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THE BROAD SPECTRUM OF CELIAC DISEASE AND GLUTEN SENSITIVE ENTEROPATHY

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Abstract

The celiac disease is an immune chronic condition with genetic transmission, caused by the intolerance to gluten. Gluten is a protein from cereals containing the following soluble proteins: gliadine, which is the most toxic, and the prolamins. The average prevalence is about 1% in USA and Europe, but high in Africa: 5.6% in West Sahara. In the pathogenesis several factors are involved: gluten as external trigger, genetic predisposition (HLA, MYO9B), viral infections, abnormal immune reaction to gluten. Severity is correlated with the number of intraepithelial lymphocytes, cryptic hyperplasia and villous atrophy, as well as with the length of intestinal involvement. The severity is assessed according to the Marsh–Oberhuber staging. Diagnostic criteria are: positive serological tests, intestinal biopsy, the reversal after gluten free diet (GFD). Beside refractory forms, new conditions have been described, like the non celiac gluten intolerance. In a time when more and more people adhere to GFD for nonscientific reasons, practitioners should be updated with the progress in celiac disease knowledge.

Keywords*:* celiac disease, gluten free-diet, non celiac gluten sensitivity

Definition and history of disease

Celiac disease (CD) is a chronic, genetically based gluten-sensitive immune-mediated enteropathic process, primarily affecting the small intestinal mucosa [1].

CD did not occur before Neolithic period (beginning about 9500 BC) because the grains have been cultivated by humans only since this time in the Fertile Crescent in Western Asia.

In 2008 at the archaeological site of Cosa, southwest of Tuscany, Italy, a skeleton of a first century AD young woman named the "case of Cosa" was found. The skeleton of the 18-20 year-old woman showed typical celiac disease damage and the presence of HLA-DQ2.5 and had signs of failure to thrive and malnutrition [2].

In 250 A.D., Aretaeus of Cappadocia described in his writings "koiliakos," which meant "suffering in the bowels". In 1856 his writings were translated from Greek into English by Francis Adams for the Sydenham Society of England. The patient symptoms were stomach pain and diarrhea, the stools were white, malodorous and flatulent. The patient was pale, feeble and incapable of work [3].

Aretaeus believed that the cause of disease was a lack of heat in the stomach, necessary to digest the food and a reduced ability to distribute the digestive products throughout the body, this incomplete digestion resulting in diarrhea. He named the disease "celiacs" or "coeliacs." Thus Europe uses the spelling coeliac disease with the "o".

The first approach of diet in celiac disease was in 1888, at the Great Ormond Street Hospital for Children in the United Kingdom, Gee stated that "food is the main part of treatment. The allowance of farinaceous foods must be small, but if the patient can be cured at all, it must be by means of diet" [4]. Another approach belongs to Sidney Haas, an American pediatrician; he treated 10 children diagnosed with CD with "banana diet."

In 1930, during World War II, a Dutch pediatrician, William Dicke, observed that a lack of access to wheat, improved the status of children with celiac disease, and in 1952 he was acknowledged for linking the ingestion of wheat proteins as cause of celiac disease. The first biopsy technique of CD was developed by Margot Shiner, a

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pediatric gastroenterologist in 1950; she observed the small intestine and the pathologic changes in celiac disease.

In 1952-1953 in Washington D.C the first "Sprue Team" with international implications was established by Crosby; the reasons were some cases of the soldiers and their families with potential celiac disease, when he directed a Mobile US Army Surgical Hospital in Korea.

Crosby also developed a capsule as a less invasive method to take tissue samples of the small intestine. In 1954 in Birmingham, England, Dicke and his colleagues, described the histological damage to the intestinal mucosa as being directly related to celiac disease, and confirmed the treatment; he also improved the diagnosis of celiac disease by intestinal biopsy, the Rubin Tube demonstrated that celiac sprue in children and in adults were identical disorders. In 1964 the anti-gliadin antibody was discovered [5].

In 1966, dermatitis herpetiformis was linked to gluten sensitivity [6]. In the 1980s celiac disease was associated with other autoimmune diseases: thyroid, diabetes, and Down's syndrome. In the 1990s genetic markers HLA-DQ2 and HLA-DQ8 and the anti-transglutaminase antibodies were identified [5].

