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Celiac Disease in the Elderly

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Abstract

It has become recently apparent that celiac disease, though once thought to be a primarily childhood disease, can affect people of any age. Epidemiologic studies have suggested that a substantial portion of patients are diagnosed after the age of 50. Indeed, in one study, the median age at the diagnosis was just under the age of 50 with one-third of new patients diagnosed over the age of 65. The purpose of this review is to address the prevalence, clinical features, diagnosis and consequences of celiac disease in the elderly. We will also review management strategies for celiac disease and adjust these with emphasis on the particular nutritional and non-nutritional consequences or associations of celiac disease as they pertain to the elderly.

Keywords

Celiac disease; Elderly; Aging

Introduction

Celiac disease is a chronic autoimmune enteropathy occurring in genetically predisposed individuals following ingestion of wheat gluten and related protein fractions of other grains.¹ In patients with celiac disease, tissue transglutaminase binds to gliadin derived peptides at the gut level and deamidates certain glutamine residues in these peptides. Antigen presenting cells which express HLA-DQ2 or -DQ8 then present these gliadin-tissue transglutaminase complexes to the T cells. The process of deamidation increases the affinity of the T cells to the gliadin peptides. These T cells then help the B cells to produce antibodies against both the gliadin and tissue transglutaminase antigens through epitope spreading. Such inflammatory response results in mucosal damage in forms of lymphocytic infiltration, crypt hyperplasia and shortening or loss of the villi, which in turn leads to malabsorption.²⁻⁴ As a

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result, patients present with diarrhea, weight loss, steatorrhea, or malnutrition syndromes such as anemia and diminished bone mass due to deficiencies of important nutrients (iron, folate, calcium and fat-soluble vitamins).

In addition to the morbidities that result from malabsorption, celiac disease is also associated with other autoimmune diseases and malignancies, leading to higher risk of morbidity and mortality among these patients.⁵⁻⁷ The risk of autoimmune disorders and cancers particularly increase in older celiac patients and is shown to be associated with both the age and the duration of gluten exposure.^{8,9}

Despite growing knowledge regarding celiac disease, very little is known about this condition in the elderly people.¹⁰ This lack of awareness along with the lower frequency of typical symptoms in older celiac patients as compared to the younger ones leads to significant delays in the diagnosis of celiac disease in this population which in turn increases the morbidity and mortality in this group.^{5,11} This review focuses on the epidemiology, clinical presentations, complications, diagnosis and management of celiac disease in the elderly population.

Epidemiology

For long time, celiac disease was considered a disease of childhood and was thought to rarely occur in older people.¹² Now there is growing evidence showing an increased rate of diagnosis among adults. Recent reports suggest a trend towards increased incidence of celiac disease, particularly among elderly people.¹³ In 1960, only 4% of newly diagnosed celiac disease patients were over 60 years of age.¹⁴ But later studies showed that 19-34% of new cases of celiac disease are diagnosed in this age group.^{11,15-18} Interestingly, a survey of 2,440 celiac patients in the United States reported that the proportion of celiac disease patients diagnosed in the elderly is similar to that of patients diagnosed before 18 years of age (16% versus 15%, respectively).¹⁰ In accord with these studies, a population-based study of Olmsted County residents in Minnesota, reported that celiac disease incidence rates (new cases of celiac disease per 100,000 person-year) in people over 65 years of age increased significantly from 0.0 in 1950-1959 to 15.1 in 2000-2001.¹³ Our recent data suggests that incidence rates are still increasing among all age groups including the elderly (Fig.1, unpublished data).

