Chapter 14

Extraintestinal Manifestations and Associated Diseases

Luis Rodrigo, Mª Eugenia Lauret-Braña, I. Pérez-Martínez

Gastroenterology Service, Asturias Central University Hospital (HUCA) and University of Oviedo, Oviedo, Spain.

lrodrigosaez@gmail.com, meugelb@hotmail.com, ipermar_79@hotmail.com

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Abstract

Celiac disease (CD) is frequently accompanied by a variety of extra-digestive manifestations, thus making it a systemic disease, rather than a disease limited to the gastrointestinal tract.

This is primarily explained by the fact that CD belongs to the autoimmune disease group, the only one with a known etiology, related to a permanent gluten intolerance. Remarkable breakthroughs have been achieved in the last decades, due to a greater interest in the diagnosis of atypical and asymptomatic patients, which are more frequent in adults. The known presence of several associated diseases provide guidance in the search of oligosymptomatic cases as well as studies performed in relatives of CD patients.

The causes for the onset and manifestation of associated diseases are diverse: some share susceptibility genes, like type 1 diabetes mellitus (T1DM); others share pathogenetic mechanisms and yet others are of an unknown nature.

General practitioners and other specialists must remember that CD may debut with extraintestinal manifestations and associated illnesses may appear both at the time of diagnosis and throughout the evolution of the disease.

The implementation of a gluten-free diet (GFD) improves the overall clinical development and the evolution of associated diseases. In some cases, such as in iron deficiency anemia, the GFD contributes to its disappearance. In other diseases, like T1DM, it helps to reduce the amount of insulin needed, thus allowing for a better control of the disease. In several other complications and/or associated diseases, an adequate adherence to a GFD may slow down their evolution, especially if it is implemented during an early stage.

1. Introduction

Celiac disease (CD) is a systemic process, autoimmune in nature, which appears in genetically predisposed individuals. Its clinical manifestations are predominantly digestive, but it is accompanied, with a certain frequency, by extradigestive manifestations that may be due to nutritional deficiencies of an autoimmune nature, of diverse types and in different locations.

Their presence speaks of a possible etiopathogenic relationship which somehow may guide diagnosis. The list of associated diseases is wide and varied, since it includes previously existing disease involvement of various organ systems, which appear simultaneously or even after the introduction of a gluten-free diet (GFD).

Sollid[1] postulates that although the CD causal antigen is a protein ingested with food, various immunopathogenic studies speak in favor of their being relevant to the development of autoimmunity. The main argument is based on genetic observations which confirm that there are multiple "loci" shared between CD and various autoimmune diseases, especially type 1 diabetes mellitus (T1DM) and rheumatoid arthritis (RA).[2] The antigenic mechanism would be effected through transglutaminase 2 (TG2).

Most of the associated diseases improve with the introduction of a GFD, although many of them also require a good substitutive or specific treatment, temporary or prolonged.

In this chapter we review a series of extraintestinal manifestations and/or diseases associated with CD, describing their frequency, possible causal relationship and recommended treatments.

2. Hematologic Manifestations (Table 1)

- Anemia:
  - Iron deficiency anemia
  - Due to folic acid and/or vitamin b12 deficiency
  - Multifactorial
  - Refractory
- Leukopenia
- Thrombopenia and Thrombocytosis
- Clotting disorders
- Venous and arterial thrombosis

Table 1. Hematological associated diseases.

2.1. Anemia

Anemia is a common finding in CD patients and it may be its most striking clinical manifestation, leading to diagnosis. Its etiology is multifactorial and its prevalence is highly variable, ranging from 12 to 70% of cases.[3-5] This anemia is usually microcytic and hypochromic, of the hypoproliferative type, reflecting a decreased intestinal absorption of iron, various vitamins and other nutrients, including folic acid and cobalamin. The presence of villous atrophy is an

important factor in the reduction of iron absorption, but the former is not required for the latter to appear.

Iron deficiency anemia occurs in up to 46% of cases of subclinical CD, with higher prevalence in adults than in children and its overall frequency in patients with refractory anemia reaches up to 20% of the cases.[6-8]

In a recent study, the prevalence of CD in patients with anemia was of 5% and of up to 8.5% in those who have iron deficiency anemia.[9]

Sustained chronic iron deficiency with low levels of serum iron, transferrin saturation and ferritin is common in celiac patients, with or without associated anemia and should be an index of suspicion for possible associated CD.

