially setting up a new nosological entity. The Italian Health Ministry in July 2015 has formally defined NCGS as follows:

“Presence, in relation to the ingestion of gluten containing foods, of intestinal and extra-intestinal symptoms in patients where celiac disease and wheat allergy have already been excluded”.

Moreover, the Health Ministry has listed the main symptoms of NCGS (**Table 1**).

Table 1 Non-celiac gluten sensitivity: Clinical presentation (Italian Health Ministry); *Other symptoms and mental disorders reported in the scientific literature.

Non-Celiac Gluten Sensitivity	
Intestinal symptoms	Extra-intestinal symptoms
Abdominal pain: very common	Tiredness: very common
Bloating: very common	Lack of well-being: very common
Flatulence	Headache
Borborygmi	Depression
Diarrhea	Anxiety
Loose stools	Foggy mind
Constipation	Aphthous stomatitis
Defecation urgency	Sensory symptoms

Incomplete evacuation perception	Joint/muscle pain
Nausea	Asthma
Heartburn	Rhinitis
Epigastric pain	Skin rash
*Alternating bowel habits	*Numbness
	*Disturbed sleep pattern
	*Hallucinations
	*Mood swings
	*Autism
	*Schizophrenia

It is clear that there is an overlap between symptoms of celiac disease, irritable bowel syndrome, and small intestine bacterial overgrowth, all of them sharing microbiota alterations [7].

We emphasize, among the extra-intestinal symptoms, the tiredness, which is often present in celiac untreated patients, even in the absence of malabsorption or of associated endocrine autoimmune diseases. Of great interest is the involvement of brain and mind in NCGS: foggy mind, depression, anxiety. We will discuss later of neurological and psychiatric disorders associated both to Celiac Disease and NCGS.

NCGS lacks serological and histopathological markers and its aetiology is not fully elucidated. Studies are underway on other wheat components such as proteins not derived from gluten: Amylase Trypsin Inhibitors (ATIs) [8]. Therefore, as a result of these researches, gluten sensitivity is more properly called wheat/gluten sensitivity.

Already in 2014, our paper Wheat-related disorders- A broad spectrum of evolving diseases [2] introduced the concept that man does not relate only with gluten, but also with the whole grain, even if refined. Then other papers have included the term wheat: Do we need to worry about eating wheat? [5]; Non-celiac gluten and wheat sensitivity [8]. The occurrence of extra-intestinal symptoms indicates that NCGS is an immune-mediated disorder.

ATIs (Amylase Trypsin Inhibitors): They are also present in rye and barley, are considered triggers of Non-Celiac Wheat/Gluten sensitivity [9,10]. They are present in commercial gluten, resist proteolytic digestion and induce innate immune response resulting in monocytes, macrophages, and dendritic cells activation of the Toll Like receptor (TLR4 complex). In celiac disease wheat ATIs increase the gluten-specific T-cell response (**Table 2**).

Table 2 Role of wheat ATIs in non-celiac gluten sensitivity.

ATIS - Amylase Trypsin Inhibitors Non-Gluten Derived Proteins; 4% of Wheat Proteins
Resistant to intestinal proteases

Natural pesticides
Stimulating innate immune response
Dose-dependent activity, absent in gluten-free cereals
Taking part to celiac disease autoimmune process
Playing a role in intestinal and extra-intestinal immune mediated diseases: Rheumatoid Arthritis, LES, Asthma, Multiple sclerosis, Non-Alcoholic Fatty Disease of the Liver, Inflammatory Bowel Diseases.

ATIs exacerbate immune-mediated intestinal and extra-intestinal diseases; in particular, as inflammatory bowel diseases are concerned.

We must be aware of the fact that ATIs have an important role in metabolic process of seed development. Moreover, they defend wheat from external aggressors, for example by inhibiting the surface protease enzymes of parasites (mealworms and meal bugs); they can be rightly considered as natural pesticides. In fact, plants have no means to defend themselves and must produce toxins and poisons against the creatures that eat their seeds; on the other hand, who eat these seeds develops countermeasures such as: increasing the perception of bitter taste and acquiring the ability to detoxify [11].

Unfortunately, the genome of wheat which ensures the best quality of bread is associated with toxic proteins, resistant to digestion. However, they are lost by cooking pasta in salted water. Instead toxic proteins remain in beer, long steam cooked couscous, and can be inhaled from raw flour. The clinical presentation of NCGS has been reported in **Table 1**.

Among the various literature papers, we cite the study [12] in which the prevalence of gastrointestinal (GI) and extra-intestinal symptoms has been reported from 78 patients with NCGS. Often two or more symptoms are associated. Abdominal pain and bloating (77% and 72% respectively) prevail between GI symptoms. As extra-intestinal symptoms, foggy mind (42%) and tiredness (36%) are prevalent.

