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'Gastroenterology in Pediatrics: Current knowledge about some common disorders'

Editor

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CELIAC DISEASE IN CHILDREN

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REVIEW ARTICLE

Celiac disease in children

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Abstract:

In this review; the definition of celiac disease, etiopathogenesis, clinical and histopathologic characteristics are viewed especially for childhood.

Key words: Celiac disease, children

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Celiac disease (gluten sensitive enteropathy, gluten enteropathy, celiac sprue) in genetically susceptible individuals, to be emerging with consumption of gluten-containing foods, involves the small intestine and characterized by permanent intolerance to gluten (1). As being the most common cause of malabsorption in childhood, this disease affects children and adults for life (1). Celiac disease (CD) was discussed with Cappadocian Aretaesus for the first time in second century, however; a residential town, Catalhoyuk, 60 km away from Konya, has taken place in the B.C. era for CD (2). Archaeological excavations are still continuing in this town which owns the first settlement in human history, the first house architecture and the first sacred structure (3). As being passed on to the first permanent settlement, more wheat was consumed resulting CD to be frequently encountered (2-4). Clinical signs of the known form of the disease were described by Samuel Gee in 1887(2-4). The criteria for the diagnosis of the disease were designated by the European Pediatric Gastroenterology, Hepatology and Nutrition Association (ESPGAN) in 1969 and the criteria were updated again in 1990. The

criteria were reviewed and discussed in ESPGHAN 2010 Congress (5).

Epidemiology

In the pathogenesis of CD, environmental factors are also active with genetic factors, territorial and racial differences are significant in terms of frequency. Disease is more common in women. Incidence of the disease is 75% in monozygotic twins and this ratio is 10% in siblings. CD incidence is more

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common in some diseases such as Type 1 diabetes mellitus, Down syndrome, IgA deficiency, thyroid diseases, Addison's disease and osteopenic bone disease than society (6,7).

It's known that CD will not arise unless presence of gluten in diets. Accordingly, CD is seen frequently in countries like Turkey, UK, Australia, Europe, North America in which wheat has an important role in nutrition, whereas it is almost never seen in China and Japan. Studies in time have revealed that genetic factors alone cannot ensure the emergence of the disease. Viral and bacterial infections, smoking, immune status and infant nutrition are suspected environmental factors to blame. Among suspected factors, the most notable one is an inverse correlation between long-term breastfeeding and risk of developing CD. With the support of the progress in endoscopic examinations and biopsy procedures in 1950's, an increase in CD diagnosis was noted (7).

Maki et al. in Finland, performed a study in 3654 healthy students on the 7-16 age groups, supported by biopsies and found CD prevalence as 1:99 (8). It is also reported that actual prevalence in this study might be more than reported value of 1:99, because biopsies were not taken from all of the seropositive cases (8). Rutz et al. in Switzerland, studied on 1450 healthy students aged 12-18 and prevalence of CD was found at a high value of 1/132 (9). This rate is 10 times higher than previous data reported from the same region 20 years ago (9). Similarly, in 15 study centers covering the whole country in Italy, 17201 students on the 6-15 age groups were searched for CD in 1996 and prevalence was found to be 1/210 (10). In the United States, previously, CD is believed to be a rare disease and affect only the European descent (11). In

recent publications prevalence is reported to be close to the values among risk groups and in the general population in both European and the Scandinavian countries (11). A study in blood donors showed a CD prevalence of 1/250 in 1998 (11). Fasano et al. reported the prevalence of CD in the United States among risk groups and in the general population as 1/22-1/39 and 1/133 respectively (12). The status in Turkey is not very different from these reports. In our country, a field work investigating the prevalence of CD in healthy adults has not been performed. Gursoy et al. studied to determine prevalence of CD in 906 patients admitted to hospital for various reasons on the 20-59 age groups in Kayseri and detected a CD prevalence of 1% (13). In this study, patients admitted to hospital or patients with chronic diseases were included, thus the results do not reflect the characteristics of a healthy population (13). In our country, the first study investigating the prevalence of CD in healthy children is the study of the school-age children on the 6-17 age groups which Ertekin and colleagues performed in Erzurum (14). In this study 1263 school-age children were included and the prevalence of CD was found as 1/115 (14). In a similar study, Demirceken et al. found the prevalence of CD as 0.9% in 1000 children (15). The first mass screening for CD in Turkish school children was carried out by Dalgic et al. Anti tTg positivity was reported as 2.4% in this study. Unfortunately intestinal biopsy was not accepted all antibody positive children. They found the biopsy proven prevalence of CD as 0.47% in Turkish children between the ages of 6-17 (16).

Immune barrier & immuno-pathogenesis & genetics

The intestinal epithelium has two critical functions. One of them is to act as a barrier preventing passage of microorganisms, toxins and antigens. The other function is filtering

nutrients, electrolytes and water from intestinal lumen. The selective permeability actualizes in two routes; the transepithelial/transcellular and paracellular pathways. Transcellular pathway is generally related with solute transport and selective transporters have a role in transport of amino acids, sugar, electrolytes and short-chain fatty acids. On the other hand, paracellular transport occurs in the space between epithelial cells and regulated by intercellular complexes. Intercellular complexes are localized at the apical-lateral membrane junction and along the lateral membrane. Desmosomes, adherens junctions and tight junctions are the components for the contact between intestinal epithelial cells. The adherens junctions and desmosomes are important in mechanical linkage of cells. Tight junctions seal the intercellular space and regulate the ionic solute transport. Both adherens junctions and tight junctions play important role in the regulation of cellular proliferation, polarization and differentiation (17-19).

Celiac disease is an immune-mediated enteropathy as a response to ingested gluten and its component gliadin. Studies suggest that altered intestinal barrier function has a role in CD by allowing gliadin to cross the barrier and activate the immune system. CD patients have enhanced intestinal permeability and altered tight junction morphology. The enhanced permeability exists prior to CD onset, and this strengthens the suggestion of these studies. Most of the healthy first degree relatives of CD patients have increased intestinal permeability. Thus, altered barrier function may be a predetermining factor in CD susceptibility (20-22).

Gluten and the toxic component gliadin directly stimulate zonulin production and cause an increase in intestinal permeability.

Normally intestinal epithelium is impermeable to gluten and gliadin. In CD, tight junction integrity is impaired and paracellular permeability is enhanced. Gliadin stimulates zonulin secretion. Clinical studies showed a positive correlation between increased intestinal permeability and intestinal zonulin levels in patients with active CD. Further studies will define the barrier function more clearly. As a result, considering the pathogenesis of CD, gluten and gliadin contains a high proline and glutamine residues. Proline has a toxic effect to intestinal lumen in CD patients. Depending on the pathogenesis as described above, these peptides pass through the subepithelial region due to tight junction damage and deaminated by tissue transglutaminase. The acidic and negative loaded glutamic acid residues are connected to the HLA-DQ2 and HLA-DQ8 molecules in antigen presenting cells. These complexes are presented to CD4+T cells and stimulate the release of cytokines. As a result of these cytokines, inflammation and tissue damage starts. Once the cytokines and tissue damage starts it will continue (23-25).