It is therefore recommended that clinicians include in their daily routine iron deficiency anemia in the CD diagnosis protocol, including serological and genetic markers as well as duodenal biopsies, especially in refractory cases.[10]

The primary indicated treatment is the establishment of a GFD and iron supplements, orally or intravenously, until reserves are replenished.

2.2. Leukopenia

Fisgin et al. described the presence of leukopenia with anemia in a group of children with CD at the time of diagnosis.[11] Its prevalence in both children and in adults with celiac disease is not well understood at present.

It has been suggested that the leukopenia is primarily due to folic acid deficiency associated with copper deficiency.

Data on treatment are also very scarce. There is usually a slow improvement after establishing a GFD and it can be supplemented with oral copper sulphate supplements, should there be any deficiency of this trace element.[12,13]

2.3. Thrombocytopenia and Thrombocytosis

The decrease in platelet count has occasionally been reported in CD patients and has been postulated as of a possible autoimmune etiology. Isolated cases have been reported associated with keratoconjunctivitis and choroidopathy, suggesting again its probable autoimmune pathogenesis.

Thrombocytopenia treatment associated with CD requires the establishment of a GFD, which by itself, in some cases, can normalize the platelet counts. When this does not happen, it is advisable to resort to corticosteroid treatment for a short period until its resolution.[14,15]

Thrombocytosis may indicate the presence of increased inflammatory activity in CD patients. Carroccio et al. described the case of an elderly patient with clear-cut thrombocytosis associated with severe anemia who was diagnosed with CD. They suggested that it may also be associated with some myeloproliferative disorders and some hematologic neoplasias.[16]

Thrombocytosis can be resolved with the establishment and monitoring of a GFD.

2.4. Clotting Disorders

Untreated CD can lead to malabsorption of various nutrients, which can be manifested by a vitamin K deficiency and thus by a decrease in the presence of its dependent clotting factors. Cavallaro et al. found a decrease in the prothrombin time (PT) of up to 20% of adult celiac patients at the time of diagnosis.[17] It is unusual to find a PT decrease alongside the malabsorption of other nutrients.

Treatment involves adhering to a GFD and vitamin K deficiency correction after parenteral administration.

2.5. Venous and Arterial Thrombosis

Ramagopalan et al.[18] suggested in a study that celiac disease has an increased risk of thrombotic events than in relation to the general population. Ludvigsson et al.[19] found a greater association for venous thromboembolism in both genders, pointing out that it may even be the first clinical sign of CD suspicion. Cassela et al.[20] found that increased serum homocystinemia is relatively frequent in celiac patients and that, as is well known, it could be a causal factor for hypercoagulability.

The clinical spectrum of thromboembolism in CD patients is variable, including deep vein thrombosis, pulmonary embolism, Budd-Chiari syndrome and splenic thrombosis, as its more frequent manifestations.[21,22]

Only a few cases of arterial thrombosis have been described and the role of CD is doubtful. Similarly debatable is its influence on the development of vascular brain lesions.

3. Mucocutaneous Facial and Oral Manifestations (Table 2)

- Canker sores
- Dental enamel defects
- Sjögren's Syndrome
- Prominent forehead

Table 2. Oral, mucocutaneous and facial manifestations.

3.1. Canker Sores

The presence of recurrent oral canker sores should urge the physician to actively search for possible associated CD, since they are present in between 10% and 40% of treated celiac patients.[23] Their diagnosis is usually done by inspection and their treatment is based on the GFD, mouthwashes and local analgesics, since they are generally quite painful.