May has been declared as "Coeliac Awareness Month" [7].

Epidemiology

The prevalence of CD is approximately 1% within the U.S. and European populations, and may be higher in Northern European countries, approximately 1.5% [8,9].

CD is a common disorder in North Africa, the Middle East and India. The diagnostic rate is low in these countries due to low availability of diagnostic facilities and poor disease awareness. The highest CD prevalence in the world (5.6%) has been described in an African population originally living in Western Sahara, the Saharawi, of Arab-Berber origin. The reasons for this high CD frequency are unclear but could be primarily related to recent dietary changes and genetic factors, given the high level of consanguinity of this population. In many developing countries, the frequency of CD is likely to increase in the near future given the diffuse tendency to adopt Western, gluten-rich dietary patterns.

The prevalence of CD in asymptomatic Tunisian school children was estimated to be about 1:157, which is close to the European prevalence. Genetic factors are: very high frequency of the DR3-DQ2 haplotype; environmental factors are: change of dietary habits in the last few decades. The reduced rates and duration of breast-feeding and increased consumption of gluten in early life as part of the staple diet, supplied by Western countries as humanitarian aids, may have played a role in this elevated CD prevalence.

The high CD prevalence in Argentina could be correlated with HLA DQ8 (>20%) in the local population [8].

Australia and New Zealand are the two countries having the highest proportion of individuals from Caucasian background, with high prevalence of HLA DQ2 and per capita wheat consumption of >150 and 75-150 kg per person per year, respectively.

CD is likely to be rare in Indonesia, South Korea, Philippines and many smaller Pacific islands.

Pathogenesis of CD

CD has some possible causes such as: genetic predisposition association (HLA, MYO9B), exogenous trigger (gluten), pro-autoimmune genetic background, viral infections, tissue damage, early termination of breastfeeding and gender contribute to the development of CD[10] is caused by a selective T lymphocyte intolerance of gluten, which produces T cell-stimulatory peptides known as neo-epitopes. This interaction of HLA-DQ2 molecules on antigen-presenting cells activates intestinal T lymphocytes via the T cell receptor. In response, T cells release pro-inflammatory cytokines, including interferon C, tumor necrosis factor A and interleukin 2, which damage enterocytes, producing the intestinal lesions typical of CD [11].

1) Genetic contributors

CD is multifactorial and multigenic in origin. Human leukocyte antigen (HLA)-DQ2 (DQA1*05/ DQB1*02) is associated with most cases of coeliac disease, whereas HLA-DQ8 (DQA1*0301/ DQB1*0302) is present in just a minority of patients [10]. Homozygous individuals who carry DQB1*02 and DQA1*05 in cis on both chromosomes have a great risk. It is found that 30% of the Caucasian populations carry HLA-DQ2 and most will eat wheat, while only 1 in 100 will develop disease with complicated forms of CD [12].

Recent experimental studies have revealed new possible genes involved in the pathogenesis of coeliac disease, including COELIAC337 and COELIAC438, at positions 2q33 and 19p13.1.

2) Immunological contributors

Initially it was thought that exogenous gluten products were directly toxic to the mucosa in coeliac disease. In contrast with earlier suggestions, intraepithelial lymphocytes (IELs) are now thought to actively contribute to mucosal damage. Antigen exposure in coeliac disease causes rapid in situ activation of a/b T cell IELs. These cells may then damage enterocytes through contributions from several possible mechanisms, including the NKG2D-major histocompatibility complex class I chain related gene A pathway [10].

Pathology

In terms of pathology, there are few major features of the mucosa suggestive of CD like: proximal small bowel involvement, decreasing distally, patchy distribution, in some cases, mucosal architectural changes, including villous atrophy, crypt hyperplasia, thickening of the basement membrane under the surface epithelium, reduced number of goblet cells, mucosal inflammation, increased

IELs, influx of immune cells in the lamina propria, enterocyte changes, cuboidal morphology, loss of basal nuclear orientation, cytoplasmic vacuoles [10].