Celiac disease has a genetic component proven by the rate that 98% of CD patients are positive for HLA-DQ2 (26-28). CD emerges in susceptible individuals with the triggering of endogen antigens; however role of exogenous antigens and other environmental factors cannot be underestimated. Gluten plays the leading role. The relevance among environmental factors, auto antigens and genetic risk factors are clarified recently. The phenomenon develops in HLA-DQ2/8 individuals by the activation of CD4C T cells in lamina propria due to gluten-derived peptides. Latest reports mention the role of proinflammatory cytokine IL-15 in intraepithelial compartment as the cause of chronic inflammatory process. IL-15 triggers the congenital immune receptors and

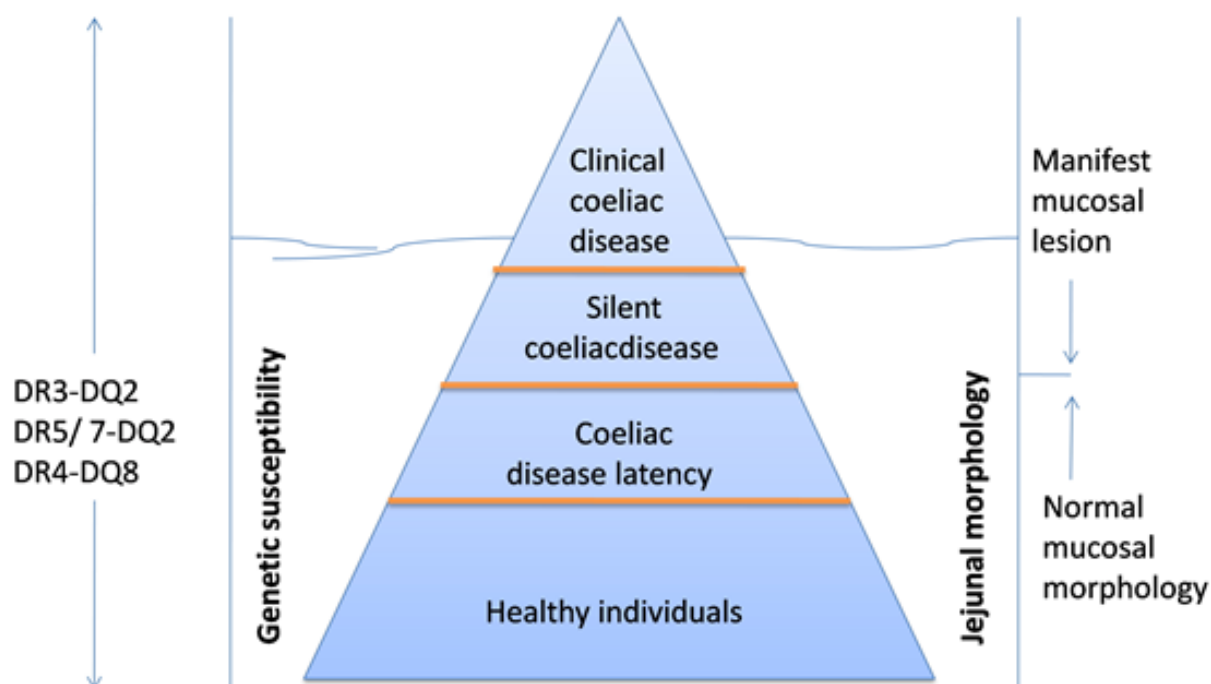


Figure 1. The celiac disease iceberg and spectrum of gluten sensitivity (Permission from Markku Mäki).

cause activation of IEL. In lamina propria, IL-15 also triggers gluten-specific CD4C response and may initiate lymphomas. For evaluating the IEL count and distribution in a situation like normal villi structure and increased IELs; the recommended practice is to use CD3 which is an immunohistochemical staining for lymphocyte marking (26-29).

Clinical features

Celiac disease has a wide clinical spectrum including classical gastrointestinal symptoms or non-classical (extraintestinal-atypical) symptoms. Classical CD is predominant clinical condition among younger children. Atypical manifestation will be dominant in the older the patient is at diagnoses. Asymptomatic CD patients (silent celiac disease and potential celiac disease) were detected during community screening. The patient without symptoms but who have mucosal injury called as 'silent CD'. The population referred to as 'latent celiacs' with

the genetic and serologic markers compatible with CD but no mucosal damage. The terminology described so far is summarized in Figure 1. Many conditions such as autoimmune disorders or some genetic syndromes occur in association with CD (30).

Gastrointestinal System:

Characteristically CD manifests itself in a wide range of manifestations from findings of a simple small bowel disease to small bowel failure in infants and pre-school childhood. The disease is characterized by gastrointestinal manifestations starting between 6 and 24 months of age, after the introduction of gluten in the diet. Infants and young children typically present with chronic diarrhea, distention, nausea, vomiting, growth retardation, muscle wasting, hypotonia, poor appetite and unhappy behaviour. Within weeks to months of starting to ingest gluten, weight gain velocity decreases and finally weight loss can be observed. The most

common gastrointestinal symptom in infants and pre-school age children is the chronic diarrhea. The diarrhea in CD is the best example of the small malabsorptive diarrhea. Constipation is an entity that we encounter less compared to other forms of clinical presentations in childhood age groups. The factors causing constipation in active celiac disease are probably anorexia, compensatory ileal hypertrophy, and reduced intestinal motility. Children diagnosed at younger age tend to have predominantly gastrointestinal symptoms (30,31)

Cardiovascular System:

In the pathogenesis of CD described in detail above, strong IgA response is known to develop against not only to gliadine but also various tissues. Examination of CD patients' serums with immunofluorescence methods revealed various IgA groups of antibodies consisting of anti-reticulin, anti-jejunal and anti-endomysial antibodies. Studies with CD patients showed that tissue transglutaminase (TTG) reacts and initiates inflammation with tissues beside the bowel, such as the heart, vascular endothelial and mesenchymal tissues (32,33). In recent years, the prevalence of CD in cardiomyopathy patients waiting for heart transplants is found to be higher than the normal population and autoimmune myocarditis with CD association has been reported (34). In the development of cardiac disease; it is believed that, autoimmune process is started by developed auto antibodies against intestinal tissues mentioned above showing cross reaction to the myocardial tissue (32-34). Guidetti et al. showed higher rates of fluorescence in their study with serum samples obtained from patients with CD and myocardial tissue of the monkeys with indirect immune fluorescence method (35). In the same study, serums of patients with treated CD showed no signs of these types of antibodies (35). Schmitt De Bem et al. (34) reported anti-endomysial

antibody positivity of 1.9% among 642 patients waiting for heart transplant. Prati et al. and Curione et al. reported the CD prevalence in dilated cardiomyopathy (DCM) patients as 2.2% and 5.8% respectively (36,37). Various mechanisms have been proposed for the CD and DCM association. Firstly, missing of micro-nutritional elements which have an important role in the metabolism of heart such as thiamine, magnesium, calcium, riboflavin, selenium, ubiquinone and carnitine may induce cardiomyopathy (38,39). Curione et al. reported that serum carnitine levels were found to be lower in patients with CD and heart failure with DCM according to non CD group (39). Carnitine plays an important role in transportation of fatty acids into the mitochondria for oxidation (39). Thus, the decrease in serum carnitine levels has led to deterioration of myocardial performance (39). In the same study, CD patients with decreased cardiac function showing compliance to the diet, serum L-carnitine levels returned to normal, and myocardial performance has led to an increase (39). Another mechanism proposed for clarifying CD and DCM association; intestinal permeability changes as a result of intestinal inflammation resulting absorption of antigenic structures and infectious agents that normally should not be absorbed (40,41). These agents cause myocardial damage and DCM with direct or immune-mediated mechanisms (40,41). Fruscati et al. detected 5 patients with myocarditis causing heart failure in their study of 187 CD patients (32). In the same study, 8 patients with cardiac auto-antibodies in the presence of lymphocytic infiltration in myocardial biopsy have been shown (32). The third mechanism held responsible for the etiopathogenesis are some genetic markers and HLA alleles (42). The most comprehensive study in this regard is performed by Not and colleagues (42). Sporadic or inherited 238 adult DCM patients

and 418 relatives and 2000 blood donors were included in the study and tissue transglutaminase levels of DCM patients and relatives were found to be higher than the control group (42). In the same study, HLA-positivity compatible with CD was encountered in 25 patients (42). The high rate of tTgG positivity and echocardiographic detection of abnormalities in DCM patients and relatives of these patients, suggest immune-mediated mechanisms of inherited assets in etiopathogenesis (42).

