

EXPERT
REVIEWS

Celiac sprue: a unique autoimmune disorder

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Celiac sprue (CS) is a gluten-sensitive enteropathy with many autoimmune features. CS involves multiple organs through immune and nonimmune processes, and is frequently associated with other autoimmune disorders. This article reviews the co-occurrence of CS with autoimmune disorders of the cutaneous, nervous, endocrine, musculoskeletal, gastrointestinal and cardiovascular systems. The types of autoimmune disorders associated with CS and the prevalence of CS in other autoimmune disorders are discussed as well. A brief review of the literature on the potential mechanisms behind these associations and the therapeutic effects of a gluten-free diet for autoimmune comorbidities in CS is also provided.

KEYWORDS: ataxia • autoimmune • autoimmune biliary cirrhosis • autoimmune hepatitis • celiac sprue • dermatitis herpetiformis • neuropathy • sjögren syndrome • thyroid disorder • Type 1 diabetes

Celiac sprue (CS), also known as celiac disease, is a chronic enteropathy occurring in genetically predisposed individuals as a result of an immune reaction to ingested wheat gluten and related protein fractions of other grains [1]. CS has several characteristics of an autoimmune disorder. These include the presence of disease-specific autoantibodies (i.e., tissue transglutaminase antibodies), strong association with MHC class II molecules, co-occurrence with other autoimmune disorders, multiorgan involvement, and dysregulation of innate and adaptive immune responses [2–4].

It is hypothesized that tissue transglutaminase at the gut level deamidates specific glutamine residues of incompletely digested gliadin-derived peptides. This results in increased affinity of T cells to these deamidated peptides [5]. Under certain conditions, tissue transglutaminase–gliadin complexes may also form. Such complexes may be important in epitope spreading from gliadin to tissue transglutaminase, resulting in the formation of tissue transglutaminase antibodies [6,7]. The T cells specific to deamidated gliadin peptides in the complex provide help to the B cells specific to tissue transglutaminase, resulting in the production of antitissue transglutaminase antibodies (FIGURE 1) [7]. Since enteropathy and autoantibodies resolve with the removal of an external trigger (gliadin), CS may be placed in a unique category of reversible autoimmune diseases, which includes seronegative arthritis and drug-induced SLE.

Celiac sprue & autoimmunity

Autoimmune disorders are three-to-ten-times more prevalent in CS than in the general population, occurring in 12–30% of CS patients [8–14]. The prevalence of autoimmune diseases among the relatives of CS patients is also significantly higher than the relatives of healthy controls (4.8–4.9% vs 0.86–1.1%, respectively) [15,16]. In the relatives of CS patients who have a positive celiac serology, the prevalence of autoimmune diseases is reported to be as high as 20%. Correspondingly, CS occurs in 1.5–7% of patients with other autoimmune diseases [17,18]. Notably, clinically silent CS (enteropathy without clinical symptoms) has been found in 25% of the individuals who are affected by autoimmune disorders and have a family history of CS [16].

Mechanism

Several potential mechanisms have been proposed to explain the association of autoimmune diseases and CS (FIGURE 2). The first mechanism is linkage disequilibrium between the genes that predispose to both CS and other autoimmune disorders [19]. The HLA molecules that are strongly associated with CS (HLA-DQ2 or HLA-DQ8) are also associated with other autoimmune disorders [20,21]. In addition, CS and other autoimmune diseases may also share multiple non-HLA loci [22]. This is further supported by the studies that showed a higher prevalence of autoimmune diseases among family members of CS patients [15,16,23].

Second, disruption of the intestinal barrier following a gluten-initiated inflammatory response may lead to the exposure of the immune system to hidden self-antigens or unknown external triggers of other autoimmune disorders [19,24]. The presence of persistent immunologic activity in the gut can then enhance the

processing and presentation of the self-antigens to the T cells [19]. The evidence for this theory comes from the studies that showed an increased prevalence of autoimmune disorders in both CS and Crohn's disease, since intestinal permeability is increased in both diseases [10,25].

