Chapter

Introductory Chapter: Celiac Disease - An Overview

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1. Introduction

Celiac disease (CD) is a systemic disorder of an autoimmune nature that occurs in genetically susceptible individuals. It is caused by gluten and related prolamins and is characterised by the presence of a variable combination of gluten-dependent clinical manifestations, the presence of CD-specific antibodies, along with genetics compatible with HLA-DQ2 or HLA-DQ8 haplotypes and the presence of varying degrees of enteropathy [1].

It is triggered by the consumption of foods that contain or are made with gluten, mainly through wheat proteins (gliadins), and also rye (secalins), barley (hordeins) and certain varieties of oats (avenins).

It is a chronic disease with a genetic basis that affects, or may affect, various organs and systems in which inflammation of the small intestine may lead to various symptoms and eventually to malabsorption of nutrients. Treatment of CD consists of permanently following a gluten-free diet (GFD), which was developed in 1951 by the Dutch paediatrician Dr. Willem Karel Dicke, in the course of treating children suffering from chronic diarrhoea with malnutrition who had been admitted to the Children's Hospital of Utrecht after the Second World War. He found that they improved when foods containing wheat flour were removed from the diet. This was the starting point for the introduction of the GFD, which is the only treatment for CD that is effective throughout the world, and it has been applied ever since [2].

Genetics, immunology and aspects of the environment are important factors in the development of CD. Its principle determinants are the class II genes of the HLA system, which are largely related to the presence of HLA-DQ2 and HLA-DQ8 [3]. It is primarily an immune disorder, mediated by T cells, that affects the intestinal mucosa of genetically predisposed individuals. CD4+ T cells recognise gluten peptides, which are selectively present in the context of the molecules HLA-DQ2(+) and DQ8(+) [4].

The enzyme transglutaminase 2 (TG2) deaminates positively charged gluten peptides. Gluten-specific CD4+ T cells, such as the cytotoxic intraepithelial CD8 T lymphocytes, play an important role in the development of intestinal lesions. Gluten is the most important environmental factor involved in its development, but other environmental factors have been implicated, such as infections, dysbiosis and exposure to drugs [5, 6].

The Consensus Conference of Experts Meeting in 2012 and 2013, celebrated in Oslo and London respectively have accurately described the terms related to CD and also the sensitivity to non-celiac gluten sensitivity (NCGS) and wheat allergy, to unify criteria and accurately define the differences between such disorders [7, 8].

2. Clinical presentations of CD in adults

In adults, the average age of presentation of CD is 44 years (with a wide age range between 14 and 81 years). It has a clear female predominance (3:1), which has been confirmed in young children. Strikingly, approximately 15–25% of cases are diagnosed in people over 60 years of age [9].

In some cases, there is a recorded history of growth retardation or other symptoms that suggest that CD was present in childhood. The classic presentation of the disease with malabsorption, diarrhoea, weight loss and abdominal distension is less common in adults than in children [10].

Diarrhoea is the main way in which CD presents itself, although it occurs in fewer than 50% of patients; constipation is not uncommon in celiac patients and is accompanied by non-specific gastrointestinal symptoms that overlap considerably with those of functional dyspepsia (FD), irritable bowel syndrome (IBS) and functional diarrhoea [11, 12].

Patients with CD may frequently have symptoms that are also characteristic of IBS, including abdominal pain (77%), abdominal distension (73%), chronic diarrhoea (52%), constipation (17%) and/or the presence of a pattern of alternating bowel movement in an intermediate percentage (24%). This means that IBS is often the initial diagnosis for many patients, before the discovery of CD several years later [13, 14].

The presence of symptoms related to gastroesophageal reflux disease (GERD) that do not respond well to treatment with anti-secretory drugs should make the doctor think that the patient may be celiac. For example, in an Argentine study, Nachman et al. evaluated the presence and intensity of GERD symptoms at the time of diagnosis of CD in adult patients and found a significantly higher mean score of reflux symptoms than in healthy controls. In baseline terms, 30.1% of patients with CD presented moderate or severe GERD symptoms, compared with 5.7% of controls [15]. A study conducted by Usai et al. of cases and controls in patients with CD and associated GERD confirmed that the GFD improved symptoms and was a useful strategy for preventing recurrences [16].

The prevalence of extra-intestinal manifestations is very high among adult patients, especially if a specific search for them is carried out. Anaemia, caused mainly by iron deficiency, osteoporosis, dermatitis herpetiformis, recurrent aphthous stomatitis, hypertransaminasaemia and a series of neuropsychiatric disorders may be a common form of presentation of CD in adults [17, 18].