Hematological System:

In the last 15 years, whilst our knowledge regarding CD symptoms and clinical information rapidly increasing, it is observed that the disease onset age and symptoms vary and approximately 50 % of newly diagnosed patients come across with non-gastrointestinal findings (43). Owing to be a small bowel disease, depending on the severity and extensity of mucosal lesions, different clinical appearance is emerged. Disruption of the normal villus structure in tissue biopsy not only decreases the surface of absorption, a change in the enzymes involved in digestion-absorption process is also seen. Disaccharidase, peptidase, alkaline phosphatase, adenosine triphosphatase and elastase activity decreases while activity of a lysosomal enzyme, acid hydrolase increases (44,45). In other words, there is not only cell loss but also there is a loss of functional enzymes (44,45). As a result, lack of trace elements absorbed in small intestines may be seen depending on the severity of the damage and on the interval that the deficiencies are maintained. Iron, folic acid and vitamin B 12 deficiencies are among common hematological findings. Considering that iron in the diet is absorbed in proximal small intestine, iron deficiency is quite common in CD. Ackerman et al. and Ransford et al. investigated the cause of iron deficiency anemia with endoscopy in their studies and

showed prevalence of CD as 3% and 12% respectively (46,47). Howard et al. reported the prevalence of CD in 333 patients known to have iron deficiency as 4.7%, while Coraza et al. reported the prevalence of CD in 200 patients known to have iron deficiency as 5% (48,49). Ucardag and colleagues from Turkey stated an increased prevalence of CD in patients with undefined iron deficiency in their study (50). In cases of unexplained iron deficiency, celiac screening is recommended. Particularly it should not be ignored that these cases will not respond to oral iron treatment.

Iron deficiency anemia is the most commonly reported hematological finding in CD, however vitamin B12 and folic acid deficiency is observed in those with severe ileal involvement (51,52). Folic acid is absorbed from jejunum. In case of involved proximal small intestine, iron and folic acid deficiencies can be seen. Ileal involvement is uncommon so Vitamin B12 deficiency is rare. Ferritin and folic acid deficiency in children goes in parallel with the degree of villous atrophy, though the relationship with vitamin B 12 could not be demonstrated. Macrocytic anemia due to B12 and folate deficiency, leucopenia, and thrombocytopenia are observed (51-53).

In CD patients left untreated for a long time, Howell-Jolly cells and thrombocytosis are observed in peripheral blood smear secondary to hyposplenism. Thrombocytosis and predisposition to thrombosis secondary to protein S deficiency is observed in CD (54).

As in all small bowel disease or CD, deficiencies and shortcomings of fat-soluble vitamins, water soluble vitamins and trace elements and the clinical presentations of these findings are observed. If we review fat-soluble vitamins, such as ADEK, night blindness, dryness of the conjunctiva and keratomalacia are observed due to vitamin A

deficiency. Osteomalacia and a decrease in bone mass are observed due to Vitamin D deficiency. Barton et al. (55) identified a CD rate of 3.4% in patients with non-significant intestinal symptoms and low bone mineral densities in their study. Enrichment of gluten-free diet in terms of vitamin D and calcium accelerates improvement, especially in growing children and post menopausal women. In CD patients, like the other fat-soluble vitamins, vitamin E deficiency symptoms may also occur (56,57). As an antioxidant vitamin, vitamin E deficiency may cause malignant cell transformation, gait disturbance, ataxia, and neurological complications such as neuropathy, hemolytic anemia and reproductive disorders (56,57). Patients with neurological symptoms due to vitamin E deficiency without other symptoms of CD have also been reported (56,57). Absorption of vitamin K is provided from both the small intestine and the colon (58). Vitamin K supplied with food is absorbed from small intestine, while those of bacterial origin are absorbed from the colon (58). CD will reduce the amount of vitamin K absorbed from small intestine, thus causes a deficiency, and this deficit cannot be met by the part absorbed from the colon (58,59). Vitamin K deficiency causes prolonged prothrombin time and bleeding diathesis (58,59). Cavallaro et al. (58) in their study on adult patients with untreated CD reported a prolonged prothrombin time in 20% of untreated adult CD patients, while 5.6% of them need to parenteral vitamin K administration.

Water-soluble vitamins such as thiamine, pyridoxine, folic acid, vitamin B12 and trace elements such as carnitine, selenium, zinc, magnesium, copper deficiencies arise due to malabsorption or increased demand. Ataxia, neuropathy, and neurological symptoms such as memory disorders may emerge. Lack of vitamins and trace elements in CD patients usually improve with gluten-free diet.

However, gluten-free diet can reduce the absorption of calcium and iron. In the diet, repository forms of wheat, barley, rye and oats are absent. Rice, corn, potatoes are used instead of foods that contain gluten. Studies in patients on gluten-free diet for long-terms show high levels of homocysteine; which is an indicator that folate, vitamin B12 and vitamin B6 deficiencies are present. The high levels of homocysteine are also known as a risk factor for cardiovascular disease, as patients who receive gluten-free diet especially adults; have to be viewed in terms of vitamin deficiencies (60,61).

Renal and Urogenital System

The progress of genetic studies of CD, showing the close relations with HLA DQ2 and HLA DQ8 haplotypes, is to explain the increased risk of patients to various autoimmune diseases. Similarly, the kidneys are involved at different rates during the course of many autoimmune diseases and causing very serious consequences determining the prognosis of the disease (62). The first studies related to CD and kidneys were performed in patients with IgA nephropathy. In patients with Ig A nephropathy, increased Ig A levels against food was established and this led the investigators to put forward hypothesis confirming the relationship between IgA nephropathy and CD (63-65). Coppo et al. reported IgA nephropathy patients who had benefit from gluten-free diet (66,67). The

importance of decreased oral tolerance in the pathophysiology of CD and food-sensitive enteropathy has been identified (66,67). When small intestinal mucosal integrity is impaired, increased intestinal permeability causing nutritional peptides to reach to the submucosa, and this has an important role in the formation of oral tolerance corruption and autoimmunity (68-70). Increased intestinal permeability has been shown to play a role in

the pathogenesis of diabetes mellitus and other autoimmune diseases (68-70). In recent years, it has been suggested that increased intestinal permeability in patients with IgA nephropathy is associated with susceptibility to CD (68-70). It has been reported that the mucosal immune system is activated, intraepithelial T cell count in the mucosa are increased and intestinal permeability is increased in patients with primary glomerulonephritis (69). The significant increase in intestinal intraepithelial T lymphocyte in primary glomerulonephritis suggest that oral tolerance diminution may to have a role in pathophysiology (71,72). The most comprehensive study about CD and kidney disease is reported by Ludvinsson et al (73). This study included 14336 children and adult with CD. They demonstrated that 1.5-fold increase for all kinds of glomerulonephritis only in adults (73). Gamma et al. studied CD patients who also have kidney stones. Hyperoxaluria and urinary oxalate excretion returned to normal in these patients on gluten-free diet (74).

