Atypical presentations of celiac disease

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SUMMARY: Celiloğlu C, Karabiber H, Selimoğlu MA. Atypical presentations of celiac disease. Turk J Pediatr 2011; 53: 241-249.

Celiac disease (CD) has a wide variety of clinical presentations; together with the "classical form", in which the intestinal symptomatology is prevalent, there are "atypical forms" with predominating extra-intestinal clinical features, and the "silent form", with no clinical symptom.

The "atypical forms" of the disease are characterized by few or no gastrointestinal symptoms, and predominating extra-intestinal features such as neurologic, dermatologic, hematologic, endocrinologic, reproductive, renal, psychiatric, skeletal, and liver involvement(s). Silent presentation of CD may be identified through screening of high-risk groups.

Today, it is well known that CD might account for several chronic health issues, so it is essential for healthcare professionals to have a high level of suspicion for the atypical presentations of CD.

Key words: celiac disease, atypical.

Celiac disease (CD) is a highly prevalent autoimmune disorder that is triggered by the ingestion of wheat gluten and related proteins of rye and barley in genetically susceptible individuals[1]. The pathogenesis is based on the sensitivity against gluten that results in inflammation and atrophy of the mucosa of the small intestine. Genetic, environmental and immunological factors may play a role in the pathogenesis[2]. CD is known to be an important causative factor for both gastrointestinal (GI) and systemic symptoms and signs, and is considered as a multisystemic disorder[3].

Clinical Presentations

Celiac disease (CD) has a wide variety of clinical presentations; together with the "classical form", in which the intestinal symptomatology is prevalent, there are "atypical forms" with predominating extra-intestinal clinical features and the "silent form" with no clinical symptom. The typical clinical manifestations of the disease are encountered during the early periods of life, and the clinical spectrum of the disease broadens during the following years[2].

The notion about CD is evolving; it is now recognized that children with CD, in whom the diagnosis is somehow delayed, the disease may present itself later with either typical or atypical manifestations. The classical form presenting with mainly diarrhea and malabsorption syndrome, which used to be the leading presentation among children, is reported to be decreasing[4,5]. The decreased rate of CD with typical symptoms is partly due to the increased awareness of the disease, introduction of several serological markers and the increased rate of the early diagnosis[6].

The Canadian Celiac Association's survey, conducted in 1989-91, which included 1294 respondents with biopsy-confirmed CD, reported that over 60% of the respondents, including both children and adults, had to consult three or more physicians before the diagnosis was made[7]. Makharia et al.[8] reported that almost half of the adult patients with CD presenting with atypical manifestations consulted physicians other than gastroenterologists.

"Atypical" Clinical Forms

The 'atypical' forms of the disease are characterized by few or no GI symptoms, and predominating extra-intestinal features such as refractory iron deficiency anemia, osteoporosis,

short stature, pubertal delay, infertility, and recurrent spontaneous abortions (Table I)[9,10].

Nervous System Involvement

After the first report of Cooke and Smith[11] in 1966, numerous papers have been published reporting the association of CD and neurological symptoms. Neurological symptoms may precede or follow the diagnosis of CD, representing sometimes the only clinical manifestations.

Peripheral neuropathy and cerebellar ataxia are the most common neurological deficits in CD[11-16]. Other neurological symptoms include occipital calcifications[17], seizures[18], headache[19], and myopathy[20].

Luostarinen et al.[21] conducted a study on 26 patients with CD and found that 31% had abnormalities in neurophysiologic studies, compared with only 4% of controls with reflux disease.

The frequency of unknown CD in patients with neuropsychological symptoms is about 16%, and in a recent study, approximately 7% of new CD cases were diagnosed in the presence of neuropsychological disorders[22].