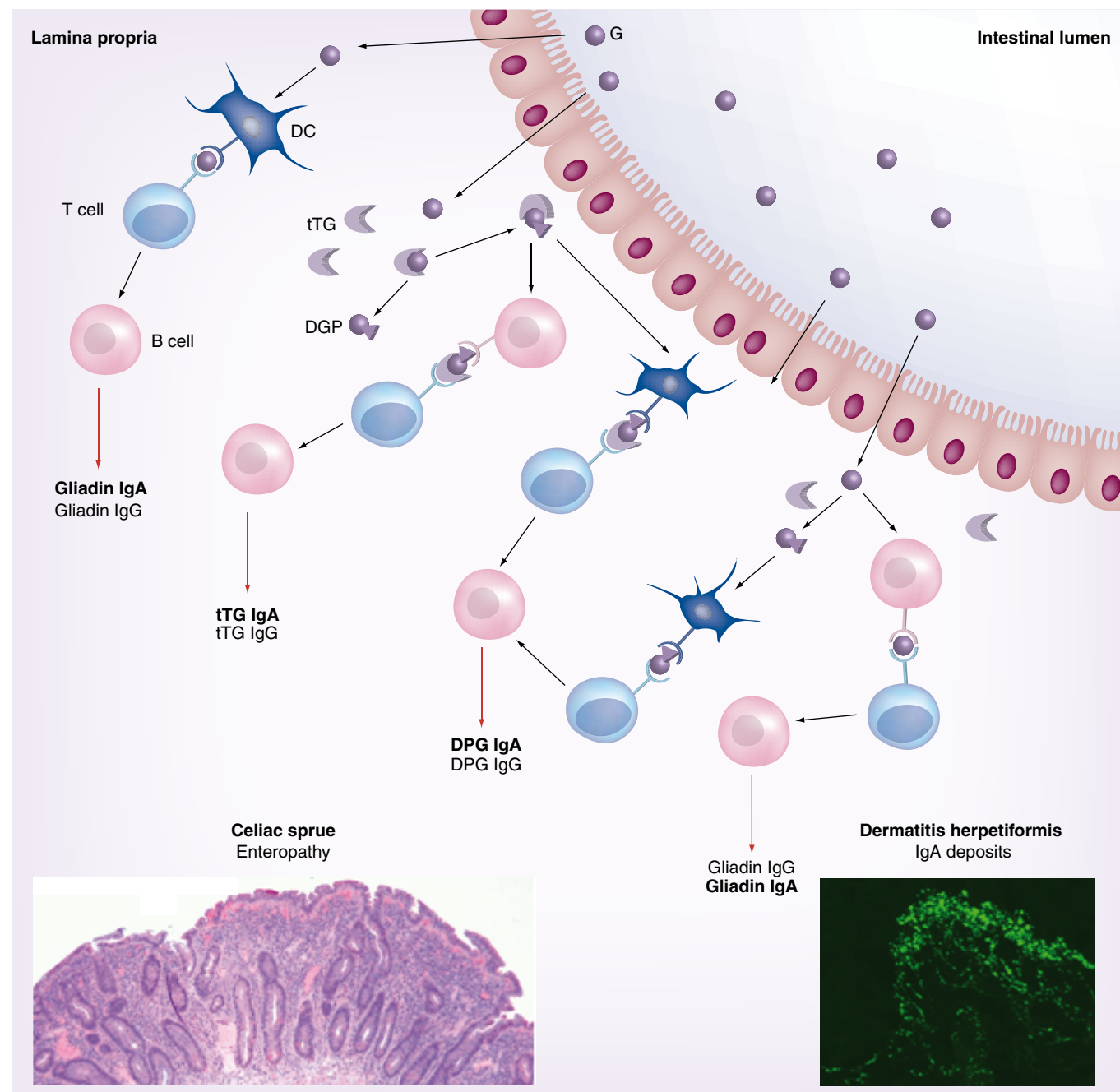


Figure 1. Pathogenesis of gluten-sensitive disorders. The two gluten-sensitive disorders, celiac sprue and dermatitis herpetiformis, are the consequences of an abnormal autoimmune response that occurs in the intestine in genetically susceptible individuals (HLA-DQ2 or -DQ8 positive). tTG forms a complex with G and deamidates specific glutamine residues of these peptides. DGP are then presented to T cells by DCs or B cells. The T cells then provide help to the B cells, resulting in the production of antibodies (mainly IgA but also IgG) against gliadin and DGP, as well as antibodies specific for tTG. These abnormal responses triggered by gliadin can result in either celiac sprue (with mucosal inflammation and loss of villi) or dermatitis herpetiformis (with IgA deposits in the dermal papillae), or even both. DC: Dendritic cell; DGP: Deamidated gliadin peptide; G: Gliadin peptide; tTG: Tissue transglutaminase.