Reproductive disorders such as infertility and pregnancy-related problems are more frequent than the normal population in patients with CD. Collin et al. performed a study with known infertile women and CD was identified in 4/150 (75). The classical signs of CD were not recorded in these patients. Spontaneous abortus were found to be higher in CD patients who were non adherent to the diet than adherent patients (76). Reproductive problems were also reported in male CD patients (77). Low birth weight was reported fivefold higher than normal population in the babies whose father has CD (77).

The effect of nutrition on reproductive health is a well known issue. Reproductive disorders in CD may be welded by malnutrition due to malabsorption. Zinc is an essential trace element which is required for DNA synthesis,

cell division, protein synthesis and immune response. Zinc deficiency in the mother leads to deficiency in FSH and LH synthesis, secretion and ovulation disorders and may cause problems like ovarian development abnormalities, spontaneous abortion, congenital malformations, stillbirth, and intrauterine growth retardation (78). It is well known that zinc deficiency may cause reproductive problems in men. In zinc deficiency, spermatogenesis is inhibited by the reducing activity of the acetylcholine esterase enzyme which reduces serum testosterone levels. Reduced activity of Zn-dependent 5-alpha reductase enzyme in men leads to deceleration in conversion of testosterone to dihydrotestosterone. This point causes deterioration in hipotaloma-pituitary axis (79).

Neurological System

Approximately 10-60% of CD patients also have neurological findings. Common neurological findings related to the development of clinical malabsorption may be due to lack of vitamins and minerals; some cases presented with neurological symptoms alone without the classic malabsorption clinic. The time of the diagnosis and treatment compliance constitute an important factor for the emergence of neurological findings. This observation might explain increasing ratio of neurological findings with advanced ages. Peripheral neuropathy, ataxia, cerebral calcifications, epilepsy, anxiety, depression, psychotic symptoms, dementia, encephalitis, vasculitis, progressive myoclonic encephalopathy, Huntington disease, myoclonus, chorea, neuro-myopathy, stiff-man syndrome, polymyozitis, neuro-myelitis optica, migraine, autonomic neuropathy, cortical blindness are the neurological disorders that showing association with Celiac disease. Pathophysiology of neurological disorders in CD is unclear (80,81).

In CD patients with neurological disorders, antineuronal and antiganglioside antibodies are found. Gluten-free diet results in the loss of auto-antibodies in some cases. Thus, neurological signs in CD might be explained by antibody mediated auto-immune mechanisms (80-83). Prevalence of CD in patients with epilepsy is 2-3 times higher than the general population and was found at a rate of 3-6% (84). Dalgic et al. (85) reported the incidence of CD as 1.17% in epileptic children. Gobbi et al. (86) studied 43 epileptic patients with cerebral calcifications and CD was identified at a rate of 77%. Reviewing the literature, although it does not seem to be effective screening all of the epileptic children for CD, screening for CD is recommended in patients with partial epilepsy, refractory epilepsy or epilepsy accompanied by calcification. The prevalence of CD in patients with idiopathic ataxia has been reported at a rate of 12-41% (82,87). The term "gluten ataxia" has taken place in the literature by these reported cases. Peripheral neuropathy prevalence in CD is not known exactly; however, CD was reported in 2,5% in these patients (88). Mono neuropathy multiplex is a form of peripheral neuropathy reported in CD (89). As a result, CD may cause diseases affecting the central and peripheral neurons. Autoimmunity might be a mechanism for neurological involvement. But it seems quite difficult to explain all the probable neurological deficits through a single mechanism.

Liver

For the first time, Hagender et al. (90) detected high levels of liver enzymes in newly diagnosed CD patients in 1977. Since then, a considerable number of studies have been done about the effects of CD over hepatobiliary system. Considering all these studies, CD has been shown to increase the risk of elevated liver enzymes, acute hepatitis, chronic hepatitis, fatty liver, primary

sclerosing cholangitis, cirrhosis, autoimmune hepatitis and primary biliary cirrhosis (91). Ludvigson et al. (92) concluded that patients with CD were found to be under increased risk in terms of liver disease in their study. Vajro et al. (93) published a series of 6 children who have persistent elevation of aminotransferase activity with different histopathological spectrum of hepatitis. The children in this group were asymptomatic; however jejunal biopsies were typical for CD and aminotransferase activity of all cases returned to normal after treatment with gluten-free diet. In the same study, histological lesions returned to normal in 2 children, while serum aminotransferase levels increased again in other 3 children after gluten containing diet. Similarly, Altuntas et al. (94) followed 3 CD patients with fibrosis and nonspecific reactive changes in liver biopsies and reported that liver enzymes returned to normal after 3 months with gluten-free diet. These findings were supported with other studies both in children and adults; persistent and cryptogenic elevations of serum aminotransferase were investigated and 9% of the patients were concluded to be asymptomatic CD patients (95-98). Thus, the term which was used as gluten hepatitis later named as celiac hepatitis and the presence of the following findings have been suggested as diagnostic criteria (99,100): (i) Lack of hepatomegaly, splenomegaly or both and along with lack of signs suggesting chronic liver disease (ii). Lack of hyper-gammaglobulinemia and serum auto-antibodies (except anti-transglutaminase associated autoantibodies) (iii). Presence of mild lobular and portal tract inflammation and reversibility of signs with gluten-free diet.

Even though these diagnostic criteria are presented as the diagnostic criteria for liver disease due to CD, Demir et al. (101) published a series of 3 girls and 2 boys in 2005, with signs of portal hypertension and

diagnosis of chronic liver disease or cirrhosis. In all of the five cases, metabolic, autoimmune, infectious, genetic and metabolic reasons which may lead to chronic liver disease were excluded. After exclusion of all these diseases, celiac serologies were found to be positive and intestinal biopsies were considered to be compatible with CD. Liver enzymes returned to normal and a regression of the portal hypertension symptoms was described after gluten free diet. The role of increased intestinal permeability in the pathogenesis of liver dysfunction in CD was first laid out by Novecek et al (102). Intestinal permeability was investigated in 178 adult CD patients with the lactulose-mannitol intestinal permeability test. Permeability was found to be significantly higher in patients with abnormal hepatic aminotransferase enzyme activity. Moreover, Lindberg et al. (103) observed liver dysfunction not only in CD, but also in patients with cow's milk protein enteropathy. As a result, mucosal damage might also be a possible factor besides gluten for liver dysfunction abnormalities in patients with CD.

It has been suggested that prolongation of intestinal transit time, bacterial overgrowth and bacterial exposure may result in immunostimulating substances such as neo-antigens to participate in the portal circulation and may affect liver functions (92,102,104,105). Development of inflammation is an important factor affecting lymphocyte circulation and distribution. Mechanisms leading to abnormal accumulation of lymphocytes are the key points in order to explain the relationship between CD and liver disease development. Eksteen et al. reported that changes in CCL25 chemokine expression causes mucosal T cells to congregate in liver in primary sclerosing cholangitis patients. In individuals with known genetic predisposition, which

environmental or other genetic factors initiate liver inflammation in CD patients is unclear (33,106,107).