The role of HLA: NCGS occurs in patients carrying celiac disease associated HLA haplotypes [13]. We underline an interesting point for clinical practice: the presence of HLA-DQ2 in patients suffering from Irritable Bowel Syndrome is a

predictive factor of response to gluten-free diet [14]. More than 50% of patients with NCGS are carriers of celiac disease HLA DQ2 or DQ8 [15,16].

The role of anti-gliadin antibodies (AGA): AGA IgA and IgG have been found in 50% of patients with NCGS [15]; in another study [17] AGA IgG were found at high titre in 56.4% of NCGS patients, while AGA IgA were found in 7.7% of cases.

Intestinal permeability: In NCGS the function of zonulin and other proteins of the junctional complexes of enterocytes have been extensively studied in celiac disease in which small intestine permeability is increased [18-20]. As to NCGS, the results are controversial [15].

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The diagnostic criteria of NCGS are resumed in **Table 3** [12].

Table 3 Diagnosis of non-celiac gluten sensitivity.

Diagnostic Criteria in Non-Celiac Gluten Sensitivity
Rapid onset of symptoms triggered by gluten ingestion from a few minutes to days
Rapid remission after gluten withdrawal
Gluten reintroduction causes symptoms relapse
IgE against gluten and wheat, and skin prick tests are negative
Absence of celiac disease serological markers
AGA IgG are positive in 50% of NCGS patients
No histopathological alterations of small bowel mucosa, except mild intraepithelial lymphocytes infiltration
HLA DQ2 or DQ8 can be found in 40% of NCGS patients

We underline the rapidity of onset of symptoms after the ingestion of gluten containing foods that does not occur in celiac diseases, the rapidity of symptoms remission after gluten withdrawal as well as their recurrence after gluten challenge. As concerns histopathological alteration, only an increased number of intraepithelial lymphocytes is reported as in grade 1 Marsh classification of small intestine mucosal lesions in Celiac Disease [21].

At the present state of knowledge diagnosis is mainly based on exclusion of other diseases, mainly celiac disease and wheat allergy [22].

We must take into account the following points:

- No biomarkers are available for NCGS;
- If gluten challenge gives a negative result, FODMAPs (Fermentable Oligo-Di-Monosaccharides and Polyols)

intolerance should be taken into consideration as well as Small Intestine Bacterial Overgrowth. Wheat FODMAPs do not justify the onset of NCGS;

- A gluten patch test [23] has been suggested (**Table 4**), which needs to be validated;
- Standardized diagnostic methods [24] have been highly advocated: a major role is played by gluten challenge (**Table 5**).

Table 4 Gluten patch test.

Oral mucosal patch test for gluten	The direct application of gluten concentrated on a small area, the upper lip mucosa, induces local and systemic reactions:
	In 75% of patients with Non-Celiac Gluten Sensitivity
	In 16% of untreated Celiac Disease Patients
	In 25% of treated celiac disease patients
	No reaction in control subjects
The main symptoms and mucosal lesions appear 48 hours after the test are as follows:	Upper lip mucosal lesions
	Diarrhea
	Foggy mind
	Abdominal pain
	Joint pain
	Symptoms disappear after 1 month gluten-free diet

Table 5 Suggested standardized methods for the diagnosis of non-celiac gluten sensitivity.

Standardization of Diagnostic Methods	
Diagnosis of non-celiac gluten sensitivity	Searching for clear cut cause-effect relationship between gluten ingestion and symptoms
Subjects are put on gluten-free diet for six months	Free diet for 6 months: Clinical evaluation is performed using a self-administered instrument: Patients identify 1 to 3 main symptoms on a numeric rating scale from 1 (mild) to 10 (severe).
Responders	Reduction >30% of at least 1 of the symptoms without worsening of the others, for at least 3 weeks.
	The diagnosis is excluded if no improvement occurs within 6 weeks.
Gluten challenge	1 week of gluten containing diet (8 g/day).
Wash out	1 week on a gluten-free diet.
	The test is positive if there is at least 30% difference between gluten and placebo.

A key point to remember is that the diagnosis of NCGS must be periodically reconsidered and verified for two main reasons:

- Celiac disease can still occur in genetically predisposed subjects; NCGS can be transient.
- Another key point to consider is that the assessment of the effects of gluten in patients with supposed NCGS must be based on double blind placebo controlled studies.

An Italian prospective multicenter survey on patients suspected of having NCGS [25] shows that this pathologic condition is closely related with female gender and adulthood. Prevalence is slightly higher than in celiac disease.

