

Extra Intestinal Manifestations of Celiac Disease and Associated Disorders

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Abstract Celiac disease (CD) is one of the most common causes of chronic malabsorption in all over the world. CD damage the small intestine epithelial layer. Reduction of absorptive surface area and digestive enzymes, cause impairment of absorption of micronutrients such as fat-soluble vitamins, iron and vitamin B12 and folic acid. Sensitivity to gluten is the main pathophysiologic cause of CD and it is characterized by intraepithelial lymphocytosis, crypt hyperplasia and villous atrophy. CD has diverse clinical features includes anemia, fatigue, weight loss, diarrhea, abdominal pain, bloating, osteoporosis and depression. CD is commonly seen in association with extra intestinal manifestations, such as the typical skin lesions and the neurologic symptoms. Because of the broad spectrum of its presentations, the diagnosis may not be so obvious or easy. Having greater awareness and lower threshold for testing for CD are necessary for diagnosis of this disease. When CD is suspected, serologic testing is required for screening and subsequently duodenal biopsies are necessary to confirm the diagnosis. In this review article we want to review the extra intestinal manifestations of CD and also describe the association between CD and other disorders. It is useful for better diagnosis of CD and improvement of treatment of associated conditions. Future studies should focus on the extra intestinal presentations and associated disorders of gluten sensitivity as they could help better understanding the pathogenesis of gluten sensitivity. In this review article we describe these issues: 1. CD and psychiatric disorders; 2. CD and neurologic disorders; 3. CD and cardiac manifestation; 4. CD and liver disease; 5. CD and Endocrine disease; 6. CD and Dermatologic disease; 7. CD and Rheumatologic disorders; 8. CD and Ophthalmologic disease; 9. CD and Reproductive problems; 10. CD and associations with some other disease.

Keywords: *celiac disease, extra intestinal manifestations*

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1. Introduction

Celiac disease (CD) is one of the most common causes of chronic malabsorption in all over the world. [1] CD damage the small intestine epithelial layer. Reduction of absorptive surface area and digestive enzymes, cause impairment of absorption of micronutrients such as fat-soluble vitamins, iron and vitamin B12 and folic acid. [2,3] Sensitivity to gluten is the main pathophysiologic cause of CD and it is characterized by intraepithelial lymphocytosis, crypt hyperplasia and villous atrophy. [4,5] CD has diverse clinical features includes anemia, fatigue, weight loss, diarrhea, abdominal pain, bloating, osteoporosis and depression. [6,7]

The prevalence of CD is estimated to be approximately 1% in western countries. [8,9,10] CD is commonly seen in association with extra intestinal manifestations, such as the typical skin lesions and the neurologic symptoms. [11,12] Because of the broad spectrum of its presentations, the diagnosis may not be so obvious or easy. [13]

Having greater awareness and lower threshold for testing for CD are necessary for diagnosis of this disease.

When CD is suspected, serologic testing is required for screening and subsequently duodenal biopsies are necessary to confirm the diagnosis. [14]

Anti-tissue transglutaminase and anti endomysial Antibodies are highly sensitive and specific for diagnosis of CD, [15,16] but histologic studies are the gold standard for establishing the diagnosis. [17]

In this article we want to review the extra intestinal manifestations of CD and also describe the association between CD and other disorders. It is useful for better diagnosis of CD and improvement of treatment of associated conditions. Future studies should focus on the extra intestinal presentations and associated disorders of gluten sensitivity as they could help better understanding the pathogenesis of gluten sensitivity.

2. CD and Psychiatric Disorders

Association of CD and schizophrenia has been described for years. [18-25] Some studies demonstrate that CD patients are at increased risk of schizophrenia and there is association between them. [18,26] It has recently showed that the immune response to gluten in schizophrenic

patients differs from that in CD. [21,22] Also some studies are against of this association. [27,28]

Association of mood disorders and CD are not obvious. Many authors found positive association [29-35] but others did not. [36,37,38,39]

A few studies have suggested that Attention Deficit Hyperactivity Disorder (ADHD) may be associated with gluten sensitivity. Gluten-free diet was showed to improved ADHD symptoms. [40]

Autism disorders have been associated with gluten sensitivity in some studies. [41,42]

2.1. Conclusion

CD patients are thought to be at elevated risk of developing schizophrenia than the general population.