Skin

Two mechanisms are thought to be responsible for skin involvement in CD patients. First, skin lesions develop as a result of vitamin deficiencies due to malabsorption (108-110). Second, abnormal small intestine permeability permits transition of endogenous and exogenous antigens, triggers the immune responses, thus developing hypersensitivity and the formation of immune complexes (108-111). Malabsorption related skin lesions are (often associated with vitamin and mineral deficiencies: iron, folic acid, zinc, vitamin B12 deficiency); alopecia, pruritus, aphthous ulcers, angular stomatitis, glossitis and koilonychia. Immune-mediated skin lesions are; dermatitis herpetiformis, linear IgA dermatosis, urticaria, hereditary angioedema, cutaneous vasculitis, erythema nodosum, erythema elevatum diutinum, necrolytic migratory erythema, psoriasis, vitiligo and alopecia areata. Dermatitis herpetiformis is an immune-mediated skin disease. Dermatitis herpetiformis is first defined by Dr. Louis Duhring in 1884; however, association with CD was reported for the first time in 1996 (109,112). Today, dermatitis herpetiformis is regarded as a special form of CD. Dermatitis herpetiformis might be the only manifestation of CD. Dermatitis herpetiformis has also a genetic basis like CD and HLA DQ2 positivity is about 90% (112). Specific B cell/macrophage antigens were found in patients with dermatitis herpetiformis and CD. Family studies showed that these antigens are independent of HLA antigens. According to the similar studies, it is claimed that in the development of lymphoid cell receptors for the response to gluten; there is a necessity of both HLA, as well as non-HLA genes (108).

Dental health

With regard to oral structures, the most obvious problems that can be seen in CD patients are enamel defects and recurrent aphthous stomatitis. As noted in the studies below; individuals with CD have more enamel defects, oral lesions and/or symptoms than normal individuals. The exact cause of enamel defects in CD patients is not known; however, suspected factors are malabsorption related hypocalcemia, immunological process due to gluten in the enamel formation period of permanent teeth. It is believed that the HLA DR3 antigen significantly increases the risk of dental lesions or defects (113-116).

Aine et al. (117) reported enamel problems for the first time in CD patients. Farmakis et al. (118) investigated enamel defects in milk teeth and permanent teeth of celiac kids. He reported that enamel defects were more frequent in CD patients compared with normal subjects. Bucci et al. (119) and Aguirre et al. (116) reported similar findings in their studies. According to these researchers, the most affected teeth are the incisors and molars. Growth retardation in CD patients is a generally well known issue; however, very few studies are available concerning the craniofacial structure, bone and teeth development of these individuals. Finizio et al. (120) reported broad forehead structures in CD patients. Similarly, Balli et al. (121) reported that children showing normal growth pattern compared to children with CD; celiac kids showed retardation in bone and teeth age. Dry mouth is common in these patients and salivary flow rate is low, thus, this point may play a major role in occurrence of oral mucosal lesions. As a result, significant oral and dental symptoms occur in CD individuals.

Accompanying syndromes and diseases

Various genetic diseases and syndromes associated with CD have taken place in the

literature. Association of CD with syndromes encountered frequently when compared to the normal population are as follows; IgA deficiency, Down syndrome, Turner syndrome, Williams syndrome, DiGeorge syndrome, 18q deletion syndrome, ring chromosome 13 syndrome, Floating-harbor syndrome, trichorhino-phalangeal syndrome type 3, kabuki syndrome, Lane- Hamilton syndrome, Plummer-Vinson syndrome, Vogt-Koyanagi-Harada's disease, polycystic ovarian syndrome, hereditary angioedema, type 1 diabetes mellitus, autoimmune thyroiditis, Sjogren's syndrome, Addison's disease, juvenile idiopathic arthritis, alopecia areata, SLE and autoimmune hepatitis (122-135).

Diagnosis

The children with symptoms suggestive of CD, first degree relatives of known CD patients and in patients with diseases known to be associated with CD must be screened for the disease. Initial screening is made by age appropriate serological tests. The following step is performing endoscopy and taking biopsy samples. Two criteria must be met as diagnostic criteria; (i) Demonstration of villous atrophy and crypt hyperplasia in intestinal epithelium under gluten containing diet (ii) Clinical, pathological and serological recovery after gluten-free diet

Serology

Antibodies developed against gliadin in the structure of IgG and IgA has been used to diagnose CD for many years (136-138). Vitoria et al. (137) and Lerner et al. (138) reported the sensitivity of AGA IgA and AGA IgG in the diagnosis of CD as 69-85% and 75-90% respectively. However, the disease specificity of IgG antigliadin antibodies was significantly lower than IgA antigliadin antibodies. These results suggest that healthy individuals who do not have CD may generate antibodies against gliadin. In addition, false-

positive AGA test may occur secondary to changes in membrane permeability in acute gastroenteritis, cystic fibrosis, cow's milk protein allergy, gastroesophageal reflux, inflammatory bowel disease and peptic ulcer disease (139). These negative aspects and the use of new autoantibodies, AGA test remain somewhat in the background during the diagnosis of CD. However; these antibodies, especially IgA AGA are used in the diagnosis of CD in children under 2 years of age for demonstrating early sensitization, also in the evaluation of treatment compliance of patients. Endomysium and reticulin are connective tissue proteins found in collagen matrix of human and monkeys. Connective tissue auto-antibodies developed against these proteins, the anti-endomysial antibody (EMA) and antireticulin antibody (ARA) have been shown in CD (140,141). The sensitivity and specificity of EMA to diagnose CD are considerably high as 85-98% and 97-100% respectively (140,141). Monkey esophagus or human umbilical cord may be used as a substrate for EMA analysis. After the addition of patient serum on substrate, a reaction due to existing EMA in the patients' serum is observed in immuno-fluorescence (IF) microscopy. Usage of monkey esophagus as a substrate increases sensitivity, whilst usage of human umbilical cord as a substrate increases specificity. EMA analysis has also some disadvantages.

IF microscopy examination of samples by a single eye depends on personal hardware and has to be done by a competent person; otherwise, inexact comments may appear (142). In addition, under 2 years of age and in phases that villous atrophy has not been settled exactly, EMA analysis has a low rate of positivity. The diagnostic specificity and

sensitivity of human originated tTG was found to be higher than pig originated tTG (139). In metaanalysis reports, human originated tTG is found to be superior in terms of sensitivity when compared with EMA (140). Regarding the ease of implementation and cost advantage of the test, it is recommended to use tTG in disease screening and follow-up testing. Since the accurate diagnosis of CD is done by biopsy, serologic tests assign the decision for endoscopy and to assess diet compliance in children under diet therapy. It is proper to use a combination of two serological tests to support the diagnosis in patients who are not suitable for biopsy. EMA test can be used as a secondary serological indicator (140-). Antireticulin antibody (ARA) is evaluated in rats, liver, kidney and stomach tissue with IF technique. Five different types of fluorescence may be obtained in these tissues, but detection of the type 1 (R1-ARA) fluorescence has been found to be valuable for CD (138). The sensitivity and specificity of R1-ARA in the diagnosis of CD has been found to be 65% and 100% respectively (138). In clinical practice, ARA remained in the background with the introduction of more sensitive and more specific antibodies like EMA and tTG. Levels of IgA antibodies synthesized in the local autoimmune process in intestinal tissue have been shown to be very close to the values of serum levels. Therefore, IgA type serologic indicators are more sensitive in diagnosis and screening for CD. However, false negative test results can be obtained in patients with IgA deficiency. Regarding the reference values of serum levels under 5mg/dl, frequency of IgA deficiency in healthy individuals is stated as 1:63 to 1:965 (143-145). Considering CD, the frequency of IgA deficiency is more common