The estimated prevalence of celiac disease is now about 1% in the general population.^{19,20} In early 1990s, the prevalence of diagnosed celiac disease in the United States was estimated to be 1 in 5,000.²¹ Around the same time, reports from Europe showed a 10-20 times higher prevalence of celiac disease in Sweden and Italy.^{22,23} Later, a large multi-center study in the United States performed serologic screening for celiac disease and found an overall prevalence of 1 in 133 among patients with no risk; a prevalence that was similar to that of European studies.¹⁹ Interestingly, the prevalence of biopsy-proven celiac disease among adults is reported to be 1.2%²⁰ and a large population-based study on people between 45-76 years of age has shown a seropositive prevalence of 1.2% for undetected celiac disease.²⁴ More recently, a study from Finland, found even a higher prevalence of biopsy-proven celiac disease (2.13%) in older people (52-74 years of age).²⁵ A recent study has demonstrated that celiac disease may truly occur for the first time in an elderly individual, despite a life-long apparent tolerance of gluten ingestion, not merely be diagnosed at this age.²⁶

Similar to other autoimmune disorders, celiac disease occurs more frequently in women, with a female to male ratio of 2:1.^{10,27} In both men and women, the incidence rate of celiac disease continues to increase until 65 years of age at which point the incidence rate begins to decrease in women, while continues to raise gradually in men. Nonetheless, the incidence

rate still remains higher in elderly female over 65 years of age as compared to the elderly males of the same age.^{13,15}

Clinical presentations

It has become apparent over the last 20 years that celiac disease produces a spectrum of clinical features that extend from severe malabsorption with profound nutritional deficiencies to presentation with a single symptom such as anemia, accelerated osteoporosis or osteomalacia. For unknown reasons, presentation of intestinal symptoms is less prominent in elderly celiac patients compared to the younger ones.²⁸ Instead, the signs of micronutrient deficiencies may be the first and often the only presentation of the disease in the elderly.

Anemia is present in 60-80% of elderly patients with celiac disease^{11,17} and has been mainly attributed to the deficiency of micronutrients, particularly iron. Deficiencies of other nutrients such as folate and vitamin B12 may account for a smaller percentage of anemias in these patients which in conjunction with iron deficiency, sometimes causes dimorphic peripheral smear.²⁸⁻³² It is hypothesized that anemia of celiac disease is multifactorial and systemic inflammation may also be a contributing factor in the etiology of anemia in celiac disease.²⁹ It is shown that some anemic celiac patients have high levels of ferritin (an acute phase reactant) and erythrocyte sedimentation rate (ESR), suggestive of systemic inflammation and anemia of chronic disease in these patients.^{29,33}

While abdominal symptoms are still common in the elderly celiac patients, many of these individuals present with milder symptoms, such as abdominal bloating, flatulence, and abdominal discomfort which make the diagnosis more difficult. The classical malabsorptive symptoms such as diarrhea, weight loss and abdominal pain are less common in elderly celiac patients.³⁴ It should be noted though that celiac disease is the most common cause of steatorrhea in people over 50 years of age and the second most common cause in those over 65 years.³⁵ Nonetheless, it appears that malabsorptive-induced bowel dysfunction is tolerated well among elderly people. Diarrhea, although a common feature, may be mild or intermittent in older celiac patients and a few patients may even present with constipation.^{17,36} In addition, some patients may not present with any intestinal symptoms at all, a condition called silent celiac disease.³⁷

Deficiencies of calcium and vitamin D may be another clinical feature of celiac disease leading to decreased bone mass, particularly in elderly patients who are already susceptible to metabolic bone disorders.^{38,39} Malnutrition can also cause hypoalbuminemia in these patients which additionally may lead to hypocalcemia and hypomagnesemia. Hypoalbuminemia itself can also present with edema and ascites in these patients.¹⁷ In about 20% of celiac patients, hepatocellular changes may occur presenting with abnormal liver function test, a condition called *celiac hepatitis*. This in turn can lead to further investigation for exclusion of other causes of the liver disease.⁴⁰ It is shown that a gluten-free diet has beneficial effects on resolution of symptoms in celiac hepatitis.⁴¹