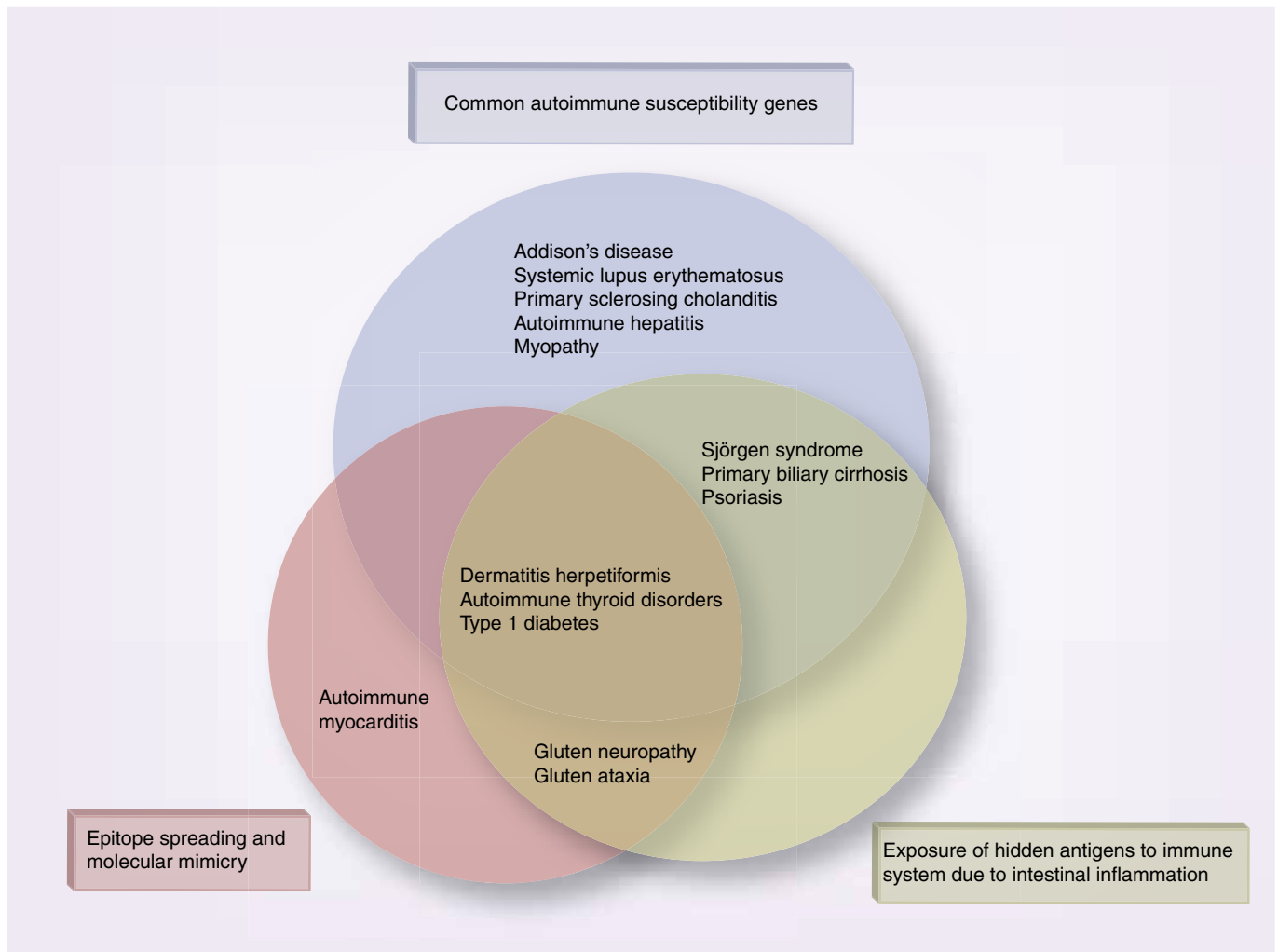


Figure 2. Potential mechanisms behind the association of celiac sprue and other autoimmune disorders.

The third potential mechanism for the co-occurrence of autoimmune diseases and CS may be epitope spreading and molecular mimicry, since a higher incidence of organ-specific autoantibodies have been found in CS patients [14,26–28]. Whether a gluten-free diet can decrease the development of autoimmune disorders in CS patients is a matter of debate. Some studies have shown a favorable effect of gluten-free diet on the incidence of autoimmune diseases [11], while others failed to show a protective effect [13,29–31].

Autoimmune diseases associated with celiac sprue **Dermatologic disorders**

Many autoimmune diseases have skin involvement and CS is no exception [32]. Several autoimmune cutaneous diseases have been described in CS, including dermatitis herpetiformis, psoriasis and alopecia areata. Vitiligo, cutaneous vasculitis, lupus erythematosus, dermatomyositis, IgA linear dermatosis and bullous pemphigoid have also been occasionally reported in CS patients. Potential mechanisms for the associations amongst these autoimmune cutaneous diseases and CS include increased intestinal permeability and shared genetic backgrounds [33,34].

Dermatitis herpetiformis

Of the autoimmune diseases that are associated with CS, dermatitis herpetiformis (DH) stands out for a number of reasons. DH is an autoimmune gluten-sensitive skin disease that presents with intensely pruritic papulovesicles and excoriations on the knees, buttocks, elbows, and back. Similar to CS, nearly 100% of DH patients have either DQ2 or DQ8 [20], and both diseases share a common pathogenesis (FIGURE 1). Discordance in monozygotic twins where one twin has developed CS and the other DH, indicates that environmental factors determine whether DH or CS will develop in individuals who are genetically predisposed to both diseases [35]. Only 10–20% of DH patients have gastrointestinal symptoms, even though most DH patients show intestinal alterations consistent with CS [7,34,36]. As such, DH has been called the ‘skin manifestation of gluten-sensitive enteropathy’ [36,37].