For accessing the association of mood disorders and CD there is not comprehensive study and contrasting results exist.

Further systematic studies are required for clarifying the probable association and for investigating the pathophysiological pathway of this conditions.

3. CD and Neurologic Disorders

Many neurological manifestations has been related to CD, with a prevalence of 10 to 12%. [43]

Gluten ataxia (GA) and peripheral neuropathy are the more common related disorders, and they can present even in the absence of an enteropathy. In gluten ataxia positive serum antigliadin antibodies exist. [44] In a study by Hadjivassiliou, et al GA accounted for 36% of cases of idiopathic sporadic ataxia. [45]

Peripheral neuropathy related to CD is a symmetrical sensorimotor axonal neuropathy. [46] Gluten sensitivity may be the cause of 34% of patients with idiopathic neuropathy. [45] In a large study the association between CD and polyneuropathy was confirmed. [47]

Early diagnosis and treatment with a gluten free diet can improve both neurological presentations, but not in all patients. [48,49]

Demyelinating diseases like multiple sclerosis have been described to be associated with CD. [50] In one study the prevalence of CD in patients with multiple sclerosis was 11%, [51] but this association was not confirmed in other studies. [52,53]

Dementia could be presented in CD. Dementia have different presentations include acalculia, confusion, amnesia, and personality disorder. [54,55,56,57]

The incidence of epilepsy in patients with CD has been reported as high as 5.5%. The prevalence of CD among epileptic patients is 1 in 127 to 1 in 40 people. [58,59] Complex partial type is the most common form of epilepsy in CD patients.

Other neurological manifestations of gluten sensitivity and CD include inflammatory myopathies, [60] headache, [61] and gluten encephalopathy. [62] White matter abnormalities associated with gluten sensitivity have also been described [63,64,65].

3.1. Conclusion

In patients with any neurological presentation and a positive familial history of CD, other autoimmune

diseases, or malabsorption manifestations, CD should be considered as a differential diagnosis.

More research is required to help differentiating CD from gluten sensitivity and clarifying the mechanisms of gluten-associated psychiatric and neurologic complications.

4. CD and Cardiac Manifestation

Recently some studies reported an increased incidence of CD in patients with idiopathic dilated cardiomyopathy (IDCM) or secondary cardiomyopathy. [66,67,68] Also improvement in cardiac performance, has been reported in patients on gluten free diet presenting CD associated with IDCM and myocarditis. [69,70]

Tugcin B. Polat, et al detected subclinical systolic dysfunction of the left ventricle in patients with CD in whom anti endomyosial antibody reactivity is prominent. [71,72]

The study of Ricardo Schmit T De Bem, et al confirmed other reports in increasing CD prevalence in dilated cardiomyopathy patients and recommended the screening for CD in these patients. [73]

There is some case report of association between CD and cardiomyopathy in the literature. [74,75,76]

But there are a few studies against this association. The study of P. Elfstrom, et al found no association between CD, later myocarditis, cardiomyopathy or pericarditis. [77] Also the study of Enrico Vizzardi, et al indicated that the prevalence of CD in patients with dilated cardiomyopathy is similar to general population. [78]

Association between CD and pericarditis has been reported, but there are limited data about it. [79,80,81]

4.1. Conclusion

The positive association between CD and dilated cardiomyopathy may be explained by nutritional deficiencies such as iron and carnitine but also both disorders could be mediated through inflammation and autoimmune mechanisms.