In addition to the gastrointestinal symptoms and malnutrition disorders that result from intestinal involvement, celiac disease may also present through its associated disorders and complications. Dermatitis herpetiformis, well recognized as the skin manifestation of celiac disease, may be the first presentation of gluten-sensitivity in celiac patients.⁴² Dermatitis herpetiformis occurs in about 25% of patients with celiac disease and is more common in men than women with a male to female ratio of about 2:1.^{43,44} The average age of presentation is about 40 years, with most patients aging between 20 to 70 years. Nonetheless, it can occur at any age, even in the childhood. The disease presents with extremely pruritic papulovesicular rash on the extensor surfaces (elbows, knees, buttocks, and scalp).^{44,45} About 80% of dermatitis herpetiformis patients show intestinal alterations

consistent with celiac disease in the endoscopic or histopathologic evaluation. However, only 20% of these patients initially have gastrointestinal symptoms of celiac disease.⁴⁶ The diagnosis is made by direct immunofluorescence staining of perilesional skin specimen showing granular IgA deposition in the dermoepidermal junction, more prominently within the papillary tips.⁴⁵ The basis of therapy relies on instruction of a gluten-free diet which controls the underlying pathology and results in slow resolution of symptoms. Dapsone therapy could be used for suppression of initial symptoms and even intermittently for occasional outbreaks.⁴⁵

Other autoimmune diseases are also frequently associated with celiac disease and may provide clues for suspicion of celiac disease in an elderly patient. Autoimmune thyroid disorders are the most common associated autoimmune diseases in elderly celiac patients, with majority of patients presenting with hypothyroidism.^{28,47} In addition, the risk of intestinal lymphoma and other celiac disease-associated malignancies is higher in elderly people⁴⁸ and some patients may present with acute complications of such diseases including intestinal obstruction or perforation.⁴⁹⁻⁵¹ Occasionally, celiac disease may present with cavitation of mesenteric lymph nodes and splenic atrophy or with intestinal ulceration with or without underlying malignancy.⁵²⁻⁵⁴

Diagnosis

Clinical diagnosis of celiac disease in elderly can be quite challenging for primary care physicians. This may be in part due to the subtle clinical symptoms, low index of suspicion for celiac disease in the elderly people, and distraction towards more threatening conditions such as malignancies.^{10,28} For example, the mild changes in the bowel habits may be easily attributed to the functional changes in the intestinal track due to diseases such as irritable bowel syndrome, mood disorders (anxiety, depression, etc.) or even be considered as part of the normal aging process. A survey of elderly celiac patients has shown that a substantial number of these patients are incorrectly diagnosed as irritable bowel syndrome many years before their celiac disease is diagnosed, leading to an average delay of 17 years in the diagnosis.¹⁰ In addition, symptoms such as anemia in an elderly celiac patient may lead to extensive evaluation to rule out colon cancer before celiac disease being even considered.

Several diseases are considered in an elderly patient who presents with symptoms of malabsorption. Small intestine bacterial overgrowth, small bowel ischemia, and exocrine pancreatic insufficiency (in association with chronic pancreatitis or pancreatic cancer) may be more common in the elderly and sometimes can manifest with chronic malabsorption. These disorders can either mimic celiac disease in an older patient or can occur in elderly celiac patients due to their advanced age.^{37,55} Autoimmune enteropathy, albeit an extremely rare condition, has also been described in older patients. Non-granulomatous enterocolitis or self-limited enteritis may be seen in the elderly patients too. Malignancies, in particular cancers of gastrointestinal tract should be listed as part of the differential diagnosis in an elderly patient presenting with anemia or weight loss.

In general, elderly celiac patients are probably just as likely to have serologic abnormalities as younger patients; and the HLA association with celiac disease persists in this age group. The diagnosis for celiac disease in the elderly patients proceeds along the same lines as in the younger celiac patients. Serologic tests are frequently used for the diagnosis and follow-up of celiac disease. The basis of serologic testing for celiac disease relies on the measurement of (auto)antibodies, particularly the IgA isotype. The diagnosis is usually confirmed by histologic evaluation of small intestinal biopsy which is the gold standard test for celiac disease diagnosis. It is important for the primary care physicians to be aware of the

advantages and disadvantages of each diagnostic test and select the best option based on each patient's individual needs.