Serological screening in high-risk groups, especially in families of patients with CD, have increased the frequency of detection of the disease in children and adults, some of whom are asymptomatic or have mild, nonspecific symptoms [19].

3. Diagnostic criteria of CD in adults

The diagnostic strategy for an adult patient with suspected CD is complex, given the diversity of possible clinical scenarios in which it can occur. Determining the specific serology for CD by measuring titres of tissue transglutaminase (tTG), endomysial (EMA) and deamidated gliadin (PGD) antibodies should be the initial diagnostic test, because of its simplicity and low cost. It should be carried out in patients presenting signs, symptoms and/or associated diseases.

When the tTG titres are 10 times higher than their normal values (>100 U/ml), they are considered to be diagnostic of CD by themselves, thereby avoiding taking duodenal biopsies, since the probability of finding associated villous atrophy is very high. Hills et al. confirmed that the finding in adults of tTG values >30 U/ml

1. Clinical symptoms suggestive or compatible with CD
2. Positive serology with high titres
3. Positive genotyping for HLA DQ2/DQ8
4. Enteropathy compatible with CD in duodenal biopsies
5. Positive response to gluten-free diet

Table 1.
Criteria of Catassi and Fassano for the diagnosis of CD [22] (five-point rule).

(N < 10) with the Celikey test has a positive reductive value of 100%. Before deciding against taking biopsies during the endoscopy, the positivity of the EMAs should be confirmed and the presence of the genetic markers (DQ2 and DQ8) determined, since their presence reinforces the diagnosis of CD [20].

Conversely, when the levels of the tTG antibodies are less than three times the normal values, a gastroscopy should be done with multiple duodenal biopsies (usually six, of which two must be from the bulb). If the histological results reveal enteropathy, a GFD should be initiated and followed strictly and permanently. In patients with CD-compatible enteropathy and negative serology, genotyping of the HLA-DQ2/DQ8 system may be useful, because if both markers are negative, they make the diagnosis unlikely [21].

Nevertheless, it should be considered that, for any case, neither serological and genetic tests, nor the results of duodenal biopsies are pathognomonic. This means that, in certain cases, it is very difficult to confirm or rule out the presence of CD, given the great variability of possible findings, and it is impossible to simplify the wide range of diagnostic possibilities available for use in the clinical setting.

However, some easily applicable algorithms are available that can be of use. In this regard, in 2010, Catassi and Fassano suggested using a simple five-point rule that is very easy to include and evaluate, assigning a unit value to responses to questions about such items as: clinical symptoms, positivity of serology, the presence of compatible genetic markers, the positivity of histological findings, and the serological and histological responses to the GFD. The presence of four of these five criteria (or three of four if genetic markers are not available) is indicative of a probable diagnosis of CD, if the patient can be or not diagnosed. This system has not yet been prospectively validated, so it is not in general use (**Table 1**) [22].

This system is only of indicative value and is little used in clinical practice because, despite its simplicity, it is difficult to interpret and the weight of each of the included items is not taken into account. Under no account should it be applied with rigid criteria, to conclude whether a particular patient is celiac or not.

4. Non-celiac gluten sensitivity

Non-celiac gluten sensitivity (NCGS) is an emerging disorder, characterised by the presence of intestinal and extra-intestinal symptoms, related to the consumption of foods containing gluten. It appears in individuals who are not affected by CD or by wheat allergy. Despite the lack of reliable epidemiological data, it is estimated that its prevalence worldwide is between 5 and 10 times that of CD (5–10% in the general population). This has contributed to the great increase (a tripling in the US, for example) in the worldwide consumption of gluten-free food in recent years.

NCGS was originally described in 1976 and 1978 [23, 24] and the first series of studies on the subject was published in 1980 [25]. However, it was not until 2010, with the sharp increase in the number of publications, that this apparently novel

A. Relationship of their presence with consumption of food containing gluten
B. Exclusion of wheat allergy
C. Serology of negative CD
D. Absence of villous atrophy

Table 2.
Diagnostic criteria compatible with the presence of an NCGS [26–28].

entity was brought to the attention of physicians and researchers, presenting a challenge to those working in the field of gluten consumption-related disorders.