5. CD and Liver Disease

As shown in the literature review in 10% of cases with the idiopathic rise on liver enzymes, CD was detected. Mild forms commonly ameliorated with a gluten free diet (GFD); but in significant forms, we need other treatments too. [82,83,84] CD has association with different liver disease such as:

1. Primary biliary cirrhosis (PBC)
2. Autoimmune hepatitis (AIH)
3. Primary sclerosing cholangitis (PSC)
4. Nonalcoholic fatty liver disease (NAFLD)
5. Wilson's disease
6. Cryptogenic liver disorder (mild/severe)
7. Viral hepatitis
8. Hemochromatosis

5.1. Primary Biliary Cirrhosis

Association between PBC and CD is around 3% which means the prevalence is 3 to 20 fold higher in PBC compare with the general population. [85,86,87]

Legan, et al in 1978 reported this association for the first time. [88] In large number of patients Kingham and Parker identified this association and found that 6% of CD patients have PBC and 3% of PBC patients have CD. [89] They use endomysial antibodies (EMA) for assessing CD and mitochondrial antibodies for PBC and found that GFD has no effect on mitochondrial antibodies; GFD may normalize the intestinal problems and have role in treatment. [90,91] conversely some other studies deny this association that it may be because of the small cases they have assessed. [92,93]

5.2. Autoimmune Hepatitis

Association between CD and AIH have been reported around 3% to 6% in AIH patients and near 2% in CD patients. [94,95,96]

For the first time, this association has been found in 1970's. [97,98] In both CD and AIH type 2 HLA exists and may explain this relation. Additionally, they have found that GFD may have an adjuvant effect on the treatment of AIH. [99,100]

5.3. Primary Sclerosing Cholangitis

Association between PSC and CD have been reported to be near 4 fold, and significant antibodies have not been found for this association. [85] Conversely Volta, et al have found an association with EMA in these situations. [101] Some studies have reported that GFD has a significant role in the treatment of PSC but the effect on the liver is in controversy and need more studies. [102,103]

5.4. Nonalcoholic Fatty Liver Disease

Some studies have reported that association between NAFLD and CD is around 3%; with 6 fold increase in fatty liver and it may be because of the increased permeability of gut in NAFLD patients. [85,104,105] Many studies have approved that it is a coincident rather than a relation. [106]

Studies have found that for detecting CD, assessing EMA is preferred to tissue trans glutaminase (TTG) because high TTG is not sufficient to confirm the diagnosis. [107]

5.5. Wilson's Disease

In some studies, high levels of copper in the urine of CD patients had detected. That may be because of abnormal copper absorption, but it needs more studies. [108]

5.6. Cryptogenic Liver Damage

This condition divided into 2 subgroups:

5.6.1. Mild Liver Damage

Association in this group has been reported near 18.6% and studies have found that with using GFD after 12 months antibodies will disappear so this kind of liver damage has called "gluten induced hepatitis". [109,110] Different histological and pathologic changes have found

in this type of disease that are reversible with GFD. [111] Bardella, et al found that one of the extra intestinal signs of CD could be unexplained transaminasemia in these patients. [112]

5.6.2. Severe Liver Damage

In a study by Lindgren, et al the prevalence of CD in patients with chronic liver damage was 1.5%. [113] But severe liver damage has an association with CD and using GFD has a significant role in treatment and in some cases even can recover liver function completely. [114]

5.7. Viral Hepatitis

The association between CD and hepatitis B virus is around 11.3% and also studies have suggested that the lack of response to HBV vaccine may be because of genetic and HLA DQ2 in CD patients. [115,116] In other studies association between CD and hepatitis C virus have been assessed to be 1.2%. Also studies found that the symptoms and histological patterns improve with using GFD and it's better to first treat CD and then start treatment for HCV; which means it is better to use GFD before using interferon. [117]

5.8. Hemochromatosis

There is a rare association between CD and hemochromatosis and this association related to genetics. According to different studies mutation in C282Y and H63D genes in CD patient are higher than the normal population. [118]

Paradoxically association between CD and iron deficiency anemia are more published. [119] Iron may deplete in CD patients because of intestinal disorders especially in the proximal small intestine mucosa. Some other studies suggest that blood loss may occur in CD by different causes and leads to iron deficiency anemia. Some other causes described for IDA in CD patients such as reduced expression of regulatory proteins and hemolytic disorders. [120]

5.9. Conclusion

As shown in different studies disorders in intestinal mucosa in CD patients cause a variety of liver disease associated with CD in mainly 15-55% of patients and using GFD is an effective treatment in these cases. Since these associations have been found studies suggest that the first step in evaluating a patient with the idiopathic rise of liver enzymes is to assess for CD and in this assessments EMA is more reliable than TTG.