3.2. Enamel Defects

The association with enamel defects is quite characteristic. Its pathogenesis has been related to both calcium uptake defects at the time of the appearance of permanent dentition as well as with possible autoimmune effects.[23]

3.3. Sjögren's Syndrome

Eye and mouth dryness appears with relative frequency in association CD, as it happens with other autoimmune diseases. Its evolution usually does not depend on a strict adherence to a GFD.[24]

3.4. Prominent Forehead

Finizio et al. described this curious finding in 2005, first connecting it to the possible presence of CD. Currently it is considered as a rather anecdotal description, partly due to the smaller size of the lower two thirds of the face, compared with the surface of the forehead.[25]

4. Associated Neurological Diseases (Table 3)

- Polineuropathies
- Headaches/Migraines
- Depression/Anxiety
- Ataxia
- Epilepsy
- Multiple sclerosis
- Guillain-Barré syndrome
- Others

Table 3. Neurological associated diseases.

4.1. Peripheral Polyneuropathy

This is the most common neurological CD-associated involvement. Thus, in an Italian series of studies, its presence was confirmed up to 49% of the patients.[26] Its most frequent clinical manifestations include the prevalence of painful paresthesias in all four limbs, occasionally on the face, and disorders associated with sensitivity. Motor weakness is less common, affecting mainly the ankles and may appear as an abnormal gait in up to 25% of the patients.[27]

4.2. Headaches

Gabrieli et al. found, in a number of celiac patients, a migraine frequency of 4.4%, which was 10 times higher than that found in a control population (0.4%).[28] Both migraines and tension headaches occur more frequently in celiac patients than in the general population.

In a follow-up study of celiac patients, more than half of those with headaches or migraines improved significantly after the introduction of a GFD, which speaks in favor of the possible existence of a causal relationship of gluten both regarding its appearance and in its maintenance.[29]

4.3. Depression and Anxiety

In celiac patients symptoms of increased anxiety, irritability and increased fatigue appear frequently, such as those observed in depressed or anxious individuals.[30,31]

In young children most of these symptoms disappear completely after introducing the GFD, but the improvement is less noticeable in adults, who usually need pharmacological treatment for a length of time.

4.4. Cerebellar Ataxia

Gluten ataxia is the second manifestation, in order of frequency. It is defined as an idiopathic sporadic process accompanied by circulating anti-gliadin antibodies, with or without associated duodenal mucosal atrophy.[32]

Its pathogenesis is related to the existence of an autoimmune pathology and some patients improve significantly with a gluten-free diet, especially when it is administered during the first six months of its appearance but it has also been described in cases in which it makes a late appearance and may have some familial aggregation, as it occurs in CD.[33-35]

4.5. Epilepsy

Several studies clearly indicate that there is an association between CD and epilepsy, estimating it has a range of 3.3-5.5%.[36] This seems to happen more frequently in children than in adults. Control of epilepsy and the frequency and severity of its seizures improve with GFD, especially if it is initiated soon after the onset of epilepsy.[37] Gobbi's syndrome can occur both in children and in adults and it is characterized by the presence of calcifications in the parieto-occipital area; it has a low frequency.[38]

4.6. Multiple Sclerosis, Guillain-Barré Syndrome and other Processes

Demyelinating diseases of which the most characteristic example is multiple sclerosis (MS) and its variant, Optic Neuritis (ON), which have a higher association prevalence with CD and lymphocytic enteritis than in the general population, as is the case with the Guillain-Barré syndrome.[39,40]

5. Dermatological Manifestations (Table 4)

- Dermatitis Herpetiformis (DH)
- Psoriasis
- Vitiligo
- Alopecia areata
- Chronic urticaria

Table 4. Dermatological associated diseases.

5.1. Dermatitis Herpetiformis (DH)

It is considered to be the CD of the skin and its presence is directly related to gluten hypersensitivity. It appears in 25% of celiac patients and it is characterized by vesicular and crusted lesions that appear anywhere on the body, especially in areas of physical friction. They have a symmetric distribution and are quite itchy. It is a rare lesion in children and a very common one from adolescence into adulthood. Its clinical development includes remissions and exacerbations which coincide with gluten exposure. It can be confirmed by the demonstration of granular IgA deposits at the dermo-epidermal junction. Its most effective treatment is a strict GFD. A better understanding of DH manifestations aids in the diagnosis of CD.[41]

5.2. Psoriasis

Psoriasis occurs in celiac patients with a higher prevalence than in the general population; adherence to GFD significantly improves both the evolution of skin lesions and of its associated complications.[42,43]