It is characterised from the clinical point of view by the presence of digestive and extra-digestive symptoms in relation to the consumption of food containing gluten. No precise diagnostic criteria are available, which is why it is fundamentally diagnosed by the exclusion of CD in patients with similar clinical characteristics. The diagnostic criteria of the NCGS are based on additionally ruling out the presence of symptoms related to wheat allergy. Antibodies to CD are negative or have low titres, and duodenal biopsies may show inflammatory changes, but always without any intestinal villous atrophy being present (**Table 2**) [26–28].

The physiopathology of NCGS is still not fully understood. Several pioneering studies have suggested an important role for innate intestinal immunity in the pathogenesis of NCGS, in contrast to CD, in which an adaptive immune response is activated [29, 30].

No cases of family aggregation, presence of associated diseases or long-term complications have been described in NCGS, unlike what occurs in the case of CD. A diagnosis of NCGS in patients with gluten-dependent symptoms, a family history of CD or associated autoimmune diseases, can call into question whether a case of NCGS is, instead, really a case of mild CD, because their very similar clinical characteristics make them very difficult to distinguish.

5. Diseases associated with CD

The extra-intestinal diseases most frequently associated with CD are iron deficiency anaemia, type 1 diabetes mellitus, osteoporosis, thyroid disorders and dermatitis herpetiformis [31]. Autoimmune diseases are generally between 3 and 10 times more frequent in patients with CD than in the general population.

Some hypotheses have been proposed to explain the increase in the prevalence of autoimmune diseases in patients with celiac disease. One of these is that a longer exposure to gluten prior to diagnosis could be a risk factor for the development and appearance of related diseases [32, 33]. However, other researchers determined that the presence of autoimmune diseases in patients with a late diagnosis of CD is not associated with the duration of gluten consumption [34].

From the immunological perspective, CD is characterised by over-expression of interleukin-15 (IL15) at the level of the mucosal surface of the small intestine. There is some evidence about its importance in the association with autoimmune diseases, because, due to the presence of these increased levels of cytokine, the effector T cells in the intestinal epithelium are not suppressed by the regulatory T cells, which would generate a loss of gluten tolerance and a greater presence of antibodies such as auto-antigens [35].

Vitamin D deficiency is another factor that has been implicated in the pathogenesis of autoimmunity in CD due to it frequently being detected at low levels in the blood of patients with CD and other autoimmune disorders. Vitamin D is an

important biological inhibitor of inflammatory hyperactivity, even in the presence of several malignant tumours. Its real role and the details of the mechanisms by which it acts have not yet been fully elucidated [36].

6. Ferropenic anaemia and associated CD

Anaemia without other clinical signs of intestinal malabsorption is one of the most common extra-intestinal manifestations of CD [37]. CD is frequently diagnosed in patients referred for evaluation for iron deficiency anaemia, which is found in 1.8–14.6% of patients [38].

A prospective study conducted in patients with iron deficiency anaemia published in 2005 [39] reported a 5% prevalence of celiac disease. Subsequent studies have confirmed that between 4 and 6% of patients with refractory iron deficiency anaemia of unknown origin have CD. Associated autoimmune gastritis is found in 20–27% of patients, 50% of whom also have an associated active *H. pylori* infection that responds effectively to the eradicating treatment.

The most obvious cause of this anaemia is a decrease in intestinal absorption of iron and other nutrients, including folate and cyanocobalamin. Villous atrophy of the intestinal mucosa is a significant cause of the decrease in iron absorption, as confirmed by the microcytic and hypochromic anaemia revealed in the haemograms of the majority of anaemic patients with CD [40].

The decreased absorption of iron in CD is also revealed by the failure of the serum iron levels to increase following oral administration of iron supplements, whereas the problem is resolved rapidly when iron is administered parenterally.

7. Diabetes mellitus type 1 (DMT1) and associated CD

In children, the first cases with CD and associated DMT1 were reported in 1969 [41]. Thus, a 10-year controlled longitudinal monitoring study of 335 adult celiac patients, diagnosed between 1980 and 1990, compared with a broad group of age- and sex-matched control subjects with various gastrointestinal symptoms, confirmed the high prevalence of endocrine diseases in patients with CD (11.9% in patients versus 4.3% in the control group; $p < 0.003$). More recently, other researchers found a higher prevalence of type 1 diabetes mellitus (5.4–7.4%) in patients with CD compared with controls [42, 43].

DMT1 is diagnosed in more than 90% of cases before CD is confirmed. Patients with diabetes mellitus and symptoms associated with CD who are following a GFD show a clear overall clinical improvement. In children, an increase in the growth rate and a rise in haemoglobin levels are often observed. Better metabolic control of diabetes mellitus is observed, as clearly confirmed by the reduction in the number of hypoglycaemic episodes, and the reduced need for daily insulin if the patient is following a GFD [44].