1) Histopathology of coeliac disease

Symptomatology in CD seems to be related to the length of the affected bowel, and not to the severity of the mucosal and submucosal lesions. CD also affects other mucosal sites, such as the esophagus, stomach and large bowel.

For CD screening there are several suggestive features, such as increased IELs, crypt hyperplasia and villous atrophy. A rapid method of screening for CD includes counting the number of IELs present at the villous apex, for example 40 IELs per 100 epithelial cells were considered to be abnormal. IELs is a criteria for excluding conditions/ disease that can mimic CD: Helicobacter pylori infection, tropical sprue, Giardia lamblia infection, prolonged viral gastroenteritis, food allergies, autoimmune enteropathy, IgA deficiency, Crohn's disease and ulcerative colitis [13].

Initially there is crypts of Lieberkuhn hyperplasia, a process that precedes villous atrophy. An absence of atrophy implies that the villi are of normal height. Mild atrophy indicates a minor to moderate amount of villous blunting; marked atrophy indicates the presence of possible CD.

The observation of moderate to total villous atrophy, particularly in a patient with longstanding CD or in a patient who proves unresponsive to diet, obliges the pathologist to attempt to exclude the presence of a more sinister concomitant lesion, such as Crohn's disease, autoimmune enteropathy, lymphoma or adenocarcinoma. The presence of cryptitis or crypt abscesses should reflexively prompt consideration of the possibility of Crohn's disease Total atrophy implies the complete absence of villi [10,14].

The modified Marsh–Oberhuber classification [13]

- Type 0: Normal crypts and villi, IEL<40.
- Type 1: Seen in patients on gluten free diet (suggesting minimal amounts of gluten or gliadin are being ingested); patients with dermatitis herpetiformis; family members of CD patients, not specific, may be seen in infections. increased IELs (>40), normal crypts and villi.
- Type 2: Very rare, seen occasionally in dermatitis herpetiformis. IEL are >40, hypertrofic crypts and normal villi.
- Type 3: Spectrum of changes seen in symptomatic CD. IEL are >40 and hypertrofic crypts but:
  - 3a) has mild atrophy of villi
  - 3b) has marked atrophy of villi
  - 3c) has total atrophy of villi
- Type 4: IEL<40, normal crypts and total atrophy of villi

Simplified system (Corazza, Roberts, Ensari)

- Grade A = Type 1 and 2
- Grade B1= Type 3a and 3b
- Grade B2= Type 3 c

Clinical presentation

The classical symptoms include gastrointestinal-related symptoms such as diarrhea, steatorrhea and weight loss due to malabsorption. About 50% of CD patients present extra intestinal or atypical symptoms, such as anemia, osteoporosis, dermatitis herpetiformis, neurological problems and dental enamel hypoplasia.

CD may have the following clinical forms:

The classical form may be diagnosed at any age of life and is often characterized by crypt hyperplasia and villous atrophy along with features of malabsorption.

The atypical form is characterized by positive celiac serology, limited abnormalities of the small intestinal mucosa or no intestinal symptoms, but associated extra intestinal conditions such as osteoporosis, peripheral neuropathy, anemia and infertility.

The latent form is defined by presence of predisposing gene HLADQ2 and/or HLA-DQ8, normal intestinal mucosa and, possible positive serology [12].

In the clinical setting, a wide range of symptoms are observed:

The Classical celiac disease have mostly gastrointestinal symptoms (diarrhea, malnutrition, weight loss, steatorrhea and edema secondary to hypoalbuminemia) [9].

In Nonclassic form, patients may present with gastrointestinal symptoms (abdominal pain, gastroesophageal reflux symptoms, vomiting, constipation, irritable bowel syndrome–like symptoms, distension, bloating, borborygmus, etc.); or nongastrointestinal symptoms, also known as extra intestinal manifestations (without gastrointestinal symptoms). These patients are usually monosymptomatic or oligosymptomatic.

In Asymptomatic CD or silent CD, the patient reports no symptoms at all, even in response to detailed questioning, despite the presence of a characteristic intestinal lesion. Studies on gluten-free diet on asymptomatic patients show improvement in their quality of life and thus support the decision to continue with dietary restriction in the long term [13].