5.3. Alopecia Areata

It is also considered a chronic autoimmune disease. It is associated, with some frequency, with CD.[44] Unlike certain studies which described a complete resolution of alopecia after GFD, most authors agree that are not resolved by the latter.[45]

5.4. Chronic Urticaria

This type of injuries can be triggered by sudden changes in temperature (both cold and heat), being erythematous and edematous.[46] Most cases improve or disappear with GFD adherence.[47]

6. Bone Manifestations (Table 5)

- Childhood rickets
- Osteomalacia
- Osteoporosis
- Increased risk of fractures

Table 5. Bone associated diseases.

Bone demineralization is commonly associated with children at the time of diagnosis; it is estimated that one third of the children with CD have osteopenia, another third have osteoporosis and only the remaining third has normal bone mineral density (BMD)[48]; its relationship with increased prevalence of rickets and osteomalacia is well known. All these disorders improve, reverse and completely normalize with a GFD.[49]

It is also quite common in adults, its prevalence increasing with age, with an overall osteoporosis (OS) prevalence in this group estimated to be about 2 times higher than in unaffected persons within the same age range.[50]

As a result of this OS increased frequency, celiac patients generally have an increased risk of fractures, which is estimated to be 3.5 to 7 times higher when compared to the general population of the same age and sex; one in four celiac patients have a history of multiple fractures.[51,52]

In a recent Spanish study on adult CD patients, García-Manzanares et al.,[53] found that 45% of the patients had osteopenia and that in patients with villous atrophy (Marsh 3) it occurred more frequently than in those that do not have it (Marsh 1 and 2). Response to the GFD is lesser than in childhood and requires frequent calcium and vitamin D replacement therapy. Smoking also leads to a greater decrease in bone mass.

7. Associated Rheumatic Diseases (Table 6)

- Seronegative oligoarthritis
- Sacroileitis
- Polyarthritis
- Stronger association with:
  - Sjögren's syndrome
  - Systemic lupus Erythematosus (SLE)

Table 6. Rheumatogical associated diseases.

Arthritis varieties, as a group, are frequently associated in their various forms and presentations with the clinical development of CD, both in children and in adults. Thus, in a series of 200 celiac patients, it was present in 26% of the cases, a much higher frequency than that of the control population, which was of 7.5%, with a prevalence of seronegative and oligoarticular forms, as it happens in those that are associated with inflammatory bowel disease, with a slightly increased sacroileitis frequency.[54]

Reverse prevalence studies have been undertaken looking for CD by means of serological marker determination (mainly ATGT) in various rheumatic diseases, such as rheumatoid arthritis (RA), scleroderma and Sjögren's syndrome, this being where higher positive values have been found at 10%.[55]

Also, in a recent population study performed in Sweden on 29,000 patients with confirmed celiac villous atrophy, the prevalence of Lupus Erythematosus (SLE) was 3 times higher than that observed in the control population.[56]

8. Liver Manifestations (Table 7)

- Prolonged hypertransaminasemia
- Cholestatic and autoimmune hepatopathies
- Chronic hepatitis due to hepatitis C virus
- Acute fulminant hepatitis

Table 7. Liver associated diseases.

8.1. Prolonged Hypertransaminasemia

The most common change observed is fluctuating or persistent transaminase elevation, which is completely asymptomatic, present in 40% of both child and adult cases and disappears or becomes normalized with the gluten-free diet, after several years.[57]

CD comprises approximately 10% of the cases of hypertransaminasemia with an unclear origin, its presence should be investigated by serological studies and, if necessary, by means of a gastroscopy and confirmatory duodenal biopsies.[58]

8.2. Cholestatic and Autoimmune Liver Disease

Primary biliary cirrhosis (PBC), especially in its mild stages, primary sclerosing cholangitis (PSC) and some types of chronic autoimmune hepatitis (AIH) have a certain frequency of association with CD and its presence should be routinely considered as part of the diagnosis protocol. Cases of negative anti-mitochondrial antibodies (AMA) with cholestatic liver diseases have been found

which turn out to be from celiac patients whose hepatopathies hence become ameliorated or, at least, stabilized with the GFD.[59]