6. CD and Endocrine Disease

There is different association between CD and endocrine disease in literature, such as:

1. Type 1 diabetes (T1D)
2. Thyroid disease
3. Addison's disease
4. Others

6.1. Type 1 Diabetes

Association between CD and T1D is around 4% and also some studies show that it is higher in children [121,122,123,124] and also these two diseases are almost coincident or sometimes CD is subsequence to diabetes. In some cases it has shown that in CD patients less than 20 years old, risk of T1D is higher. [125] In additional studies, the effect of GFD is discussed and suggest that with using GFD the risk of vascular complications in T1D decreases. Osteopenia in GFD users is lower compared with patients who do not use GFD. [126,127] Some studies have suggested screening for CD in T1D patients. [128]

6.2. Thyroid Disease

Association between CD and thyroid disease such as graves and Hashimoto is near 2-7% that it means 3 fold higher compared to normal population. [129,130,131,132] In several studies, they have suggested different mechanisms for this association such as genetics and gene encoding and the reaction of TTG-2 IgA with thyroid tissue. [132,133] Usage of GFD is in controversy; in some studies they deny protection of GFD and in others they find that using GFD can normalize thyroid antibodies and function after 3 and 1 years. [134,135]

The most frequent manifestation of thyroid disease with CD is hypothyroidism with weight loss and needs of using levothyroxine. [128]

6.3. Addison's Disease

Association between Addison and CD is around 5-12 % and it means patients with Addison are at higher risk for CD. [136,137] In additional studies they have not found any role for GFD in the treatment of Addison disease yet.

6.4. Others

In different studies they have suggested different associations for CD such as adrenal insufficiency (12.5%), hyperparathyroidism (0.3%), alopecia areata (2%) and some with autoimmune hypophysitis. [128]

6.5. Conclusion

Altogether different studies have shown that CD is associated with a variety of endocrine problems such as short stature, delay puberty that these problems may be the only manifestation of CD. Additionally, according to the high association between CD and hypothyroidism and T1D, some papers suggest screening for CD in these patients.

7. CD and Dermatologic Disease

1. Dermatitis herpetiformis(DH)
2. Psoriasis
3. Others

7.1. Dermatitis Herpetiformis

This skin manifestation is now characteristics for CD

and the best treatment is GFD. Different studies have suggested different pathophysiology for DH such as genetics, environmental factors, immune system, predisposing individuals. [138] Gold standard test for diagnosis of DH is immunofluorescence. [139] Also, these patients have positive TTG-2, TTG-3 autoantibodies. In some of the studies they have suggested to do family screening for CD in DH patients. [140]

7.2. Psoriasis

Association between psoriasis and CD has been reported around 4.34% [141] and GFD has an effect on patients' improvement, but studies have shown that with the reintroduction of gluten protein the disease flare-ups. [142,143]

Mechanisms suggested for this association are vitamin D deficiency, exposure to gliadin and intestinal problems in CD. [144,145]

7.3. Others

CD has unclear associations with vitiligo and dermatomyositis, too but it needs more studies to confirm. [144,146]

7.4. Conclusion

According to different mechanisms such as genetics and environmental factors CD have an association with different dermatologic disease such as DH and psoriasis. Studies have shown that GFD is useful in both of these diseases. Also, some studies have shown a rare and unclear relation between CD and vitiligo and dermatomyositis that more studies are needed in this field.