Extra intestinal features included iron deficiency anemia, osteopenia, peripheral neuropathy, infertility, abnormal liver chemistry tests, or skin rash characterized as dermatitis herpeformis, depression [1,15]. Malabsorption, weight loss and vitamin/mineral-deficiencies characterize CD. Involvement of the small bowel can lead to water soluble (B12, folic acid) and fat-soluble (A, D, K, E) vitamin malnutrition and calcium deficiency. Thus patients may go on to develop such symptoms as peripheral neuropathy, osteoporosis, ataxia and coagulopathy [9,16]. Osteoporosis affects many patients with celiac disease (CD), representing the consequence of calcium malabsorption and persistent activation of mucosal inflammation [17].

Associated diseases

There are particular associations between coeliac disease and thyroiditis, type I diabetes, inflammatory bowel disease (IBD), Systemic lupus erythematosus (SLE) and Addison's disease (AD) [3,9].

Dermatitis herpetiformis (DH) is the cutaneous manifestation of gluten-sensitive enteropathy precipitated by exposure to dietary gluten. Clinically it is characterized by herpetiform clusters, intensely itchy urticated papules and small blisters distributed on the extensor aspects of the elbows and knees and over the buttocks and on the scalp [10].

CD is associated with CNS's demyelinating diseases: multiple sclerosis (MS) and neuromyelitis optica (NMO), both autoimmune demyelinating diseases of the CNS, whose evolution could be unfavorably influenced by gluten intolerance. MS therapy is not associated with a particular diet [18].

Diagnosis

Based on guides patients with a first-degree family member who has a confirmed diagnosis of CD should be tested if they show possible signs or symptoms or laboratory evidence of CD [10].

The CD diagnosis includes three major steps:

• blood tests positive,

• small bowel biopsy and histological confirmation to assess gut damage,

• implementation and response to gluten-free diet.

The blood tests used are:

• anti-tissue transglutaminase antibodies IgA-ELISA test (tTG-IgA) has a sensitivity of 93%

• endomysial antibodies (EMA) are measured by indirect immunofluorescent assay, EMA-IgA is highly specific for celiac disease, with 99% accuracy

• Deaminated antigliadin antibodies (DGP, either IgA or IgG isotype) with the higher sensibility and specificity