An Italian randomized, double blind, placebo controlled, cross over trial [26] in subjects with suspected NCGS showed that small amounts of gluten ingested for a week worsen the symptoms, compared to controls.

Another recent study by Uhde et al. [27] conducted on 80 patients with NCWS (Non-Celiac Wheat Sensitivity) has identified markers of systemic immune activation and of damage of enterocytes, in the absence of celiac disease. High serum levels of soluble CD14 and of LPS (Lipopolysaccharide) binding protein were found, as well as antibodies against LPS and flagellin of bacteria.

High levels of FABP2 (Fatty Acid Binding Protein) were also found as a marker of enterocyte damage. This interesting finding supports the hypothesis that also in NCGS there is an increased permeability of the mucosal barrier.

Wheat belly

In addition to the above-mentioned wheat/gluten related disorders, this cereal, which is the staple nutrient of the Mediterranean diet, is further charged with being the cause of Obesity and Diabetes. In a very popular book from Dr. Davis, entitled *Wheat Belly*, it is even reported: lose the wheat, lose the weight and find your path back to health.

A recent experimental study [28] on animal models fed with diets of the same caloric composition, while supplemented with different nutrients, shows that diets enriched with gluten cause an increased expression of Interleukin-6 which is involved in diabetes, rheumatoid arthritis, and cancer. Moreover, weight gain occurs and fat deposits increase.

Wheat/gluten free diet is now widespread as it is considered healthy. This is the result of auto medication caused by erroneous information media. Conversely gluten free diet is an unbalanced diet low in high value nutrients; industrial products contain too much Kcalories, simple carbohydrates, saturated fats and lipids, while are mainly poor in fibers, B, D, vitamins, essential amino acids (Lysine), folate, zinc, iron, magnesium, calcium, unsaturated fatty acids [29,30].

Wheat/gluten-bread related mental disorders

During the Neolithic period of the age of the stone, humans started agriculture and animal domestication. Humans and grains are grown together; they each were fitted to the other and have had a parallel development through genetic mutations. Wheat progressively shortened to resist wind and

to be easily harvested; the human face changed as jaws and teeth have shrunk due to easily chewable foods [11].

Cereal grains are the most abundant food source. Civilization has brought to an increased use of starchy foods. This type of unbalanced diet resulted in short stature, short life span, increased infant mortality and infectious diseases, osteoporosis and dental caries [11].

During the II World War, when wheat was scarce in Europe, hospitalization for Schizophrenia was dramatically lowered. On the contrary, when grain become available in USA, the prevalence of Schizophrenia increased from 1: 100000 to 1: 100.

In celiac disease, anti-transglutaminase-6 autoantibodies directed against cerebellar substance, myelin sheath of nerves, GABA (Gamma Amino Butyric Acid), can cause neurological disorders (Ataxia from gluten-related cerebellar atrophy, peripheral neuropathies as a consequence of inflammation in peripheral nerve fibers, and psychosis (Schizophrenia), Depression and Anxiety. Antibodies triggered by gluten and directed against brain cause neurological and psychiatric disorders even in non-celiac subjects. Anti-gluten antibodies were also found in non-celiac patients such as in 78% of autistic patients [11].

We delved into the psychological problems of celiacs, the so-called social phobia (30). Depression and psychosis improve when also clinical conditions improve after a gluten-free diet.

Anxiety and Depression are symptoms also found in NCGS. The integrity of intestinal mucosal barrier as well as of the hemato-encephalic barrier plays an important role. It is assumed that the interference of gluten with man's behaviour is caused by indigested gluten fragments passing through the brain barrier; these gluten fragments are opioid like compounds called exorphins or gliadorphins [11].

A recent paper [31] deals with gluten induced cognitive impairment ("brain fog") in untreated celiac disease. Foggy mind has also been reported as frequent extra-intestinal symptom in NCGS.

Brain fog refers to severe and degenerative loss of global cognitive function, in particular memory function, up to dementia. The prevalence (2-20%) is higher in elderly patients with a late diagnosis of CD, with long exposure to gluten, as well as in patients not compliant with gluten-free diet. Diffuse structural brain alterations are associated with brain fog and represent the silent neurological complications of CD. The onset of cognitive function impairment is subtle and progressive: loss of memory, attention, decision- making, speed of cognitive process.

This field of research is starting now; the causative agent of fog brain after exposure to gluten is supposed to be the release of inflammatory cytokines which occurs both in CD and in NCGS.

A role for gut microbiota must be investigated; its composition varies according to different type of diets [32], it

could be related to the risk of developing Celiac Disease [33], and it may affect brain and mind functions [34].