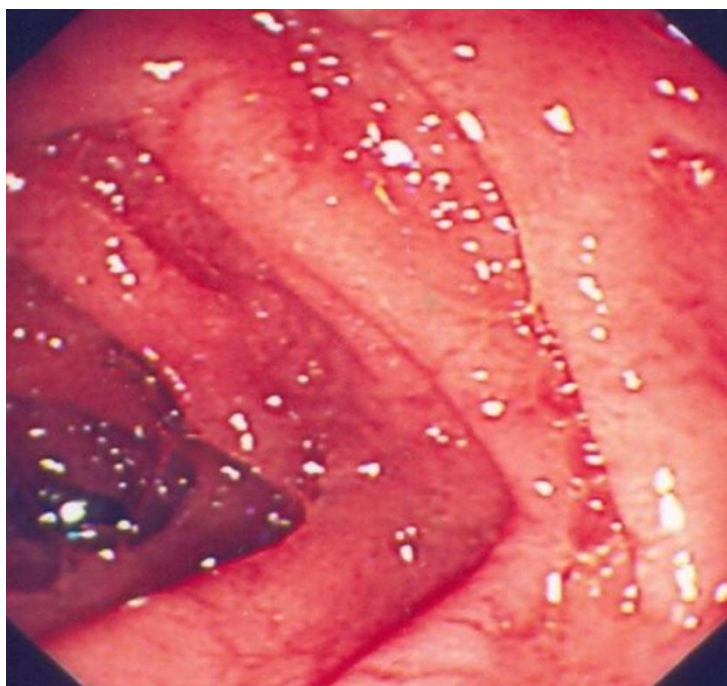


Figure 2. Endoscopic findings in celiac disease.

than the normal population. Basturk et al. (146) reported the prevalence of IgA deficiency in Turkey as 0,52%. Thus, in the screening and follow-up of high risk individuals, if concomitant selective IgA deficiency is detected, tTG IgG is recommended primarily for screening. CD is a major health and social field problem; nevertheless serological tests have led to a breakthrough in diagnosis, screening and follow-up of this disease.

Endoscopy

Intestinal biopsy is still the gold standard for the diagnosis of CD according to today's knowledge. Histopathological disease severity may be different in each part of the proximal bowel. It is recommended that multiple biopsies should be taken from visible lesions and normal regions, both from the distal and proximal part of duodenum (136).

Frequently encountered endoscopic findings in CD are; mosaic structure, a decrease or flattening of duodenal folds, scalloping of valvulae conniventes, nodular pattern of

bulbar mucosa, and visible submucosal blood vessels (Figure 2) (147-152). Coarse, notched, or scalloped duodenal folds have also been reported in children with CD (153,154). Steven et al. (148) described the mosaic appearance of the duodenal mucosa in CD for the first time in 1976; Jabbari et al. (150) described comb-like appearance of duodenal folds in addition to similar mosaic view in 1988.

Some researchers reported the sensitivity and specificity of endoscopic findings higher than the others. Brocchi et al. (151) studied 65 adult CD patients and reported that the sensitivity and specificity of reduction in duodenal folds and/or fold loss to demonstrate subtotal villous atrophy (SVA) are 88% to 83% respectively. The same investigator identified sensitivity and specificity of micronodular pattern as 57.7% and 100% in another study (155). Maguzzu et al. (156) identified mosaic pattern together with the reduction of folds, and, founded the sensitivity as 100%, specificity as 99%, and positive predictive value as 91%.

Histopathological changes in CD do not show diffuse distribution through small intestine, mostly patchy and is known to be in different intensities. Distinctive sensitivity rates were found in studies demonstrating the value of endoscopy to show partial villous atrophy (PVA). Dickey et al. (157) found at least one endoscopic finding in 77% of 129 patients diagnosed with CD; the sensitivity of endoscopic findings for total villous atrophy (TVA) and/or SVA was reported as 77% in these patients, while the sensitivity in showing PVA was found to be significantly lower (58%). From Turkey, Savas et al. (158) reported that patients with CD have at least one abnormal finding in endoscopy in their study. The most sensitive endoscopic finding reported as mosaic view (50%); the second as deletion of folds and comb-like appearance (38.5%) and least sensitive as the nodular view (15.4%). Similar results were obtained in children following the adult studies mentioned above. Sanflippo et al. (159) determined that coarse and milled duodenal folds or mosaic pattern appearance in children with CD as an indicator of PVA or TVA. Ravelli et al. (147) evaluated 140 patients with suspected CD and dyspepsia. The endoscopic appearance and biopsy of these patients were compared; and mosaic pattern is noted as the most important finding of TVA. As a result, the rough jagged mosaic pattern, nodular structure, duodenal folds, reduction in folds, mucosal irregularity and erosions takes place in endoscopic findings of CD.

Patology

To understand the pathological structure of CD, first of all it is important to know the structure of normal small intestine. Generally accepted that comment and sufficient circumstances for considering small bowel biopsy specimen as normal is monitoring protected normal villi and crypt ratio and structure of 3 or 4 villi. Small intestinal mucosa normally has long and thin villi. In

the duodenum, the height of the villi are short, whereas villi height increases from jejunum to ileum and with a overall ratio ranging between 3;1 to 5;1 depending on the biopsy site. The distribution of intraepithelial lymphocytes (IEL) along the villi shows a characteristic decrease from the base of the villus toward the villous tip. The possible patchiness of mucosal lesions has to be kept in mind when differentiating normal mucosa from CD. For the correct orientation, the specimen should be examined initially by low-power microscopy for architecture and cellular distribution. Afterwards, high power microscopy will allow viewing cellular content and epithelia. Few inflammatory cells comprising plasma cells, lymphocytes, eosinophils and macrophages are found in the lower one- third of the lamina propria, while villous lamina propria is virtually empty. In inflammatory states, cells including polymorphonuclear leukocytes infiltrate upper parts of the lamina propria causing obliteration of the villi (160, 161).

Celiac disease damages the small intestine mucosa from proximal to distal starting from the duodenum and jejunum; however, the healing process moves from distal towards proximal small intestine (161). Duration of mucosal healing process varies between 6 months and 24 months (162, 163). Considering the slow pace of IEL within the histopathologic healing process, IEL count may be the last feature to return to normal after a gluten-free diet (164,165). Showing the mosaic pattern in endoscopy as it seems may show a high specificity to exhibit villous atrophy in CD; many investigators warn about false negative diagnosis when there is inadequate sampling especially in pediatric patients due to patchy involvement as well as observation of pathological and normal intestinal mucosa together. Nevertheless, the optimal number of biopsy specimens necessary to confirm the diagnosis of CD is a

point of interrogation. There are no recommendations about optimal number of biopsy specimens in North American Society for Pediatric Gastroenterology, Hepatology and Nutrition guidelines, while according to American Gastroenterology Association, six biopsy specimens are recommended as “necessary” for the diagnosis of CD. In general practice, taking at least 4 endoscopic biopsy samples from distal duodenum with 2 samples from the bulbous seems reasonable for detecting patchy and subtle mucosal lesions in CD (139,166-168).

Morphologic spectrum of CD:

Presences of architectural abnormalities like villous shortening and crypt hyperplasia or the increased IELs count either alone or together are the histological evidence of CD. Shortened, widened villi and even flat mucosa with hyperplastic crypts are the classical appearance. Villus to crypt ratio decreases however overall thickness remains almost the same. IELs count increases as a cell mediated immune response (164,165).