8.3. Chronic Hepatitis C

Both diseases have been epidemiologically analyzed for a possible relation since both are relatively common and it is not exceptional that they coincide in the same patient. It is well known that antiviral treatment with interferon-alpha may unmask an associated latent CD, but routine CD screening in patients with chronic hepatitis due to HCV does not currently seem to be justified.[60]

8.4. Acute Fulminant Hepatitis

Some cases of fulminant liver failure have been described in which in a timely diagnosis of associated CD has not only improved the clinical situation but also helped to prevent a liver transplant, so an urgent systematic screening is worth making in this clinical situation due to its associated high morbidity and mortality.[61]

9. Gynecological Manifestations and Impaired Fertility (Table 8)

Menstrual disorders in women are varied and frequent, including delayed puberty, episodes of amenorrhea and early menopause. All these disorders are usually associated with iron deficiency or chronic iron deficiency anemia.[62]

Thus, in a study conducted in Italy on 62 celiac women who were compared with 186 controls, it was found that 19.4% of the former had amenorrhea versus 2.2% in the latter (OR = 33, 95% CI = 7.17-151.8 p = 0.000). It was possible to also observe an association between other menstrual disorders such as oligomenorrhea, hypomenorrhea, dysmenorrhea and metrorrhage ($p < 0.05$) between groups. The likelihood of complications during pregnancy is estimated to be 4 times higher in women with celiac disease (OR = 4.1, 95% CI = 2-8.6, p = 0.000). A significant correlation for CD with the threat of abortion, gestational hypertension, placental abruption, recurrent gravidarum cholestasis, premature birth and low weight pregnancies was also found ($p < 0.001$).[63]

- Delayed puberty
- Amenorrhea
- Menstrual disorder
- Infertility in both genders
- Repeated abortions
- Pregnancies with low fetal weight
- Premature births
- Gestational hypertension
- Pregnancy cholestasis
- Loss of libido

Table 8. Gynecological associated diseases.

All these findings clearly support the relationship between several very common gynecological disorders in celiac women, some serious, and some even grave, both for the mother and the fetus, which underscores the importance of an early CD diagnosis in women in order to improve their health and their offspring's, as the GFD normalizes and prevents most of these possible gynecological and obstetric complications. There is no consensus on the appropriateness of screening for CD in pregnant women within the routine checks carried out in their first trimester.[64-68]

In males, CD is also related to the existence of sexual disorders, manifested as decreased libido and sexual potency as well as infertility.[69,70]

10. Endocrine Diseases Associated (Table 9)

- Autoimmune Polyglandular Syndrome (APS):
  - Addison's disease
  - Primary Hypogonadism
  - Hypoparathyroidism
  - Pituitary deficiencies
- Type 1 Diabetes Mellitus
- Thyroid disorders:
  - Hashimoto's Thyroiditis
  - Hypothyroidism
  - Hyperthyroidism

Table 9. Endocrine associated diseases.

In epidemiological terms, autoimmune thyroiditis (AIT) and type 1 diabetes mellitus (T1DM), are the endocrine processes most frequently associated with CD. These diseases, apart from

bronchial asthma, are the most common chronic diseases in children, and often can be associated.[71-73]

10.1. Autoimmune Polyglandular Syndrome (APS)

It includes two or more endocrine diseases associated within the same patient and which usually manifest hypofunction, excepting Graves' disease. The main processes are T1DM, AIT, adrenal insufficiency (Addison's disease), primary hypogonadism, hypoparathyroidism and some pituitary shortcomings.[74-76]

These syndromes can also be associated with other non-endocrine diseases. Four different types have been described, according to their associations.

10.2. Type 1 Diabetes Mellitus (T1DM)

Insulin-dependent diabetes and CD are commonly associated. The main reason for this is that both diseases share common susceptibility genes, HLA-II predominantly, or even some belonging to type I. Specifically, T1DM is strongly associated with the DR3-DQ2 haplotypes and also with DR4-DQ8 though less frequently than with the latter, as is the case for about 50 different diseases.[77] In all of these diseases an increase in intestinal permeability has been found, allowing the passage of different antigens, including gluten, which can trigger the appearance of these associated diseases.