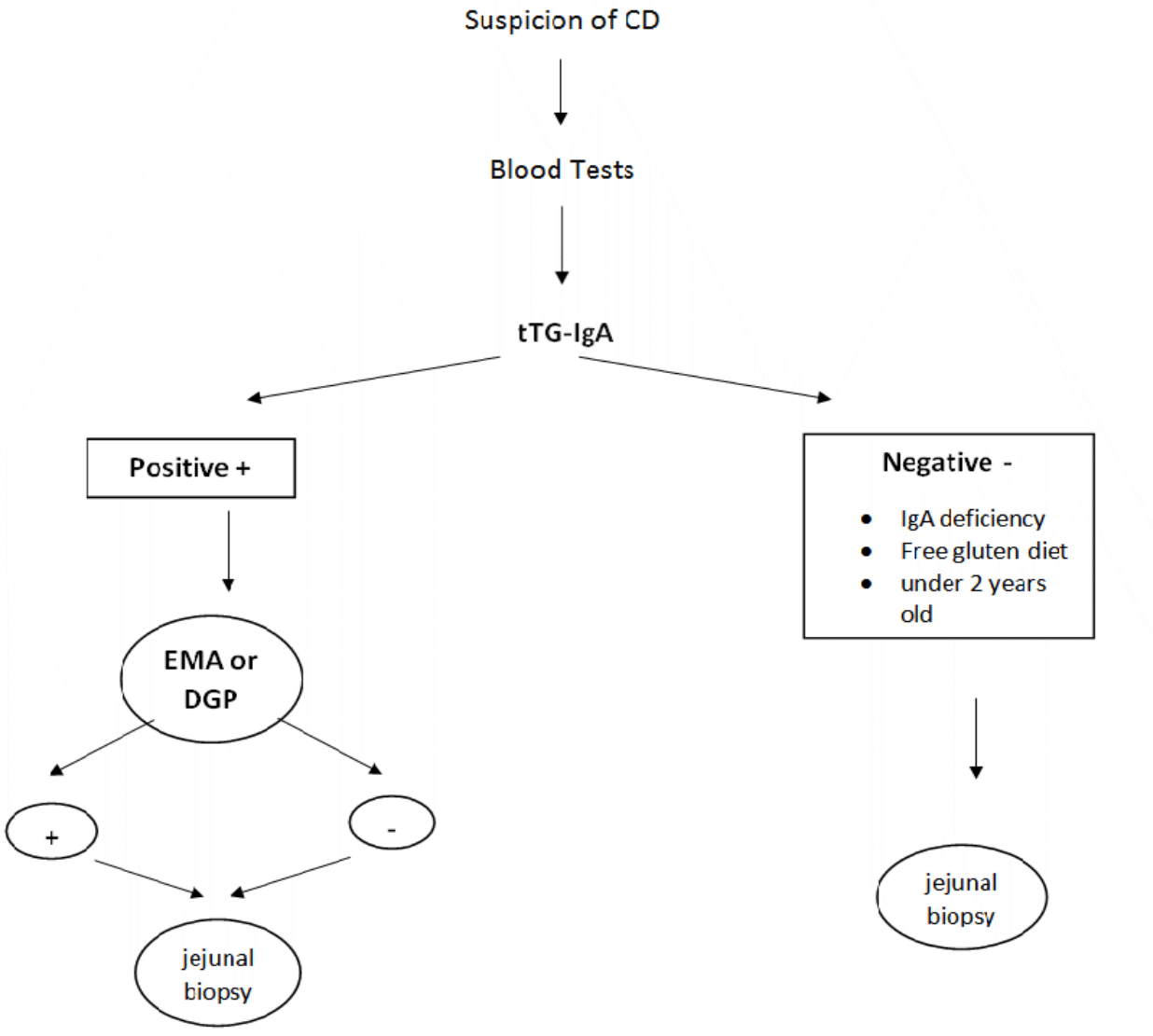

Figure 1. Positive diagnosis of CD.
CD-celiac disease; tTG-IgA- anti-tissue transglutaminase antibodies IgA; EMA -endomysial antibodies; + positive; - negative

Biochemical research has identified gliadin as responsible for the harmful action on the absorbent epithelium, for an allergic mechanism or specific enzyme deficiencies [19].

DGP is a positive antibody test suggests that a person might have celiac disease, but it is not a conclusive test; a biopsy will be needed to confirm the diagnosis [11].

Patients with CD should be monitored lifelong with annual weight, complete blood counts, folic acid, calcium, alkaline phosphatase and ferritin level determinations. Routine imaging should not be performed in patients with CD. In patients who do not respond or partially respond to a gluten-free diet it is necessary to exclude complications such as lymphoma, carcinoma, or ulcerative jejunoileitis [16].

Endoscopy in seronegative individuals

The prevalence of seronegative CD is 6–22% of all diagnosed cases. Individuals of white European, Middle Eastern, North African or North Indian origin who undergo upper endoscopy for anemia, weight loss or diarrhea should therefore have duodenal biopsies performed, irrespective of whether they have had serology for CD.

For CD diagnosis international protocols recommend (Grade C) that in individuals with laboratory tests or symptoms or endoscopic features suggesting CD, duodenal biopsy should be considered.

Grade B recommendations for HLA Typing diagnosis CD:

• HLA typing should be used to rule out CD.

• A positive DQ2.5 or DQ8 can never confirm the diagnosis.

• HLA typing can be used to rule out CD, and minimize future testing, in high-risk individuals with CD, for example, first-degree relatives.

Recommendations Grade B for duodenal biopsy when the patient is on a gluten-containing diet and for patients with positive serology are:

• Duodenal biopsy should be retained as the mainstay for the diagnosis of adult CD and cannot be replaced by serology. (Grade B)

• For suspicion of CD, at least four biopsy specimens should be obtained, including a duodenal bulb biopsy. (Grade C)

• In serologically negative patients showing signs of malabsorption (such as anemia or diarrhea) or a family history of CD, a duodenal biopsy should be considered. (Grade C)

Some studies promote novel diagnostic methods such as EMA assay in the culture medium of small intestinal biopsies.