The pathogenesis of neurological damage is poorly understood, and the response to a gluten-free diet (GFD) is still controversial[23]. Humoral immune mechanisms have been proposed in the pathogenesis of both ataxia and peripheral neuropathy. Antibodies to gliadin that cross- react with Purkinje cells have been inconsistently reported in the sera of celiac patients with ataxia[24,25], antibody reactivity to neural antigens was identified[26], and IgG antibodies to gangliosides have been found in adult CD patients with neuropathy and other neurological manifestations[12,27,28]. The possible role of auto reactivity to gangliosides in CD is unclear[29]. A recent study in a cohort of celiac children did not find a correlation between antibodies to gangliosides and neurological manifestations or GFD[29]. Nutritional factors have also been suspected in the etiology of the neurological deficits, but clear evidence is lacking. Today, the link between CD and neurological disorders is partly attributed to the genetic background, most importantly the HLA region on chromosome 6 and other markers[3]. The link between the most frequent neurological deficits described and gluten sensitivity remains to be identified through further molecular/immunological studies.

Musculoskeletal System Involvement

Both osteomalacia and osteoporosis have been reported to be associated with CD (30,31). Numerous factors including secondary hyperparathyroidism due to vitamin D deficiency as well as systemic inflammation seen with CD (32-34) have been postulated to affect bone mineral density (BMD) in CD. Vitamin D activity is also impaired, with reduced vitamin D-dependent transporter protein seen in active CD[35-37]. Indeed, decreased BMD has been reported even in patients with clinically silent CD[4]. CD has also been linked to impaired zinc absorption, leading to a reduction of insulin-like growth factor (IGF)-1, which has been correlated with decreased BMD[34,38-41] and to amenorrhea or male hypogonadism, which could also contribute to decreased bone mass[42,43]. The reduced BMD, associated with an increased risk of fracture, improves after a GFD, but reduced BMD might not attain the normal levels[44].

Neuromuscular disorders may be the presenting feature of CD. Muscle involvement is reported as a rare complication of CD. Vitamin E deficiency was reported as an etiologic factor in the pathogenesis of the myopathies associated with CD[45].

Arthritis is reported as an infrequent presentation of CD[46].

Liver Involvement

In 1977, Pollock[47] first reported a possible association between CD and liver dysfunction. During the following decades, several hepatic disorders have been described in association with CD.

Today, it is well known that isolated hypertransaminasemia with nonspecific histological changes in a liver biopsy is the most common hepatic presentation of CD. In one study, a total of 114 consecutive pediatric CD patients were included, and hypertransaminasemia was found in 32% of them; in 5 patients, it was the only manifestation of CD (4.3%). Younger age was reported to be significantly associated with hypertransaminasemia, and the aminotran-

Table I. Summary of Disorders Associated with CD and/or Atypical Manifestations of CD

NERVOUS SYSTEM
Peripheral neuropathy
Cerebellar ataxia
Occipital calcifications
Seizures
Headache
Myopathy
Neuropsychological disorders

LIVER DISORDERS
Isolated hypertransaminasemia
Autoimmune hepatitis
Primary biliary cirrhosis
Primary sclerosing cholangitis
Hemochromatosis
Massive hepatic steatosis
Cirrhosis

HEMATOLOGICAL SYSTEM
Iron deficiency anemia
Macrocytic anemia
Blood-count abnormalities (leukopenia, thrombocytopenia)
Splenic hypofunction
Thrombocytosis
Venous thrombosis
Prolongation of coagulation assays
Selective IgA deficiency

ENDOCRINOLOGIC AND AUTOIMMUNE DISORDERS
Insulin-dependent diabetes mellitus
Autoimmune thyroid disease
Sjögren's syndrome
Addison's disease
Autoimmune liver disease
Cardiomyopathy

ONCOLOGICAL DISORDERS
Non-Hodgkin lymphoma
Small bowel adenocarcinoma
Esophageal and oropharyngeal squamous carcinomas

RENAL SYSTEM
IgA nephropathy
Chronic glomerulonephritis
Renal failure

PULMONARY SYSTEM
Idiopathic pulmonary hemosiderosis

MUSCULOSKELETAL SYSTEM
Osteomalacia
Osteoporosis
Arthritis
Myopathy

DERMATOLOGIC SYSTEM
Dermatitis herpetiformis
Xerosis
Alopecia areata
Dermatomyositis
Cutaneous vasculitis
Urticaria
Atopic dermatitis
Prurigo nodularis
Psoriasis
Chronic ulcerative stomatitis
Linear IgA dermatosis
Vitiligo
Lupus erythematosus
Lichen sclerosus
Palmoplantar pustulosis
Keratosis pilaris
Pityriasis rubra pilaris
Erythroderma
Necrolytic migratory erythema
Cutaneous amyloidosis
Annular erythema
Partial lipodystrophy
Generalized acquired cutis laxa
Ichthyosis
Transverse leukonychia
Erythema elevatum diutinum
Cutaneous sarcoidosic granuloma