The similarities between DH and CS extend to the autoantibodies as well, although the presentation, titer and affinity are different between the two groups of patients [7,38]. The two main autoantibodies are antitissue transglutaminase (tTG) and anti-epidermal transglutaminase (TGe), with anti-TGe found in DH, and anti-tTG in CS and in most cases of DH. Elastin has also been suggested as

a possible autoantigen in DH owing to the cross-reactivity between glutenin and dermal elastin [39]. As such, these antibodies are clearly directed against self-proteins and can be considered an autoimmune feature of both CS and DH. It is not clear, however, whether these antibodies alone are pathognomonic. With DH, the IgA deposits in the dermal/epidermal junction are considered to be pathogenic, since lesions only develop in areas that have IgA deposits. However, studies carried out with severe combined immunodeficient mice using sera from DH patients would suggest that the circulating antibodies in the DH sera are not pathogenic alone [40]. Our studies with an HLA-transgenic mouse model of DH have also yielded similar results in that sera from blistered mice transferred to non-blistered mice did not yield blistering lesions [MARIETTA EV, DAVID CS, PITTELKOW MR, MURRAY JA, UNPUBLISHED DATA]. Thus, the antibodies against transglutaminases found in DH are elements of autoimmunity, but may not be sufficient alone for pathology to occur.

Owing to the role of DQ2 and DQ8 in the generation of gliadin-specific T cells in CS, it is thought that at some point, T cells specific for gliadin may play a significant role in the development of DH. However, as of now, no gliadin-specific T cells have been cloned or detected in the small intestine of DH patients as was found with CS patients. Differences were found in the variable regions of the β -chain of the TCR however, indicating that there are some differences in the T-cell repertoire of the DH patients versus healthy controls [41].

Current therapies available for treating DH are dapsone and a gluten-free diet [42]. The gluten-free diet is quite effective in resolving the blistering and also decreases the likelihood of developing lymphomas [43]. Dapsone can be used in conjunction with a gluten-free diet for initial suppression of the rash or during the occasional outbreaks. Nonetheless, dapsone therapy alone does not have a favorable effect on enteropathy; for example, it does not decrease the likelihood of developing lymphomas. There are also toxicity problems associated with the use of dapsone, including hemolysis, methemoglobinemia and agranulocytosis [44].

Psoriasis

Psoriasis presents with inflamed raised scaly plaques, usually on the extensor surfaces. Psoriasis is considered an autoimmune disorder, since self-reacting T lymphocytes play a central role in keratinocyte hyperproliferation [45,46]. Autoantigens that have been identified include self-DNA as well as an antimicrobial peptide known as LL37, which is secreted by keratinocytes and neutrophils in response to damage to the skin. Specifically, plasmacytoid dendritic cells aberrantly sense extracellular self-DNA coupled with LL37, resulting in skin inflammation and the development of psoriasis [47].

Common pathologies with CS include high levels of anti-gliadin antibodies, which are reported in 8–16% psoriasis patients, and villous atrophy, which is found in 4.3% of psoriasis patients [48,49]. A gluten-free diet was shown to improve psoriatic lesions significantly in patients with high titers of gliadin antibodies [50].

Alopecia areata

Alopecia areata is a T-cell-mediated autoimmune disease presenting with nonscarring patchy hair loss on the scalp or other hair-bearing surfaces. The co-occurrence of CS and alopecia areata has

been mainly based on case reports. Some authors have shown an increased prevalence of CS among patients with alopecia areata, while others did not find any association between the two diseases in the large series of CS patients [23,51–53]. The effect of a gluten-free diet in alopecia areata is controversial. Regrowth of hair after administration of a gluten-free diet has been reported in several cases [14,51,52,54], while others failed to show a beneficial effect [55,56].

Endocrine disorders

Type 1 diabetes

Type 1 diabetes (T1D) is closely associated with CS. The risk of CS is eight-times higher in T1D patients than in the general population [57], occurring in 3–7% of these patients [58,59]. Similarly, 2–7% of CS patients have T1D, showing a two to tenfold increased risk compared with the general population [11,23,60,61]. T1D-related autoantibodies occurs in 2–11% of CS patients [14,62,63]. This is owing in great part to the association of HLA-DQ2 and -DQ8 with both diseases [21,64]. CS autoantibodies (anti-tTG IgA) are found in one-third of the DQ2-positive T1D patients, but only in 2% of those without DQ2 [65]. Nonetheless, CS and T1D also share several non-HLA loci, as assessed through genotyping the DNA samples from large number of CS patients, T1D patients and controls [22]. It appears that in the majority of cases, the diagnosis of T1D precedes that of CS [14]. It may be possible that the ongoing intestinal inflammation in undiagnosed CS results in the migration of self-reactive lymphocytes from the gut to the intestinal lymphoid tissue (draining lymph nodes) and the islet cells of the pancreas leading to the development of T1D [66,67]. It is also shown that many celiac patients develop autoantibodies specific to the other organs, suggesting a role for humoral immunity in the development of T1D [62]. Gluten ingestion may therefore induce autoimmunity in organs other than the intestine [10].