The current available serologic tests for celiac disease diagnosis include anti-endomysial (EMA) and anti-tissue transglutaminase (TTG) autoantibodies as well as antibodies against gliadin peptides (Tab.1). For EMA testing, monkey esophagus or human umbilical cord is used as a substrate. The test is considered highly specific, with a reported specificity of close to 100% in most studies.^{56,57} The sensitivity is also high (>90%) in most reports; however, recent studies have shown that the sensitivity decreases significantly in patients with milder degree of intestinal damage and can reach to as low as 30% in patients with partial villous atrophy.⁵⁶⁻⁵⁸ The cost of EMA testing is high which in addition to the subjective and qualitative nature of the test, limits its applicability for routine diagnosis of celiac disease. TTG IgA test, on the other hand, does not have these limitations of EMA testing and has a comparable sensitivity (~90%) and specificity (~95%) to that of EMA.⁵⁹ TTG IgA measurement is therefore recommended as the initial screening test for celiac disease.¹ Anti-gliadin antibodies that were once used frequently for celiac disease diagnosis are no longer recommended due to their poor sensitivity and specificity.⁵⁹ Instead, newly-developed assay that uses deamidated gliadin peptides (DGP) as the antigen is shown to be significantly more accurate than the conventional gliadin antibody testing for celiac disease diagnosis.^{60,61}

Despite good sensitivity and specificity of these antibody tests, a number of celiac patients may be missed on the basis of serologic testing alone. Similar to EMA testing, TTG and DGP antibodies have more false negative results in patients with milder degree of enteropathy.^{60,62} Another possibility for a false negative test in a celiac patient is IgA deficiency. In this setting, IgG isotype of relevant antibodies can be used as a diagnostic test. It is shown that DGP IgG is significantly more sensitive than TTG IgG for celiac disease diagnosis and therefore may be more helpful in these circumstances.^{60,62} Recently-developed multiplex immunoassay can simultaneously measure TTG and DGP IgA and IgG antibodies with a similar accuracy to that of enzyme linked immunosorbent assay.⁶² The combination testing may increase the sensitivity and the detection of IgA deficient patients, but still a number of celiac patients, particularly those with partial villous atrophy, remain seronegative for all of the relevant antibodies. It is therefore important that patients undergo intestinal biopsy when there is a high suspicion for celiac disease despite a negative serology.^{60,63} Intestinal biopsy can also confirm the diagnosis in seropositive patients and provide baseline information regarding the degree of intestinal damage for further evaluation of response to the treatment.

The histologic diagnosis of celiac disease is made by the presence of enteropathy in the duodenal biopsy specimens. Increased intraepithelial lymphocyte infiltrate, crypt hyperplasia, and villous atrophy are the three histologic features of celiac enteropathy.⁶⁴ There are no age-related changes in the intestine of older individuals and therefore histologic diagnosis of celiac disease does not differ from that of young patients.³⁷ While one might hesitate to subject a very elderly patient with multiple comorbidities to intestinal biopsy as a primary or initial test for celiac disease, older patients are more likely to undergo endoscopy (to exclude other causes of their symptoms) and to have their first diagnosis made by duodenal biopsies rather than serology. It would be important in these patients to provide supportive evidence by means of specific serologic testing and, if negative, compatible HLA genetic susceptibility for celiac disease.^{60,62,63} Close follow-up of the elderly patients is important to ensure appropriate response and the correction of symptoms and consequences of malabsorption. It should be noted that healing of the intestine may be slow in older patients diagnosed with celiac disease.