REPRODUCTIVE SYSTEM

Male	Female
Hypogonadism	Delayed menarche
Impotence	Amenorrhea
Immature secondary sex characteristics	Recurrent abortions
Reduced semen quality	Reduced pregnancy rate
Altered spermatic motility	Early menopause
Loss of libido	Loss of libido
Infertility	Infertility

PSYCHIATRIC
Schizophrenic symptoms
Major depression
Affective disorders
Social phobia

sferases normalized with a GFD in all 35 patients who were followed for an average period of one year[48]. On the other hand, hypertransaminasemia observed in CD may be partly attributed to muscle injury including rhabdomyolysis[45]. Two pediatric cases pointing to this possible association have been reported[49].

Celiac disease (CD) can coexist with autoimmune liver disorders such as autoimmune hepatitis, primary biliary cirrhosis and primary sclerosing cholangitis. Primary biliary cirrhosis was clearly linked to CD with two large population-based studies[50,51]. Primary sclerosing cholangitis was first found to be associated with CD in 1988 in three patients with diarrhea and steatorrhea, but larger series

regarding the link between primary sclerosing cholangitis and CD are missing. Association of autoimmune hepatitis and CD has been evaluated in only a limited number of case reports and survey studies. Unfortunately, many appeared before hepatitis C testing[52]. The possible association between these disorders and CD was attributed to the possibly common immunologic/pathological pathways.

Celiac disease (CD) has also been associated with hemochromatosis; both are associated with the HLA-region on chromosome 6[52,53-55]. Butterworth et al.[56] observed that HFE (hemochromatosis susceptibility gene) locus mutations are common in CD patients from the United Kingdom and may be important in protecting CD patients from iron deficiency, while others suggested that the significance of these observations may be controversial[57].

In addition to the immune-based damage, chronic changes in liver chemistry tests may reflect a direct effect of CD. For instance, impaired absorption and resultant malnutrition may lead to deposition of fat in the liver, which leads to reduced fat mobilization from hepatocytes. Indeed, massive hepatic steatosis has occasionally been reported in CD. Finally, but very rarely, patients may develop a specific complication of CD that involves the liver, such as a T-cell form of lymphoma[52].

Mildly abnormal liver biochemistry may provide a shortcut for the early diagnosis of CD. Routine investigations for undiagnosed liver disease should include tissue transglutaminase testing. If left untreated, celiac-induced hepatitis may rarely progress to end-stage liver disease.

Dermatologic Findings

Various visceral and skin-mucosal involvements have been described in association with CD[58]. Dermatitis herpetiformis (DH), alopecia areata, dermatomyositis, cutaneous vasculitis, urticaria, atopic dermatitis, prurigo nodularis, psoriasis, and chronic ulcerative stomatitis are the main dermatological associations of CD that have been reported[58].

Linear IgA dermatosis, vitiligo, lupus erythematosus, lichen sclerosus, palmoplantar pustulosis, pityriasis rubra pilaris, erythroderma, necrolytic migratory erythema, cutaneous amyloidosis, annular erythema, partial lipodystrophy, generalized acquired cutis laxa, ichthyosis, transverse leukonychia, erythema elevatum diutinum, and cutaneous sarcoidosic granuloma cases linked to CD were also reported[58-61]. One of the few studies conducted in Turkey describing the dermatologic findings associated with CD showed that cutaneous, mucosal, nail, and hair findings were detected in 74.5%, 27.3%, 20.0%, and 7.3% of patients, respectively. The most prevalent dermatologic diagnosis was xerosis (69.1%) followed by keratosis pilaris (32.7%). No significant relationship was detected between the cutaneous findings and the duration of the illness[62].