The effect of a gluten-free diet on T1D-related autoantibodies and the likelihood of developing T1D is a matter of controversy [24,62,63,68]. The nonobese diabetic mouse model of T1D has suggested that a gluten-containing diet will increase the incidence of diabetes. This gluten-induced diabetes is associated with an increased level of inflammation in the form of inflammatory T cells, cytokines and chemokines [69]. However, none of these studies have demonstrated convincingly that a gluten-free diet will cure or prevent diabetes. More studies need to be done on the effect that a gluten-containing diet has upon the generation of T1D autoantibodies. Studies in HLA-transgenic mice that have served to be useful models of both T1D and gluten sensitivity are ongoing [70–74].

Thyroid disorders

Autoimmune thyroid disorders are two to 4.4-times more prevalent among CS patients than the general population [75–77]. In a prospective study of 14,021 CS patients (1964–2003), the hazard ratios (HRs) for development of thyroid disorders were 4.4 for hypothyroidism, 3.6 for thyroiditis and 2.9 for hyperthyroidism [77]. In a smaller study of 107 CS patients, 15 (14%) had autoimmune thyroid disorders, with 10.3% being hypothyroid and 3.7% hyperthyroid [78]. This is while the expected numbers in the population were 1.5 and 0.7% for hypothyroidism and

hyperthyroidism, respectively [78]. Of 15 patients with both thyroid disorders and CS, the diagnosis of thyroid disease preceded that of CS in 11 patients and was made simultaneously with CS diagnosis in three patients. In one patient, thyroid disease was developed 5 months after celiac disease diagnosis while the patient was on a gluten-free diet [72].

The prevalence of CS in autoimmune thyroid disorders is 2–5%, which is higher than expected [17,75,79]. These associations may be due to genetic predisposition generated by specific HLA genes, as well as non-HLA genes such as cytotoxic T lymphocyte-associated antigen-4. Another potential explanation for the associations would be molecular mimicry between gliadin epitopes and self epitopes, resulting in cross-reactive T cells [17,80]. Antithyroid (antithyroglobulin and antimicrosomal) autoantibodies are found in 26–29% of CS patients [76,78]. While several studies have shown a decrease in the levels of these antibodies after gluten exclusion [62,81], others failed to report such a beneficial effect [76].

Addison's disease

Autoimmune Addison's disease is a primary failure of the adrenal gland, caused by the lymphocytic aggression and destruction of the adrenal cortex in genetically susceptible individuals. Adrenal cortex autoantibodies or 21-hydroxylase autoantibodies are present in more than 90% of patients at the onset of the disease [82]. The prevalence of CS in patients with Addison's disease is 5–12% [83–86]. Conversely, in a cohort of 14,366 Swedish CS patients, 0.25% of CS patients had Addison's disease compared with 0.02% of controls (HR: 11.4; 95% CI: 4.4–29.6). Shared genetic traits have been proposed to explain this association [87].

Neurologic disorders

Diverse neurologic manifestations are commonly associated with CS, occurring in 6–23% of these patients [88–91]. These include neuropathy, ataxia, epilepsy (with cerebral calcification), headache, depression, neuromuscular complications, movement disorders, cerebral vasculitis, dementia and autism [88,89,92–97]. Among these, gluten neuropathy and ataxia are the most common and probably occur through an autoimmune process [98].

Neuropathy

Peripheral neuropathy is one of the most common neurologic manifestations of CS. One systematic study found evidence of chronic axonal neuropathy in six out of 26 CS patients (23%), as measured by quantitative needle electromyography [99]. Another study reported three or more signs of peripheral neuropathy in approximately 28% of CS patients [100]. Conversely, CS is found in 1.5–8% of patients with neuropathy [101], although not all studies agree [102]. It should be noted, however, that in a study that failed to report a higher prevalence of CS in neuropathy patients with unknown etiology, all subjects with ataxia or symptoms of small-fiber neuropathy were excluded, and 15 patients were not evaluated as they had either died or were lost to follow-up [102,103].