Juvenile diabetic patients present an average prevalence of CD of about 5% of cases. This strong association is largely due to the fact that celiac patients with and without diabetes share the same genetic base represented by the presence of the HLA-II haplotype, DR3-DQ2, demonstrating that it is appropriate to systematically screen for CD in patients with T1DM. Strategies for follow-up include periodic serological determinations for specific antibodies, first at the time of diagnosis, then, repeated every 6 months for the first year and at least annually for 5 years or more. Patients with positive responses to specific serological tests and in whom genetic susceptibility markers (HLA-DQ2 and/or HLA-DQ8) are present require duodenal biopsies to be taken to confirm the diagnosis of CD. Although many clinical

guidelines recommend carrying out systematic screening for CD, their application in clinical practice, particularly in children, adolescents and young adults, has not yet reached the desired level of performance in many countries of the world [45, 46].

8. Altered bone metabolism: osteopenia, osteoporosis and CD

The association of celiac disease with metabolic bone disorders was known even before the origin and treatment of celiac disease was understood. Osteomalacia, a condition characterised by low bone mineral density (BMD), marked deformities and rickets, has frequently been described in the medical literature. This disease preferentially affects children with CD [47], but is rarely part of their routine clinical presentation of CD [48]. The development and availability of the means to measure bone mineral density by non-invasive techniques has confirmed the clear relationship between low BMD and the presence of CD. BMD determination has been routinely used for adult celiac patients since 2005 [49]. Metabolic bone disease remains a significant and very frequent complication of CD determined at the time of diagnosis in children and adults.

The presence of low BMD leads to a deterioration in the quality of life [50], aggravated by its frequent complications, such as the presence of various repeated bone fractures, spontaneously, or after minor trauma. Currently, the finding of a low BMD is the first diagnostic criterion for confirming the presence of osteoporosis, metabolic and skeletal disease defined by lesions at the level of the bone microarchitecture, increased bone fragility and susceptibility to an increased risk of breaks. The WHO has established diagnoses of osteoporosis when bone mass values are less than −2.5 times the standard deviation (SD) of the maximum bone mass (the maximum value of BMD in an adult), and of osteopenia when these values are between −1 and −2.5 SD less than the maximum.

It is estimated that, at the time of diagnosis, one-third of paediatric patients present osteoporosis, and one-third have osteopenia. Only the remaining third of patients with CD have normal BMD [51]. Although more than half the children with CD have low BMD at the time of diagnosis [52], once a GFD has been initiated, most children with CD achieve a normal height and weight for their age, and their rate of bone mineralisation accelerates, in such a way that most of them attain their maximum bone mass when their bones finish growing [48]. The most serious problem arises when CD is diagnosed during adulthood, by which time bone growth is complete and maximum bone mass has been reached. The prevalence of osteoporosis in adult patients with CD is twice that of adults of the same age in the unaffected population [53]. The average prevalence of low BMD in adult CD patients is 40%, compared with 15% in the general adult population. In one series of adult patients with CD, the prevalence of low BMD reached 75% [54]. This low BMD is also characteristic of patients with dermatitis herpetiformis [55].

The first-line treatment for osteoporosis in CD is to establish a permanent GFD. Several studies, of children and adults, have demonstrated its effect on bone density and calcium absorption [56–58]. The greatest gain in bone mass described in these studies has been shown to occur during the first year on the GFD. It leads to an increase of at least 5% in bone mass after 1 year, although this is not enough for the bone mass to become normalised. In clinical practice, the degree of adherence to the GFD also determines the extent of recovery of bone mass, which is generally estimated at around 30% [59]. In addition, the recovery rate is higher in young patients with CD than in adults. This is explained by the fact that 97% of the bone mass accumulates during the first two decades of life, and because complete recovery is difficult for people older than 20 years of age [60].

In addition to the GFD, an adequate supply of calcium and vitamin D should be ensured, since they are critical factors for the acquisition and maintenance of good bone mass. Adult patients with untreated CD typically experience a decrease of 45% in the level of intestinal absorption of calcium that is followed by a 52% improvement 6 months after beginning the GFD. Serum vitamin D levels at diagnosis are very low in most adult patients. The intake of 1200-1500/day (suppress daily and long-term) calcium and 400 U of vitamin D is recommended, administered in exactly the same way as it is in cases of osteoporosis that are not associated with CD [61].