For the differential diagnostic of diarrhea with other diseases like malabsorption, thyroid dysfunction, infectious diseases, inflammatory diseases, blood tests, fecal examination and fecal examination TTG/EMA, thyroid hormones, motility studies are required [10].

PROCONSUL Score

Is a score that shows the risk of a newly diagnosed celiac patient developing complications that will set up the follow-up of coeliac patients with great benefits not only for their health but also for management of economic resources.

Formula to obtain the Proconsul score:

PCP-pattern of critical presentation assign 0 if non classical/asymptomatic and 1 if classical;

DD- diagnostic delay: assign 0 if < 6 months and 1 if >6 months.

Score= 3x PCP-2xD

A practical and easy system to calculate the prognostic score in patients with CD [20]. PROgnosticating COeliac patieNts SUrvivaL: The PROCONSUL Score

Table I. The PROCONSUL Score.

Pattern of clinical presentation	Diagnostic delay	Result of the score	Risk of complication
Non classical/ asymptomatic	>6 month	-2	Low
	<6 months	0	Low
Classical	<6 months	1	Intermediate
	<6 months	3	High

Differential diagnosis

Differentiation from other small bowel pathologies that have increased IELs like: allergies to proteins other than gluten, autoimmune conditions, blind loop syndrome, DH, giardiasis, graft-versus-host disease, helicobacter pylori, inflammatory bowel disease, irritable bowel syndrome, microscopic colitis, non-steroidal anti-inflammatory drugs, tropical sprue (entities cause both raised intraepithelial counts and villous architectural changes), viral enteritis, crypt hyperplasia or villous flattening, allergies to proteins other than gluten (eg, chicken, cow's milk, eggs, fish and soy; entities cause both raised intraepithelial counts and villous architectural changes), autoimmune enteropathy, collagenous sprue, common variable immunodeficiency, drug-induced, hypogammaglobulinaemic sprue, ischemia, kwashiorkor, T cell lymphoma, associated enteropathy, Zollinger–Ellison syndrome, radiation therapy, etc. [14].

Treatment

1) Existing Treatment

At present, the only effective treatment available for CD individuals is a strict life-long gluten-free diet (GFD). There is a need for an alternative, because GFD is costly, not universally available and compliance is difficult. Approaches to modify dietary gluten have been made to render gliadin non-toxic, since it is a non-invasive approach to CD patients, these modification are made by hydrolysis of toxic gliadin peptide by Prolyl endopeptidases, which are endoproteolytic enzymes expressed in micro-organisms

and plants.

2) Alternative and novel treatments:

Prolylendopeptidase activities derived from Aspergillus niger were shown to inhibit a gliadin stimulated immune response by gluten-specific T-cells. Proline- and Prior studies using a combination of a barley-derived endoprotease and prolyl-endopeptidase in powder or tablet form appeared to be stable and caused breakdown of wheat gluten with reduced immune effects [9]. Lactobacilli added to sourdough for fermentation are able to lyse the proline-/glutamine-rich gluten peptides and thus decrease immunotoxicity.

cVSL#3: VSL#3 is a probiotic containing lyophilised bacteria, including bifidobacteria (Bifidobacterium longum, Bifidobacterium infantis and Bifidobacterium breve), lactobacilli (Lactobacillus acidophilus, Lactobacillus casei, Lactobacillus delbrueckii subsp., Lactobacillus bulgaricus and Lactobacillus plantarum) and Streptococcus salivarius subsp., Thermophiles.

Larazotide (AT-1001, Alba Therapeutics, Baltimore, MA), is a synthetic hexapeptide derived from Zonula Occludens toxin of Vibrio cholera.

Synthetic polymer poly (hydroxyethylmethacrylateco-styrene sulfonate- P (HEMA-co-SS) forms supramolecular particles upon gliadin complexation in gastric and intestinal conditions, and deteriorates gliadin effects on epithelial cells [9].