Antibodies to ganglioside molecules of the peripheral nerves are commonly found in neuropathic patients. These antibodies have been reported in as many as 65% of CS patients with

neuropathy [101], but there is an inconsistency regarding the correlation of these antibodies with neurologic dysfunction [91,104]. The effect of a gluten-free diet in the disappearance of these antibodies is also controversial [104,105]. Several reports have described a beneficial effect of a gluten-free diet in the resolution of neuropathic symptoms [106–108], while other studies did not support any favorable outcome for gluten exclusion in well-established neurologic symptoms of CS [99,105].

Celiac sprue is also associated with autonomic neuropathy. Biopsy-proven CS is detected in 2.4% of patients evaluated for autonomic dysfunction [109]; and autonomic neuropathy (defined by attaining a pathologic score in the standardized measurement of cardiovascular reflexes) is reported in 19% of CS patients [110]. Another study has found evidence of autonomic nerve damage in 25% of CS patients who had autonomic symptoms such as vertigo, weakness, (pre)syncope and postural nausea [105]. The pathogenic mechanisms behind the development of autonomic neuropathy in CS are still unclear, although autoimmune processes and metabolic disturbances have been proposed as potential mechanisms [110]. It appears that a gluten-free diet does not favorably change the outcome of autonomic dysfunction in CS patients [105,109].

Cerebellar ataxia

Cerebellar ataxia is the other common neurologic manifestation of CS. Biopsy-proven CS is found in 2–17% of patients with unexplained cerebellar ataxia [89]. A higher prevalence of positive antigliadin antibodies (on average 30%) has also been reported in patients with idiopathic ataxia, a condition described as 'gluten ataxia' [89,111,112]. Nonetheless, the role and relevance of gliadin antibodies is not clear in unexplained ataxia [113], since a high prevalence of these antibodies is also found in Huntington's disease and hereditary ataxia [114,115]. One study has shown that anti-tTG IgA deposits are present in the jejuni of patients with unexplained ataxia and increased gliadin antibodies, in a pattern similar to the intestine of CS patients [116]. By contrast, no villous atrophy or intestinal deposition of tTG antibody was found in gliadin antibody-positive patients who had a known etiology for their ataxia [116]. Similarly, the level of tTG and deamidated gliadin antibodies, which are more specific for CS than the gliadin antibodies, are found to be significantly higher in patients with ataxia and CS as compared with those without intestinal pathology [113,117–120]. These data suggest that the intestinal damage is probably a crucial step in the development of ataxia in these patients, and that native gliadin antibodies alone are not indicative of gluten-mediated damage in ataxic patients with no mucosal pathology.

The beneficial effect of a gluten-free diet has not been clearly demonstrated in gluten ataxia [121]. Nonetheless, reports on improvement of symptoms after intravenous immunoglobulin treatment in some patients are suggestive of an immune pathogenesis for ataxia in CS [122]. There is no systematic study on the role of cell-mediated immunity in neurologic complications of CS [103]; however, a humoral response has been implicated as the pathogenesis of ataxia in CS patients. The evidence for this comes from a study showing high titers of antibodies against Purkinje cells in the sera of CS patients with ataxia but to a much lesser

degree in those without ataxia. Cross-reactivity of gliadin antibodies with epitopes on Purkinje cells and synapsin I is another potential mechanism [123,124]. It is not clear how antigliadin and antineuronal antibodies gain access to the central nervous system. Deposition of anti-tTG IgA in the brain vessels may cause vascular inflammation and disruption of the blood–brain barrier, leading to the entrance of these antibodies into the brain [116].

Myopathy

Various neuromuscular disorders have been reported in CS, such as inclusion body myositis and idiopathic polymyositis. Nonetheless, myopathy is a less common manifestation of CS. The etiology of inclusion body myositis is unknown; however, a cytotoxic T-cell-mediated autoimmune process is implicated in the pathogenesis of this condition. Evidence for the autoimmune pathogenesis of muscular involvement in CS comes from the strong association with HLA-DQ2, the presence of autoantibodies, and the co-occurrence with other autoimmune diseases [96,97,125].

Rheumatologic disorders

Sjögren syndrome

Celiac sprue affects as many as 15% of patients with primary Sjögren syndrome [126]. In a study of 111 Hungarian Sjögren patients, the prevalence of biopsy-proven CS was 4.5%, significantly higher than the general population [127]. A shared genetic background and autoimmune predisposition may explain the association between CS and primary Sjögren syndrome [128]. However, mucosal gluten sensitivity measured by mucosal production of nitric oxide after rectal challenge with gluten has been reported in 25% out of 20 patients with Sjögren syndrome, even in the absence of CS [128].

Other rheumatologic disorders

Celiac sprue has been reported in 2.5% of juvenile rheumatoid arthritis patients [129]. While gliadin IgG antibodies are detected in as many as 47% of rheumatoid arthritis patients [130], their presence is not shown to be a predictor of CS [131]. In a study of 267 children with CS, juvenile rheumatoid arthritis was found in two (0.7%) patients, one of which went into remission 15 months after treatment with a gluten-free diet [14].