9. Thyroid diseases and CD

It is well known that CD is present in a higher proportion of patients with autoimmune-based thyroid diseases (e.g., Graves' disease and Hashimoto's thyroiditis), with a prevalence of 2–7% [62–65]. Similar observations have been made in celiac patients, whereby their serological signs of autoimmune thyroid disease were present in up to 26% of cases. Thyroid dysfunction was detected in up to 10% of the cases of CD and it was estimated that the risk of disease was at least three times higher than in healthy controls [66–69].

It has been reported that patients with CD who follow a GFD could develop thyroid problems of an autoimmune nature. In contrast, other studies have described declining anti-thyroid antibody titres after a period of 2–3 years on the GFD [70, 71]. These different results could have arisen because patients had been on their GFD for different lengths of time. The authors prospectively evaluated the presence of thyroid autoimmunity in children and adolescents with CD who had adopted a GFD. After 2 years on the diet, a 7% increase in thyroid autoimmunity was observed, based on levels of L-thyroxine in the CD patients. Thyroid autoimmunity did not appear to be more frequent in paediatric patients and adolescents with CD who followed a GFD than in control groups. Since their clinical development does not seem to affect growth, the authors concluded that a long-term programme screening for thyroid disease might not be necessary for all patients with CD who follow a GFD, but may be advisable for those for whom there is a suspicion of thyroid disease [72].

The coexistence of CD and autoimmune thyroid disease has been explained in terms of several mechanisms, such as the genetic predisposition and the association of both diseases with the gene that codes for antigen 4, which is associated with cytotoxic T lymphocytes and which confers susceptibility to thyroid autoimmunity. It has also been shown that the tTG-2 IgA reacts with thyroid tissue and that this association could contribute to the onset and development of thyroid disease in patients with CD [73].

10. Dermatitis herpetiformis and EC

Dermatitis herpetiformis (DH) was first described in 1885 by the French dermatologist Louis Duhring, and, indeed, is still known as Duhring's disease in some countries. In 1966, Marks et al. identified the presence of histological alterations in the small intestine of these patients that were identical to those observed in individuals with CD [74, 75].

The primary cutaneous lesions appear as erythematous papules, associated with liquid-containing vesicles in different areas of the body, especially those where there is rubbing, where they are distributed symmetrically on the extensor surfaces of the extremities. The vesicles produce a great deal of itching, causing patients to scratch themselves frequently, bursting their blisters, which releases their liquid content,

and causing erosions and abrasions. Subsequently, the papules become scabs that later detach, leaving a slightly hyperpigmented area. Generally, they predominate in young adults, but they can also affect children and older adults, especially atopic children. The vast majority of patients note the onset of symptoms during the warm months from the beginning of spring to the end of summer [76, 77].

The majority of patients with DH have no intestinal manifestations, or else only very mild ones. Sometimes patients only have iron deficiency anaemia. Males are more likely to be affected than are women (1.5–2:1) in contrast to CD, which clearly predominates in the female sex (2–4:1) [78].

The most characteristic histological finding is the presence of IgA-type granular deposits located in the papillae of the dermis and throughout the basement membrane, as can be demonstrated by direct immunofluorescence in skin biopsies. These accumulations promote an inflammatory response with infiltration of neutrophils around the vesicles of the affected areas [79]. The immunological basis of its development is linked to the pathogenesis of gluten intolerance in CD. The tTG-3 antibody is the main responsible auto-antigen, which is located in the skin of these patients, leading to the appearance and maintenance of the inflammatory response [80].

The main treatment for DH is the adoption of a GFD, which must be adhered to strictly and constantly throughout life. The skin lesions disappear several weeks after starting the GFD. Some cases may require a brief complementary treatment with Dapsone. This drug targets rashes by inhibiting neutrophil migration, and is used until the skin lesions have completely disappeared [81]. A Finnish study, carried out between 1971 and 2010, on the death rate and causes of death of 476 consecutive patients with DH, found significant reductions in all-cause mortality and cerebrovascular disease. The standardised mortality rate for all-cause mortality was significantly reduced to 0.70 (95% CI: 0.55–0.87). This value was similar in both sexes and was almost identical to that in dermatitis herpetiformis patients (0.73) without villous atrophy of the small intestine [82].

11. Cerebellar ataxia and EC

This disease encompasses cases previously known as "idiopathic sporadic ataxia," which are accompanied by positive antibodies against gluten. It is a type of cerebellar ataxia that appears in patients with associated gluten intolerance.