However, the only proven association of CD with dermatological disorders is DH[58]. DH, an intensely pruritic vesicular rash found anywhere on the body, is one of the leading modes of clinical manifestation of CD[3,63]. The skin biopsy shows the characteristic lineal, granular deposits of IgA in the dermal papillae[3]. This condition affects about 15-25% of patients with CD[3]. Although dapsone controls skin lesions of DH, a GFD allows patients to discontinue the drug.

Patients with alopecia areata were found to be at high risk of CD, but sufficient evidence for this association is missing[58]. Recurrent aphthous ulceration is the presenting symptom of CD in 10-40% of patients with untreated CD. Other oral lesions can also occur, including the geographic atrophic glossitis due to B vitamin deficiency and the dental enamel hypoplasia related to a deficit in the dentin synthesis (64).

Hematologic Findings

Celiac disease (CD) is a common cause of various hematological disorders, the most common of which is anemia. The proximal intestine, the absorption site of dietary iron, is damaged during the course of CD, and it is not surprising that iron deficiency anemia is prevalent among newly diagnosed cases. The anemia associated with CD may also be due to malabsorption of micronutrients such as folic acid and vitamin B12[65]. It is also frequently implicated in the etiology of other blood-count abnormalities, splenic hypofunction and intestinal lymphomas[66].

Bottaro et al.[4] reported iron deficiency anemia as the most frequent extra-intestinal symptom among both pediatric and adult CD patients[4]. According to an Indian report, besides short stature, refractory iron deficiency anemia was found to be one of the leading modes of presentation of atypical CD[67]. The prevalence of CD in patients referred for GI endoscopy for investigation of iron deficiency anemia varies from 3% to 12%[68,69]. The iron deficiency in CD primarily results from impaired absorption of iron but there may also be occult blood loss in the GI tract[70,71]. Occult GI blood loss was seen in 26.7% of children with CD and appears to respond to treatment with a GFD[72] More recent studies have suggested, however, that occult GI bleeding in patients with CD may be much less common[73,74].

Celiac disease (CD) may also induce folate deficiency[75] and vitamin B12 deficiency presenting with macrocytic anemia, leukopenia and thrombocytopenia[65]. Copper deficiency has also been described in adults and children with CD and may result in anemia and thrombocytopenia[76,77]. Deficiencies of both folate and copper have been implicated as a possible etiology for the leukopenia[65].

Thrombocytopenia has been reported rarely in patients with CD and may be autoimmune in nature[65]. Thrombocytosis in association with CD appears to be more common than thrombocytopenia, occurring in up to 60% of patients[65]. The exact etiology of the thrombocytosis is unknown, but it may be secondary to inflammatory mediators or, in some cases, secondary to iron deficiency anemia or functional hyposplenia. The thrombocytosis may resolve after institution of a GFD[65].

Venous thrombosis has been reported in CD. Hyperhomocysteinemia is a frequent finding in CD and may be related to an increased tendency to form clots[78]. CD may also be associated with coagulopathy. Malabsorption of vitamin K results in a decrease in K vitamin–dependent coagulation factors and results in prolongation of coagulation assays such as the prothrombin time (PT), international normalized ratio (INR) and the activated partial thromboplastin time (aPTT)[79]. Nevertheless, it was found irrational to screen for CD in patients with isolated coagulation disorders[80].

Endocrinologic and Autoimmune Presentation

Autoimmune disorders arise 10 times more often in patients with CD compared to the general population[81], including type 1 diabetes mellitus (DM), thyroid disease, Sjögren's syndrome, Addison's disease, autoimmune liver disease, cardiomyopathy, and neurological disorders. The association of autoimmune disorders and CD is thought to be related to a shared genetic tendency (HLA alleles) and a common immunological mechanism in addition to the presence of CD itself[81].

The two most common forms of endocrinologic pathologies seen with CD are type 1 DM, and thyroid disease[3]. Ansaldi et al.[82] performed a study in Italian children and found a high incidence of autoimmune thyroid disease in 90 of 343 (26.2%) patients with CD (62 on GFD) and in 20 (10%) of the control subjects ($p=0.001$). The high prevalence of CD among type 1 DM emphasizes the need for routine screening in that population[83].