Anti-gliadin egg yolk antibody: Oral antibody passive immunotherapy may be of value due to the advantages of reduced cost, ease of administration, and potential to treat localized conditions in the gastrointestinal tract.

Blockage of selective deamination of specific glutamine residues by tissue transglutaminase 2 inhibitor. A peptide vaccine that could promote tolerance of some immunologically-active mucosal cells involved in the pathogenesis of celiac disease may be possible. Nexvax peptide vaccine employs three different gluten peptides to can hypothetically lead to tolerance in celiacs. Other therapies may include: modulation of immune response to dietary gliadin HLA-DQ blocker, interleukin blocker and NKG2D antagonists [15].

Monitoring of CD

The Guidelines from the British Society of Gastroenterology 10 June 2014 suggests:

- Newly diagnosed patients should have vaccination for Pneumococcus. (Grade C)
- Bone density should be measured after 1 year of diet in patients who have additional risk factors for osteoporosis or if over the age of 55 years. (Grade D)
- Adult patients with CD should have a calcium intake of at least 1000 mg per day. (Grade D)
- Patients with CD require follow-up by a dietitian and/or clinician with an interest or expertise in this field. (Grade D)
- Patients should have annual hematological and biochemical profiles. (Grade D)
- A GFD is the core management strategy for prevention of osteoporosis. (Grade D)
- Patients should adhere to a GFD and have an intake of less than 10 mg gluten per day. (Grade B)
- Gluten challenge is not recommended in the ordinary patient with CD, but in patients in whom the diagnosis remains unclear despite a follow-up biopsy, gluten challenge should be performed. (Grade C)
- Patients may commence GFD at diagnosis. (Grade D)
- A GFD is recommended to decrease the excess risk of adverse fetal outcome and of lymphoma among patients with CD. (Grade C)

At diagnosis, patients should be encouraged to join their national coeliac support group [10].

Persistence of symptoms

Major reason is continued ingestion of gluten. Other reasons for the persistence of symptoms include: wrong diagnosis or refractory CD (RCD). A diagnosis of RCD is made when symptoms persist and when there is villous atrophy and failure to respond to a gluten-free diet. This may occur at presentation (primary), or after an initial response to a gluten-free diet (secondary) and must be considered particularly in patients who are diagnosed over the age of 50 [15].

There are two subtypes of RCD: type I, with normal IELs and Type II, with clonal expansion of IELs and an aberrant phenotype lacking CD3, CD8, and T-cell receptors.

Type II disease is considered to be a form of low-grade intraepithelial lymphoma, revealed by severe malabsorption that is not responsive to a gluten-free diet. This is the most severe form and it is associated with a high mortality rate [10].

Non coeliac gluten sensitivity (NCGS)

Is a new syndrome of gluten intolerance, is a condition where intestinal and extra-intestinal symptoms are triggered by gluten ingestion in the absence of CD and wheat allergy, as defined by discussions held at three different international consensus conferences. The clinical picture of NCGS is a combination of IBS-like symptoms, behavior disturbances and systemic manifestations. In literature some other names have been suggested for this disorder, such as gluten sensitivity (GS), gluten hypersensitivity or non-celiac gluten intolerance [21].

History of NCGS

In 2011 it was proposed by members of the First Expert Meeting on gluten sensitivity. The new definition (the Oslo Definition) of CD suggested the disorder should be named NCGS, which made it distinguishable from CD. The Second Expert Meeting on GS that was held in Munich in 2012 decided to change the name of this disorder to

NCGS in order to avoid confusion with CD. The first case reports of NCGS in children were described in 2012. NCGS can be diagnosed in those patients with gluten intolerance who do not develop antibodies that are typical neither of CD nor of wheat allergy (WA) and who do not suffer from lesions in the duodenal mucosa, which is characteristic of CD. The gluten-free diet leads to complete regression of symptoms [22].

Genetic background of NCGS

Half of the NCGS patients have the genes encoding DQ2 or DQ8 molecules in their HLA system. The genes encoding DQ2 or DQ8 molecules are present in 95% of the CD patients. Negative results for both HLA-DQ2 and HLA-DQ8 excluded the diagnosis of CD in at least 95%.