About 4.5% of children and up to 6% of adults with T1DM exhibit associated CD.[78] This correlation between these two diseases is stronger as the patient's age increases. Epidemiological data vary depending on the population studied and the diagnostic criteria used. Thus in a recent study undertaken in Greece, Kakleas et al.[79] found a CD prevalence of 8.6% and the highest prevalence has been reported in Italy by Picarelli et al.,[80] reaching 13.8% for T1DM.

CD associated with T1DM, may be asymptomatic, or in most cases it manifests only mild symptoms.[81,82] Both diabetic adults and children with CD have an increased sepsis risk, especially pneumococcal, and it is recommended to vaccinate against this infectious agent.[83]

The GFD improves diabetes control and slightly reduces the insulin requirements, it improves or makes digestive discomfort disappear and normal growth weight gain are resumed in children, improving BMI.[84]

A routine annual study in T1DM patients is recommended for systematic and continuous CD screening.

10.3. Thyroid Diseases

There is a frequent association between CD and various thyroid diseases, which can occur both before and after diagnosis and thus also treated with GFD.[85-90]

Autoimmune thyroiditis occurs between 3 to 10% of celiac patients. It is characterized by the presence of circulating anti-peroxidase antibodies (anti-TPO) that may be asymptomatic with

thyroid normal function, such as Hashimoto's thyroiditis, or else associated with thyroid function disorder, generally with subclinical hypothyroidism.[86,88,90,91]

In a retrospective Swedish epidemiological study, including about 14,000 patients with celiac disease diagnosed over a period of 40 years, were compared against 68,000 controls and the relative risk (RR) was compared in CD for thyroid disease, finding that, for hypothyroidism and thyroiditis, it is 4 times higher, half of which belongs to hyperthyroidism, which is only 2 times higher than in the general population.[92]

11. Autoimmune Diseases (Table 10)

- Cardiac:
  - Dilated Myocardiopathy
  - Autoimmune myocarditis
- Neurological:
  - Peripheral neuropathy
  - Cerebellous ataxia
  - Headaches
  - Epilepsy
  - Anxiety/Depression
- Liver:
  - Autoimmune hepatitis(AIH)
  - Autoimmune cholangitis(AIC)
  - Primary biliary cirrhosis (PBC)
- Endocrine:
  - Type 1 diabetes mellitus
  - Autoimmune thyroiditis
  - Addison's disease
- Rheumatic:
  - Oligoarhtritis
  - Juvenile arthritis
  - Sjögren's syndrome

Table 10. Autoimmune associated diseases.

These are much more frequent and are associated with CD, in a ratio 3 to 10 times higher than in the general population.[93-100] These diseases, of which we have spoken in their respective sections, are varied and include such diverse processes as thyroiditis, autoimmune hepatitis, cholangitis, primary biliary cirrhosis, type 1 diabetes mellitus, Sjögren's syndrome, Addison's disease, peripheral neuropathy, cardiomyopathy and psoriasis, among others.

There are several reasons for these frequent associations. The principal one is that they share the same genetic predisposition, especially with certain human leukocyte HLA system haplotypes. Another reason lies in the response to various antigenic markers such as transglutaminase-2 and the presence itself of CD, which also contributes.

The duration of exposure to gluten, determined by the age at which the CD diagnosis is made, has also been considered as an important risk factor for the development of autoimmune diseases, as they are more common in adults than in children. This underscores the need for the realization of an earlier CD diagnosis, which could have a beneficial effect on the development of associated autoimmune diseases. However, other studies have refuted this hypothesis.[101,102]

Various autoimmune diseases associated with CD improve after a strict GFD. Among these are neuropathies,[103] cardiomyopathies,[104] thyroid diseases[105] and both type 1 and type 2 diabetes mellitus.[106,107] These last usually have lymphocytic enteritis as seen in duodenal biopsies.[108]

However, in many other autoimmune diseases, their clinical evolution hardly changes after the establishment and monitoring of the GFD.

12. Inflammatory Bowel Disease

It can occur associated with CD in either of its two varieties, Crohn's disease and ulcerative colitis, with a higher frequency than in the general population.[109]

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