Marsh is the first author who identified the morphology related to CD (169). In histopathological examination, the increase of IEL in villus structure, flat mucosa with crypt hyperplasia, epithelial destruction and increased inflammation in lamina propria are the monitored changes. Although intraepithelial lymphocytes increase is a situation developed in response to epithelial injury in CD patients, the basic mechanism initiating the event remains unknown. Most of IEL's consist of T lymphocytes and cytotoxic T cells expressing $\alpha\beta$ T-cell receptor (TCR) on their surface holds the majority. The population specifically expanded in CD is the CD3/D4⁺/CD8⁻, $\delta\beta$ TCR-bearing IELs which

is only 5% of the total in normal mucosa (170,171).

The normal upper limit of intraepithelial lymphocytes in hematoxylin–eosin sections and CD3 immunostained sections are accepted as 20 lymphocytes per 100 enterocytes (a ratio of 1 intraepithelial lymphocytes per 5 enterocytes) and 25 intraepithelial lymphocytes per 100 enterocytes (or ratio of 1:4) respectively.

Intraepithelial lymphocytes is an active element of mucosal immune system. Intraepithelial lymphocytes emerges as a response to epithelial damage formed by the effect of gluten, microorganisms, drugs, and other toxic agents. As inferred, intraepithelial lymphocytes increase is a situation not specific for CD. Intraepithelial lymphocytes increase may be observed, whether villous structure is corrupted or not in food allergies other than gluten, helicobacter pylori associated duodenitis, giardiasis, immune insufficiency, viral enteritis, graft versus host disease, autoimmune enteropathy, bacterial over-growth, Crohn's disease and with non steroid anti-inflammatory drug (NSAID) usage. Many studies concerning CD focus on increased intraepithelial lymphocytes; however, changes in the lamina propria are at least important as the increase in IEL. Gliadin peptides cause inflammation in lamina propria through the antigen presenting cells, which is as a result of T cell activation and cytokine release. Neutrophils, eosinophilia and mast cells participate in this inflammatory process (172,173).

Marsh classification:

Marsh type 1-Infiltrative lesions: Normal mucosal villus crypt structure while there is

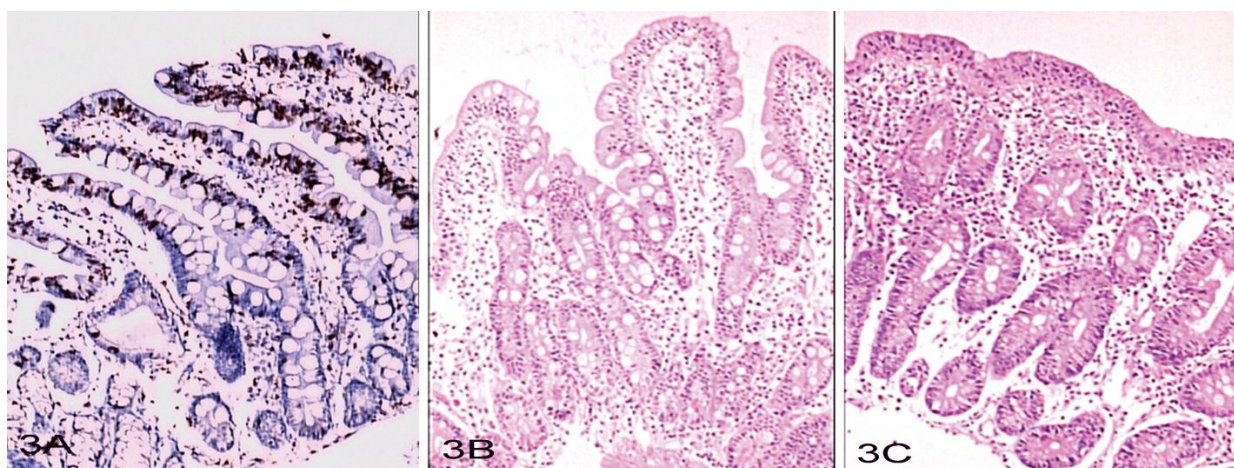


Figure 3. New proposal for classification of mucosal pathology in celiac disease (Permission from Arzu Ensari). New proposal for classification of mucosal pathology in celiac disease. A, Type 1 lesion showing normal mucosa with diffuse increase in intraepithelial lymphocytes (IELs). B, Type 2 lesion with villous shortening and diffuse increase in IELs. C, Type 3 lesion with completely flat mucosa and diffuse increase in IELs (anti-CD3 immunostain, streptavidin-biotin-px, original magnification $\times 200$ [A]; hematoxylin-eosin, original magnifications $\times 200$ [B and C]).

an increase of IEL in villus epithelium. Marsh type 1 may be seen in patients with known CD, under diet treatment where small amounts of gluten ingestion is still present. Villus and crypt structure returns to normal over time with the treatment; however, considering that IEL's are the mucosal cells thought to be cleared at last, the healing process is still ongoing. Other possible state for Marsh 1 lesions is potentially CD (latent) patients. The disease may encounter as a biopsy finding in cases without clinical symptoms especially in family members of known CD patient. Even though IEL increase is non-specific for CD, it holds the most characteristic feature and has high sensitivity for CD. Although CD is a small bowel disease, similar IEL increase may be observed in esophagus, stomach and large intestine (174,175,176,177).

Marsh type 2-Hyperplastic lesions: These lesions are described as observation of crypt hyperplasia and increased IEL in the normal villus structure. The characteristics of type 2 lesions were described by Mowat and Ferguson (178) for the first time in the

neonatal mouse model of graft-versus-host disease. This is an indication of T cell-mediated immune response in intestinal mucosa. Crypt hyperplasia without shortened villi, namely Marsh type 2, is an extremely rare situation and may be observed in experimental conditions or time-dose-related gluten challenge studies. Many pathologists drew attention to the fact that crypt hyperplasia is accompanied by at least shortened villi. In practical terms, this point showed that a demand in modification was required for the original Marsh type 2 criteria. In the new pathologic classification of Marsh by Ensari (136) (Table 1) the short villi structure is accompanied by crypt hyperplasia and intraepithelial lymphocytosis in type 2; in practical terms this is a condition faced by pathologists, and deemed as appropriate and acceptable. Compared with the period that Marsh made the first classification, a relatively standardized event today is the increase in IEL. The modified classification indicates 40 IELs per 100 enterocytes from jejunal mucosal biopsies as the cutoff point for normal (173). High IEL counts may be

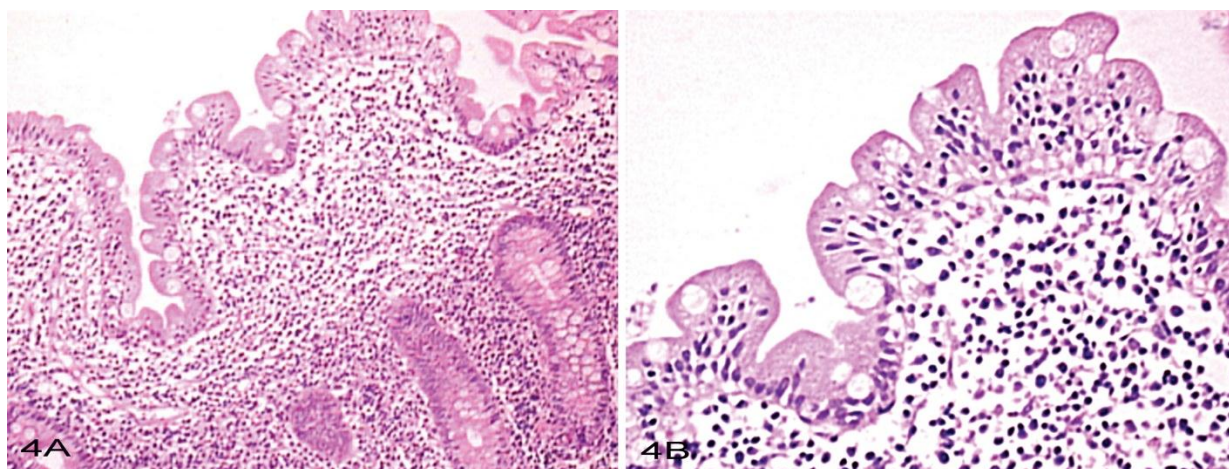


Figure 4. Histopathologic findings in celiac disease (Permission from Arzu Ensari). A, Flat mucosa with crypt hypoplasia and diffuse lymphoid infiltration in the lamina propria. B, Medium-sized lymphocytes infiltrating lamina propria and surface epithelium (hematoxylin-eosin, original magnifications $\times 200$ [A] and $\times 400$ [B]).