These genes are present in healthy people as well (30%), but less frequently than in the case of the NCGS patients (50%).

Clinical of NCGS

Symptoms observed on 347 patients treated at the Center for Celiac Research University of Maryland in 2004–2010 (1) are: intestinal disturbances (abdominal pains 68%, diarrhea 33%, nausea, body mass loss, bloating and flatulence), cutaneous 40% (erythema, eczema), general (headache 35%, bone and joint pain 11%, muscle contractions 34%, numbness of hands and feet 20%, chronic tiredness 33%), anemia 20%, behavioral (disturbance in attention, depression 22%, hyperactivity, ataxia) and chronic ulcerative stomatitis.

Pathogenesis of NCGS

The adaptive immune response may play a role in the NCGS pathogenesis. Contrary to CD, where the secondary immune response is up-regulation, the NCGS patients demonstrate mainly up-regulation of the primary response [10] and there is no increased expression of the genes of the secondary immune response including IL-6, IL-21 and INFγ, which is characteristic of CD [21].

Histological manifestation

The NCGS patients' gastrointestinal tracts and their intestinal permeability are normal and the lesions in the histological picture of their duodenal mucosa are minor. IELs infiltrations in mucosa were observed which are rated at 0 or I in Marsh's classification.

Marsh I and II lesions can also be the initial phase of mucosal atrophy in CD, but then patients develop more antibodies characteristic of the CD, mainly anti-transglutaminase (tTG) and anti-endomysium (EMA) antibodies, which does not take place in the case of NCGS.

Increased infiltration of duodenal lamina propria with eosinophils and activation of circulating basophils have been described in NCGS patients [22].

Diagnosis of NCGS

The diagnosis cannot be made until CD and WA have been eliminated. There are no laboratory markers specific to NCGS. The diagnosis is confirmed by a food provocation test, i.e. the same test which is applied in the WA diagnostics, food challenge must be performed my means of a double-blind placebo controlled test.

In NCGS the adverse symptoms appear several hours or days after gluten consumption, while in IgE-dependent WA symptoms appear within 2 h from the food intake. Experts recommend food challenge with wheat to be performed after at least 3 weeks of the gluten-free diet.

The only known antibodies observed in the NCGS patients are: IgG antigliadin antibodies (IgG-AGA) which are present in some patients with NCGS, yet their share is smaller than in the case of CD. The negativation of IgG-AGA was significantly related to good clinical response to gluten-free diet.

Table II. Comparison between CD and NCGS features [23].

	Celiac disease	***Non-celiac gluten sensitivity***
Epidemiology	1%	To be defined (range 0.63%–6%)
Duration	Permanent	Unknown
Prevalent immune pathogenic mechanism	Adaptive immunity	Innate immunity
Onset	At any age	Adults (rare in pediatric age)
sex	Female/male ratio 2:1	Female/male ratio >3:1
Time interval between gluten ingestion and symptoms	Weeks to years	Hours or a few days
	Celiac disease	***Non-celiac gluten sensitivity***
Clinical picture	Intestinal and extraintestinal (systemic)	Intestinal and extra-intestinal (mainly neurological)
Biomarkers	tTGA, EmA, DGP	None (positivity for AGA in approximately 50% of cases but low specificity)
Genetics	HLA-DQ2 and -DQ8 linked	No known genetic link
Duodenal histology	From mild lesions to villous atrophy	Normal or less frequently mild lesions
Familiarity	3%–17% of first degree relatives are celiacs	Unknown, but more than 10% of NCGS pts have a relative with celiac disease
Autoimmune disorders	Frequent association (present in 10%–25% of celiac patients)	Unknown (a longer follow-up is needed)
Outcome (complications)	Refractory celiac disease, lymphoma, small-bowel carcinoma (rare (<1%) but with a poor prognosis)	Unknown (a longer follow-up is needed)

AGA- anti-gliadin antibodies; DGP- deamidated gliadin peptide antibodies; HLA- histocompatibility leukocyte antigen; NCGS- non-celiac gluten sensitivity; tTG-IgA- anti-tissue transglutaminase antibodies IgA

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