8. CD and Rheumatologic Disorders

CD has association with rheumatologic disease that have been suggested in different studies. These diseases are including:

1. Sjogren's syndrome (SS)
2. Systemic lupus erythematosus(SLE)
3. Juvenile idiopathic arthritis (JIA)

8.1. Sjogren's Syndrome

Association between SS and CD have been reported around 4.5-15% [147,148] and conversely GFD has no effect on SS sign or symptoms and according to different studies this two diseases must treat separately. [149]

8.2. Systemic Lupus Erythematosus

Developing SLE in CD patients is 3 fold higher than the normal population. Some studies have shown an association between HLA-B8 and DR3 and this relation. In additional studies, the marker of CD in SLE patients was an anti gliadin antibody and this association has no relation with sex specificity. [150] Freeman described 6 out of 246 individuals with CD who developed systemic lupus erythematosus during a period of 25 years. [151]

8.3. Juvenile Idiopathic Arthritis

Association between JIA and CD is around 2.5-7% according to different studies. [152,153,154] They have found a genetic role in this association that means cases of JIA in first grade family of CD patients are higher. [155]

8.4. Conclusion

CD has an association with a variety of rheumatologic diseases such as Sjogren's syndrome, systemic lupus erythematosus, and juvenile idiopathic arthritis. In these cases conversely GFD have no effect on treatment.

9. CD and Ophthalmologic Disease

CD has some extra intestinal manifestations that ophthalmologic diseases are in this category. These ophthalmologic diseases are such as:

1. Retinopathy
2. Cataract
3. Pseudo tumor cerebri
4. Orbital myositis
5. Uveitis

9.1. Retinopathy

Retinopathy has an association with CD according to vitamin A deficiency that may happen in CD patients. [156]

9.2. Cataract

Association between CD and cataract caused by diarrhea have been reported. Diarrhea can cause dehydration and rise of urea and ammonia and low level of Ca in aqueous humor and causes lens opacification. [157,158,159]

9.3. Pseudo Tumor Cerebri

Association between CD and pseudotumor cerebri is also because of the low level of vitamin A. [160,161]

9.4. Orbital Myositis

In several case reports, they have suggested a relation between CD and myositis that may because of common immunological basis and high level of anti gliadin antibodies. [162]

9.5. Uveitis

CD also has a rare association with uveitis that early treatment is very important in these conditions. [163]

9.6. Conclusion

Different ophthalmologic manifestations can occur leads to immunological basis, nutrition and damage of intestine and malabsorption in CD patients.

10. CD and Reproductive Problems

Association between idiopathic infertility and CD in women is around 2.1%. 55% of infertile women have gastrointestinal symptoms mostly bloating. [164] Some studies suggest that this association is lower in the Asian population. [165] Additionally, in several studies they have found an association between CD and maternal complications such as low birth weight, fetal loss, preterm labor and also gynecologic complications like endometriosis and amenorrhea. But the effect on sperm motility and androgen level is unknown. [166,167,168,169]

Preferred tests that were used in these studies were EMA and TTG antibodies that have enough specificity and sensitivity. [170] Conversely many cohort studies have not found this association. [171]

Studies have suggested that using GFD would be a good treatment for infertility and in some case reports, they have confirmed the effect of GFD on infertility. [164]

10.1. Conclusion

Different studies have shown association between CD and infertility that the prevalence varied in different studies and altogether the prevalence was higher in European or Middle Eastern and lower in the Asian population.

Additionally, in other studies they have found a relation between CD and maternal and gynecological complications and have found GFD useful for treatment.

11. CD and Associations with Some Other Disease

11.1. Sarcoidosis

Studies suggest that the cause of this association may be genetic and immunological. [172,173]

11.2. Hematologic Disorders

Association of CD and ITP described in 1982 and the mechanism may be due to genetics issue. [174]

11.3. Pancreatic Disease

Association between CD and different type of pancreatic disorders have different prevalence such as 1.86% in non-gall stone acute pancreatitis and 1.59% in gall stone acute pancreatitis and 3.33% in chronic pancreatitis. [175,176]

11.4. Microscopic Colitis

Association between microscopic colitis and CD is up to 15% and microscopic colitis found in 4% of CD patients. [177,178].

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