The association between CS and systemic lupus erythematosus (SLE) is mainly limited to a few case reports in the literature. However, of 246 CS patients followed for 2–10 years 2.4% developed SLE, despite being on a gluten-free diet [132]. The coincidence of CS and SLE may be due to the presence of HLA-DR3 in both diseases [132,133]. Although gliadin antibodies are frequently found in SLE patients, they are not predictors of CS in this population [134].

There may also be an association between CS and Kawasaki disease (febrile systemic vasculitis of children), since a high prevalence of CS (5.5%) has been reported in these patients [135].

Gastrointestinal disorders

Two main categories of liver damage are associated with CS. The most common form is celiac hepatitis. This occurs in almost half of CS patients and is characterized by increased levels of transaminases

and mild liver dysfunction. This form of hepatitis usually responds to gluten exclusion. CS is also associated with immune-mediated liver disorders such as autoimmune hepatitis, primary biliary cirrhosis and primary sclerosing cholangitis. By contrast to celiac hepatitis, gluten-free diet does not seem to have a beneficial effect on CS-associated autoimmune liver disorders [136,137].

Autoimmune hepatitis

Celiac sprue is found in 3–6% of patients with autoimmune hepatitis [136,138,139]. Anti-tTG antibodies are frequently elevated in autoimmune hepatitis patients [140,141], particularly in those with a HLA-DQ2 or -DQ8 background. It is shown, however, that these antibodies regress after liver transplantation without gluten exclusion and many of such patients do not have intestinal pathology [140]. In patients with liver disorder, there is a high number of false-positive results with tTG-IgA testing [142,143]. On the other hand, the specificity of anti-endomysial antibodies remains high in patients with autoimmune liver disorders (~100%). It is therefore recommended that patients with autoimmune hepatitis and positive tTG-IgA be tested for anti-endomysial antibody prior to intestinal biopsy to avoid unnecessary endoscopy and biopsy [137,141].

Primary biliary cirrhosis

Primary biliary cirrhosis (PBC) is characterized by a slowly progressive autoimmune destruction of the intrahepatic bile ducts and primarily affects women [144]. The prevalence of biopsy-proven CS is found to be 4–7% in patients with PBC [137,145]. Conversely, PBC is more prevalent in CS patients than the general population, with a standardized incidence ratio of greater than 25 [146]. In a study of 4732 adults with CS, PBC was found in 0.17% of these patients (odds ratio: 3.6) [147]. In another population based study of 250,000 people, the prevalence of PBC was 3% in 143 CS patients [145]. A shared susceptibility of biliary and small bowel epithelium to autoimmune destruction may explain this association [145]. It is been shown that liver enzyme levels and PBC symptoms do not improve on a gluten-free diet [148].

Primary sclerosing cholangitis

Primary sclerosing cholangitis (PSC) is a progressive inflammation and scarring of the large bile ducts of the liver. Although the association of CS with PSC is weaker than with other autoimmune liver disorders, CS is reported in approximately 2–3.7% of patients with PSC [136,149]. In a population-based study of approximately 14,000 CS patients, PSC was found in 0.19% of patients, a prevalence significantly higher than the general population (HR: 4.5) [150]. The association between CS and PSC is probably due to the presence of a shared genetic risk factor, HLA-DQ2 [151].

Cardiovascular disorders

The association between CS and cardiac diseases comes from reports showing an increased prevalence of CS in patients with myocarditis. After serologic screening of 187 consecutive cases of autoimmune myocarditis, biopsy-proven CS was found in nine

of these patients (4.8%). All nine patients had HLA-DQ2, and their myocarditis improved after the administration of a gluten-free diet [152]. A common autoimmune reaction towards cardiac antigens, perhaps due to antigenic mimicry, has been proposed as a potential mechanism [152]. Co-occurrence of CS and dilated cardiomyopathy is reported in a few cases [153,154]. CS is found in 2.1% of patients with inherited or sporadic dilated cardiomyopathy and in 2.6% of patients with advanced cardiomyopathy upon serologic screening [155,156]. Nonetheless, a population-based study of CS patients did not reveal an increased prevalence of myocarditis or dilated cardiomyopathy among them [157].

Childhood celiac sprue & autoimmunity

Celiac sprue is one of the most common chronic diseases in children. Similar to the adult population, CS is more prevalent in children with autoimmune disorders as compared with controls. The prevalence of CS is reported to be 7.8% in children with autoimmune thyroid disorders [158] and 1–16% (4.5% on average) in those with T1D [159]. In a multicenter study of pediatric patients in Italy, CS was present in 16% of children with autoimmune liver diseases [160]. Conversely, a higher prevalence of autoimmune disorders (14%) is found in children and adolescents with CS as compared with healthy controls [10]. Another study on 267 children with CS has shown that 12% of these patients have clinical autoimmune disease (with signs/symptoms), and 15% have subclinical (with autoantibodies and subclinical impairment of the target organ) or potential (with autoantibodies only) autoimmune disease.