The high frequency of autoimmune thyroid disease found among patients with CD, even those on a GFD, may justify a thyroid status assessment at diagnosis and at follow-up evaluation of patients with CD[84].

Oncological Aspects

It is generally accepted that CD is associated with an increased risk of non-Hodgkin lymphoma, small bowel adenocarcinoma and esophageal and oropharyngeal squamous carcinomas[81,85]. The predominant celiac-associated lymphoma is the enteropathy-associated T-cell lymphoma, which has a poor prognosis and is rapidly fatal[85].

The mechanisms responsible for the development of malignancies during the course of CD are not established[3]. A strict GFD is thought to be protective against the development of malignant disease[86], although this might not be the case for the development of non-Hodgkin lymphoma[87].

Reproductive System Problems

Both males and females with CD may present disorders related to the reproductive system. In particular, female CD patients may present with delayed menarche, amenorrhea, infertility

with recurrent abortions, early menopause, and a reduced pregnancy rate[43,88]. In male CD patients, hypogonadism, impotence, immature secondary sex characteristics, reduced semen quality, altered spermatic motility, and infertility have been described[43,88].

The pathogenesis of reproductive disorders associated with CD is not clear, and various hypotheses have been suggested[89]. The first is that gluten acts as an auto-antigen and produces immunogenic response toward organs and hormones required for pubertal development. This hypothesis can explain the pubertal delay in girls; however, it cannot explain the androgen resistance detected in boys. Another hypothesis is malabsorption of micronutrients required for sex hormone–binding globulins, metabolism of receptor proteins and increased cytokine (particularly interleukin 6) production. As iron, folic acid and B vitamins are critical for development in children and adolescents, dietary deficiencies or absorption disorders might result in pubertal delay[88,90].

Celiac disease (CD) is also associated with reduced frequency of sexual intercourse[91]. Hyperprolactinemia is seen in 25% of celiac patients, which causes impotence and loss of libido. Gluten withdrawal and correction of deficient dietary elements can lead to a return of fertility in both men and women[43].

Patients with CD were also reported to have premature babies or babies with low birth weight with increased perinatal mortality and a shorter duration of breast feeding[92-94]. According to our unpublished data, the CD prevalence was found to be 1.3% and 1.9%, respectively, in the mothers and fathers of babies either born prematurely or with low birth weight. The prevalence of CD in those with healthy babies was 0.8%.

Nephrologic Findings

Various reports contributing to the association of renal diseases and CD have been conducted. Collin et al.[95] reported that patients with IgA nephropathy are at increased risk for CD. Fornasieri et al.[96] found evidence of CD in 2/121 patients with IgA nephropathy. Recently, Ludvigsson et al.[97] reported that CD is associated with an increased risk of chronic glomerulonephritis and renal failure. Immune characteristics associated with CD were suspected to increase the risk of chronic renal disease; individuals with CD were also reported to be at a moderately increased risk of any form of glomerulonephritis[97].

Psychiatric Findings

Patients with CD may present with schizophrenic symptoms, major depression[75,98], as well as affective disorders such as the state-reactive form of anxiety and current depression[64]. A significantly higher prevalence of social phobia in CD patients compared with healthy subjects was also reported[99].

Several possible factors and mechanisms have been hypothesized in order to explain the high prevalence of affective disorders in CD patients. A reduced neuronal production of monoaminergics represents one of the mechanisms currently implicated in the pathogenesis of behavioral disorders. Hallert et al.[100] showed a significant reduction of serotonin metabolites in cerebrospinal fluid of CD patients.

Pulmonary Involvement

Idiopathic pulmonary hemosiderosis (IPH) is a rare disease of unknown autoimmune etiology mainly affecting children and adolescents[101]. The association of IPH and CD is well known and is attributed to the common pathogenetic/immunological mechanisms. For IPH patients with CD, GFD without any steroids or immunosuppressants was reported to be very effective. Patients suffering from IPH should be screened for CD even in the absence of the GI symptoms.

CONCLUSION

Celiac disease (CD) may present with a wide spectrum of symptoms and signs (Table I). It is a frequent disorder, and since many patients with CD have the silent/atypical form, physicians should be aware of those atypical manifestations and high-risk populations in order to avoid underdiagnosis of the disease.

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