due to section thickness of the specimens in the past; however, section thicknesses are about 3-4 μ in most of the pathology laboratories today. Duodenal mucosa is accepted as the preferred site for biopsy and upper limits of IEL count is 25 IEL per 100 enterocytes.

Marsh type 3 Destructive lesions: Flat mucosa with crypt hyperplasia and increased IEL count are characteristic findings of type 3 lesion.

Marsh type 4 Atrophic lesions: Characteristics of this type is flat mucosa with crypt hypoplasia and mild inflammation. This rare condition, usually observed in patients with RCD or in patients with enteropathy induced T-cell lymphoma (169,178,179).

As a result, as we acquire new knowledge about the disease and with the increasing immuno-histochemical skills, pathological classification of CD is related to other changes (Figure 3-4).

Challenge

CD requires lifelong diet; a definitive diagnosis with all the necessary diagnostic procedures is needed before the recommended diet treatment. ESPGAN defined the diagnostic criteria for the first time in 1969 (180). According to these criteria; in clinically suspected patients or patients with a potential risk, serology and endoscopic biopsies were performed. Following the determination of full or partial villous atrophy, a gluten-free diet was implemented.

After the patients return to normal with diet, a gluten challenge test had to be performed. The recurrence in clinical and histopathological state and observation of rehearsal of the disease was essential for diagnosis. According to these criteria, three biopsies (before treatment, under diet and after suspending the diet) had to be done from the patients in this period. In time, although getting positive serology after gluten challenge test, it might take 3 months, 7 years and even 14 years for the settlement of the clinical state in some

patients. Thus, for the last condition to be fulfilled, a discussion arose in terms of patients' ethical issues as well as practical difficulties. ESPGAN renewed diagnostic criteria over time, but the essential gold standard which is the duodenum biopsy remained unchanged. Thus, gluten challenge test is practically quite limited in time. Considering these circumstances, all diagnostic methods for the definitive diagnosis of CD should be used in a suitable manner. However, none of the tests including gluten challenge test has no definitive reliability alone for confirming the diagnosis retrospectively. Thus, gluten challenge test is not mandatory except for some cases with initial suspected diagnosis (5).

Treatment

The basic treatment of CD is life-long elimination of wheat, barley and rye from the diet. The details of this diet have to be described to CD patients and their families and remind them the importance of viewing "does not contain gluten" labels on every supermarket food. The problems in practical life are; the reliability of foods with "does not contain gluten" label, or how much gluten consumed daily is safe for CD patients. These questions have been emerged with uncovering that the produced and marketed foods with "does not contain gluten" labels contain an actual amount of gluten and so the term "gluten contamination" came into use. Definition and classification of gluten contamination is determined by Food Codex Commission (CAC) which was established by United Nations Food and Agriculture Organization (FAO) in partnership with World Health Organization. According to CAC, gluten free products are required to contain gluten content less than 20 ppm (less than 20 mg in kilogram). According to the U.S. Food and Drug Administration agency (FDA), foods without any gluten are "foods without gluten" and foods containing gluten

less than 200 ppm are defined as low gluten content. After researches, the upper limit of acceptable quantity of gluten is determined as 100 ppm in foods sold under the name of "gluten-free products" (139,181).

The studies show no doubt about eliminating foods that contain gluten, i.e. wheat, barley and rye, whereas there is not a clear consensus about the oats. Janatuinen et al. (182) gathered 40 newly diagnosed adult CD patients and 52 CD patients in remission receiving gluten-free diet and added oat to diets in their study. In the endoscopic examinations performed 12 months and 6 months later, they observed that oat does not cause any mucosal damage. However, Lundin and colleagues (183) reported abdominal distension and dyspepsia complaints and also villous atrophy and dermatitis herpetiformis development in a patient after the installation of oats in their study group of 19 adult CD patients. This report has led to suspicious approach for reliable use of oat in CD patients. Oat is somehow prepared in the same environment with wheat, barley, rye which has proven toxic effects; thus, the products might be contaminated. In our center, we don't recommend oat to CD patient. A dramatic and rapid clinical response is achieved in children with CD by removing gluten from the diet. Symptoms such as diarrhea and abdominal distension have to be vanished as a treatment response in patients by the second week of the diet. If there is no recovery after a few weeks of gluten-free diet, the consumed foods should be examined carefully ensuring the elimination of gluten in the diet. Clinical symptoms show no change in some patients despite diet. The patients showing signs of malabsorption related to persistent villous atrophy and increased IELs are called refractory celiac disease (RCD) patients (26). When these types of cases are encountered, the initial diagnose must be confirmed. This

confirmation is easily done in following situations; typical clinical findings, serology positivity, intestinal biopsy that confirms CD, CD permissive gene pairs encoding the human Leucocyte antigens (HLA) It must be kept in mind that; overt or inadvertent gluten contamination is the most common cause of CD irresponsiveness to diet treatment. All the cases with persistent or recurrent symptoms, positive celiac serology or ongoing villous atrophy despite 6-12 months of gluten-free diet implementation, deserve further investigation. Before saying RCD, problems causing similar symptoms under GFD; like microscopic colitis, pancreatic insufficiency, bacterial overgrowth and irritable bowel syndrome should be reviewed (26).

In RCD classification, immune typing of IELs and clinical evaluation are used. Abnormal (clonal) IELs are the hallmark of type 2 RCD. RCD type 2 has a poor prognosis despite conventional treatment and five years survival is about 40-58% (27,28,184,185). Poor prognosis of type 2 RCD may be explained by more frequent observation of enteropathy associated T-cell lymphoma in this type. From the perspective of prognosis, type 1 RCD is known to be better than type 2 RCD. However; considering the complications and mortality rates, RCD remains poorer than non-complicated CD. From the perspective of the development of lymphoma in patients with RCD; age over 65, albumin level less than 3.2 g/dl, Hb less than 11gr/dl and presence of total villous atrophy at the time of diagnosis constitute a significant risk. In this group of patients not responding to gluten-free diet; such agents like corticosteroids, 6-mercaptopurine and azathioprine are used (28).

Complications

Vitamin and mineral deficiencies may emerge with or without malabsorption findings. As being a chronic illness and a life-long diet

might reveal accompanying psychosocial problems. In long terms, the connection between CD and lymphoma has been understood for the first time in 1984 (186). Gough et al. (187) propounded that, the mucosal lesions in CD creates a "pre-malignant" situation. Similarly, Cooper and Read (188) reported that the risk of lymphoma development increases 50-100 times in patients with CD. As a result; the risk of malignant disease development in long-terms and complications might be highly encountered due to diagnostic delays.

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