Several studies have shown that the age at diagnosis of CS is significantly associated with increased risk of autoimmunity [10,31]. While some attribute this association to the duration exposure to gluten [10], others have not found gluten exposure as an important factor in increasing the risk for autoimmunity [31]. However, early introduction of gluten to the infants' diet (before 3 months of age) is associated with an increased risk for the development of both anti-islet and anti-tTG autoantibodies [159].

Expert commentary

The association of CS with other autoimmune disorders is well established. There is a higher prevalence of CS in autoimmune diseases such as T1D, autoimmune thyroiditis, Addison's disease, Sjögren syndrome, autoimmune hepatitis and primary biliary cirrhosis than the general population. Conversely, these autoimmune disorders are more common among CS patients than expected. Currently, there is not enough evidence to justify routine screening for CS in all patients with such autoimmune diseases. Exceptions might include hepatitis, as celiac hepatitis may mimic autoimmune hepatitis. It is very important for the physicians to be aware of these associations and to keep CS in mind when they encounter patients afflicted by autoimmune disorders. It should be noted that most studies regarding the association of CS with autoimmune diseases followed the patients for only a short time. With long-term follow-up, a stronger association between CS and other autoimmune disorders may become evident. Currently, there is enough evidence to justify testing

for CS in patients with these associated autoimmune disorders who also have another risk factor for CS such as a positive family history or atypical symptoms (i.e., unexplained anemia).

Serologic tests are frequently used to detect CS. These include tissue transglutaminase antibodies, anti-endomysial antibodies and newly developed deamidated gliadin antibodies. HLA typing may not be particularly useful in this circumstance, since many of these patients share the same HLA as the CS patients, resulting in a low positive-predictive value. When serology is positive, intestinal biopsy should be performed to confirm the diagnosis of CS and evaluate the degree of mucosal damage. It is not evident that early treatment with a gluten-free diet can cure or prevent the progression of the autoimmune diseases in CS patients. Nonetheless, a gluten-free diet would certainly benefit these patients by lowering the CS-associated morbidity and mortality [161,162]. Whether CS patients should be screened for other autoimmune diseases is also a matter of debate. Screening in presymptomatic settings may be done by measurement of specific autoantibodies to predict future development of each autoimmune disorder. Yet, therapeutic options to prevent overt autoimmune disorders in at-risk patients are still lacking. In conclusion, understanding the association between CS and other autoimmune diseases can increase awareness towards each condition, leading to fewer numbers of undiagnosed cases and increased patient care. Studies on potential therapeutic options are necessary to prevent future disease development in those who are found to be at increased risk.

Five-year view

In 5 years, we would expect that the advances in intestinal and mucosal immunology will provide answers as to why disruptions to gut integrity can affect the development of many autoimmune disorders. There is clear evidence today that components of autoimmunity in CS are a direct consequence of the consumption of gliadin. Other studies would suggest that gliadin consumption results in a combination of nonspecific and multi-antigenic stimulation of the intestine, which then contributes to the development of autoimmune diseases secondary to celiac disease, such as T1D. Several experimental approaches are being tested in human trials. It is also expected that therapies for CS that interrupt or abrogate the aberrant intestinal immune response to gliadin will be forthcoming, based on a group of abstracts presented at the *13th International Coeliac Disease Symposium 2009* that focused on future therapies [163]. In addition, genetic analysis of HLA-associated autoimmune diseases will probably provide a better understanding of the complex genetic makeup of the individual diseases, which in turn would allow us to better predict future development of each specific disorder.

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Key issues

- Celiac sprue (CS) is a unique autoimmune disorder caused by sensitivity to gluten and characterized by enteropathy.
- CS involves multiple organs and is associated with other autoimmune diseases.
- Dermatitis herpetiformis is the skin manifestation of CS and peripheral neuropathy and cerebellar ataxia are common neurologic complications in CS.
- CS is associated with several autoimmune disorders, including, but not limited to, Type 1 diabetes, autoimmune thyroid disorders, autoimmune Addison's disease, Sjögren syndrome, primary biliary cirrhosis and autoimmune hepatitis.
- Potential mechanisms for the co-occurrence of CS and other autoimmune diseases include a common autoimmune susceptibility, shared genetic background, exposure of hidden antigens to the immune system (due to loss of intestinal barrier), epitope spreading and molecular mimicry.
- Physicians should be aware of such associations and bear CS in mind when they encounter patients with related autoimmune disorders. Screening for CS is particularly justified in the presence of additional risk factors such as a positive family history or the presence of atypical symptoms.

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