The most common form of clinical presentation consists of balance and gait disorders with associated dysarthria. Less frequently, it manifests as diffuse or focal myoclonic contractions. It is accompanied by nystagmus and other ocular signs in more than 70% of cases. In general, it begins gradually, appearing in individuals aged over 50 years, and with equal prevalence in men and women. It usually has a slow evolution, with a stationary clinical course and intermittent episodes of aggravation. Most patients have a prior history of recurrent digestive symptoms, and many patients have not been previously diagnosed with CD or with associated NCGS.

The Sheffield group led by Dr. Hadjivassiliou was the first to describe this type of association, and has made significant contributions to the field since 1970 [83]. The diagnosis of gluten ataxia is confirmed by the presence of anti-gliadin antibodies (AGAs) [84] as well as anti-tTG- and, when available, anti-tTG-2–6.

Fewer than 40% of patients with gluten ataxia present anti-tTG-2-positive IgA. When combined with anti-tTG-6, it can attain a positivity of 85% [85]. Autoantibodies to tTG-6 have been identified in immune-mediated ataxia patients with gluten sensitivity, suggesting an important role for transglutaminase 6 in cortical and cerebellar neurons [86, 87]. Gluten ataxia occasionally presents a familial character, affecting several first-degree relatives [88].

Gluten ataxia is considered an autoimmune disease characterised by the presence of cerebellar damage, mainly localised at the level of Purkinje cells, and the presence of circulating antibodies against gluten or related enzymes. Affected patients must follow a strict and sustained GFD. The degree of response to the withdrawal of gluten from the diet depends on the time elapsed between the appearance of the first signs of ataxia and the commencement of the GFD: the sooner it is established, the greater the chances of remission or recovery from the signs of ataxia.

It is important to remember that coexisting nutritional deficiency and autoimmunity can also cause neurological dysfunction in CD. A wide variety of neurological phenotypes with different aetiologies was found in 68 gliadin-positive patients with CD or non-CD over a period of 10 years (2002–2012): cerebellar ataxia, neuropathy, dementia, myeloneuropathy, autoimmune disease, deficiencies of vitamin E, folate and copper, genetic disorders and metabolic or toxic syndrome, among others. The authors concluded that exposure to gluten can cause neurological dysfunction even in those patients without established CD [89].

12. Neurogluten

Non-celiac gluten sensitivity (NCGS) is a clinical entity related to the ingestion of gluten-containing food, but the patients are not affected by celiac disease (CD). NCGS does display the typical histology of CD, although it may share a low level of duodenal intraepithelial lymphocytosis, but not crypt hyperplasia or villous atrophy. Neither does NCGS have the typical serology of CD, in which anti-transglutaminase type 2 IgA antibodies are present in the serum. However, they have a low level of them, and sometimes they are positive for antigliadin IgG antibodies. The sensitivity and specificity of both processes are limited. NCGS may affect individual or familial cases, but unlike in CD, the HLA-DQ2/DQ8 haplotype is not required in order for it to develop [90–93].

Like CD, NCGS is a common, chronic process, and often responds well to a GFD, even in severe cases. To date, in the absence of other biomarkers, the most specific method for confirming the diagnosis is a positive, self-reported response by the patient to a strict GFD, adhered to for a period of 6–12 months, and the verified improvement of the clinical signs when examined. To sustain the benefits, long-term or lifelong adherence, according to the severity of the syndrome, to a GFD will be the most widely recommended therapy [94, 95].

NCGS gives rise to important neurological and neuropsychiatric disorders. The most frequent of these are gluten ataxia and peripheral neuropathy, which have both frequently been associated with depression and anxiety. All patients can improve with early adoption of a GFD. However, without that therapy, progressive neurological dysfunction and cerebellar atrophy, and axonal nerve injury appear in MRI and neurophysiological patterns, respectively. Cerebrospinal fluid alterations are less frequent [96–99].

Other cases have been described that are associated with CD, but these probably correspond more closely to NCGS. They are all grouped together as neurogluten, a term that evokes different disorders in the nervous system that have the same cause, as is the case in neurosyphilis [100, 101].

Controversy arises when neurological entities without a determined diagnosis are included and related to that cause by a functional improvement that has not been objectively verified over a sufficiently long period. Given the current convenience and availability of GFD, safer diagnostic criteria, based on expert consensus, are needed to make more accurate diagnoses until such times as reliable biomarkers become established.

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