Therapeutic Approach to Wheat Gluten Related Disorders

Celiac disease

Current knowledge indicates strict and continuous gluten-free diet for life. Researches are ongoing to determine if there are alternatives: Gluten-free diet is deficient in nutrients and unbalanced; moreover, it may contain nickel as corn contaminant that can give rise to allergy.

Other therapeutic strategies are under consideration. The aim is to maintain the mucosal barrier function of enterocyte junctional complex and its connection with intracellular actin filaments: in fact zonulin, whose secretion increases in CD, favors intestinal permeability through tight junctions and zonulae occludens; other proteins alterations intervene in the intracellular cytoskeleton functions, such as claudin, e-cadherin, beta catenin, beta cadherin, occludin causing loss of cell polarity and increasing para cellular permeability [18-20]. Larazotide and glutenase enzyme are under investigation to modulate permeability and to detoxify gluten respectively [35,36]. Wheat allergy requires wheat-gluten free diet.

NCGS (Non-Celiac Gluten Sensitivity)

To date, as we know too little about the etio-pathogenesis of the disease, the only effective therapy is gluten free-diet, even if we don't know how long it has to be maintained.

Mental disorders

Gluten free diet is mandatory when CD or NCGS are associated. Further studies are needed to demonstrate that following a gluten free diet is a cure for neuro-psychiatric disorders, regardless of the absence of CD and NCGS.

Another approach could be based on the possible therapeutic role of food itself by different mechanisms of action, including also the influence on microbiota composition. This concept had already been expressed by Hippocrates 400 BC: let food be your medicine.

The concept of functional food has been defined in a Consensus Document in Europe [37]: A food can be considered as functional if it has been satisfactorily demonstrated to affect beneficially one or more target functions in the body beyond adequate nutritional effects in a way that is relevant either to an improved state of health and well-being and/or a reduction of risk of disease. Fermented milk and milk products were the first functional foods [38].

Tightly related to functional food is the concept of nutraceutical food, defined as a food (or part of the food) that provides medical or health benefits, including the prevention and/or treatment of a disease [39].

In the above-mentioned review [39], further definition of nutraceuticals has been reported: a product isolated or purified from foods that is generally sold in medicinal forms not usually associated with food. It is demonstrated to have a physiological benefit or provide protection against chronic disease. Nutraceuticals have been classified and divided in two categories: traditional, all the substances contained naturally in foods; non-traditional, substances externally added to the foods by bio-engineering actions.

Conclusion

We aim to point out what we believe to be major points of reflection and the basis for future biological and clinical researches and therapeutic strategies.

The prevalence of celiac disease is considerably increased during the last decades for the possible following reasons:

- Increase in diagnostic sensibility due to the awareness that the clinical spectrum of the disease is wide, with prevalence of non-classical presentation;
- Increase in diagnostic accuracy due to new high sensitive and specific serological markers and standardized criteria for small intestinal biopsy evaluation;
- Increase in dietary wheat consumption, due to its availability and low cost; in fact, wheat production increased as the speed of the wheat flour processing was increased too by eliminating fermentation before baking. Gluten was also used as additive in industrial foods;
- Wheat genome has been modified to increase the amount of gluten in wheat flour, in order to improve dough quality.

Etio-pathogenetic role of proteins other than gluten, ATIs, must be taken into consideration in pathogenesis of NCGS. A possible role of ATIs in celiac disease must be considered too; in fact, CD shares with NCGS gastrointestinal and extra-intestinal symptoms. In this case gluten-free diet that is a wheat-free diet excludes the damaging proteins in both diseases.

Gluten-free diet is an unbalanced diet as lacks the high nutritional components of wheat grain, favors Diabetes and Obesity, and also colonic cancer due to low fiber content. Gluten-free diet must be integrated with other non-cereals nutrients.

Prevention strategies go through genetic modification of grain to obtain less toxic gluten fractions. It would also be important to determine with accuracy the minimal quantity of gluten allowable for celiac patients. As regards celiac disease, ongoing researches indicate a possible role of Larazotide and Glutenase enzyme able to modulate permeability and to detoxify gluten respectively. Naturally gluten free products are recommended: Quinoa and Amaranth contains high amount of folic acid. Moreover, fruits and vegetables should supplement gluten-free diet. Future researches should also be devoted to study the interaction between wheat and mind: gluten free diet could be a cure for mental disorders?

Moreover, we must not neglect the role of gut microbiota in intestinal and extra-intestinal wheat/gluten related disorders. Further investigations are also needed to a better knowledge of the therapeutic properties of functional and nutraceutical foods.

Finally, in clinical practice, we have to consider possible gluten adverse reactions also in patients not at risk.

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