Complications

Autoimmune disorders

Celiac disease has many features of an autoimmune disorder including strong association with MHC class II molecules, presence of (anti-tissue transglutaminase) autoantibodies, multi-organ involvement, and dysregulation of innate and adaptive immune responses.⁶⁵⁻⁶⁹ One of the autoimmune features of celiac disease is its common occurrence with other autoimmune disorders.^{67,68} It is important for the physicians to be aware of these associations, as it can particularly improve case finding among elderly patients with less typical symptoms. Moreover, knowing increased risk of such diseases in celiac patients leads to better management of these patients in terms of diagnosis and treatment of the associated autoimmune disorder.

In general, autoimmune disorders are 3-10 times more prevalent in celiac patients and 5 times more prevalent in family members of celiac patients as compared to the general population.⁷⁰⁻⁷⁴ Similarly, celiac disease occurs more frequently in patients with autoimmune disorders⁷⁵⁻⁷⁷ as well as in those who have a relative affected with celiac disease.¹⁹ The risk is much higher when both conditions are present together. About 25% of the individuals who have both an autoimmune disorder and a positive family history of celiac disease are found to have celiac enteropathy through screening.⁷⁴ It is shown that the risk of autoimmunity is directly associated with age at the diagnosis of celiac disease.^{8,78} Although some authors attribute this association to the duration of gluten exposure,⁸ others have only found age as a significant predictor of autoimmunity in adult population.⁷⁸

The association of celiac disease with autoimmune diseases such as type 1 diabetes and autoimmune thyroid disorders (Hashimoto thyroiditis and Graves' disease) is well established.⁷⁹⁻⁸⁴ In contrast to children population, where type 1 diabetes is more commonly associated with celiac disease,^{80,81} older celiac patients present with lower prevalence of type 1 diabetes. Instead autoimmune thyroid disorders are frequently associated with celiac disease in the elderly.^{82,85}

Involvement of hepatobiliary and nervous system in celiac disease also occurs through immune-mediated processes. Autoimmune cholestatic liver disorders such as autoimmune hepatitis, primary biliary cirrhosis, and primary sclerosing cholangitis are more frequent in celiac patients than the general population.^{41,86} These are different from celiac hepatitis which does not occur through autoimmune processes. The response to the dietary treatment is also different between autoimmune liver diseases and celiac hepatitis. In contrast to celiac hepatitis that has a good response to a gluten-free diet, autoimmune cholestatic liver damage does not seem to respond efficiently to gluten exclusion.^{41,86}

Ataxia and neuropathy are two main neurologic complications of celiac disease which can particularly be problematic in the elderly patients.⁸⁷⁻⁸⁹ The disturbance of balance control due to involvement of nervous system leads to higher risk of falls in these patients which further increases the risk of bone fractures particularly in the elderly celiac patients with low bone density. Cognitive impairment, in particular accelerated dementia, has also been seen in older patients with celiac disease and unfortunately may not respond to a gluten-free diet.⁹⁰

Refractory Celiac Disease

Refractory celiac disease (RCD) is defined as significant malabsorption in a patient with severe enteropathy who has had a lack of initial response to a gluten-free diet or recurrence of symptoms despite strict adherence to the diet. RCD is a diagnosis of exclusion. The most common cause of unresponsiveness in celiac disease is gluten contamination of the diet.⁹¹

Even minute amounts of gluten used in pills, capsules, envelope adhesive, modified food starch, preservatives, and stabilizers can prevent healing of the intestine resulting in the persistence of symptoms. Other conditions that should be ruled out before the diagnosis of RCD is made include microscopic colitis, pancreatic insufficiency, small bacterial overgrowth, irritable bowel syndrome and lactose intolerance.^{91,92} There are rare enteropathies which can mimic celiac disease pathology in the elderly and may cause apparent failure of response to treatment. These include self-limited enteritis, autoimmune enteropathy, collagenous sprue and even NSAID injury.^{93,94}

RCD is categorized into two types based on the immunophenotype of intraepithelial lymphocytes; polyclonal with normal phenotype in RCD I and monoclonal with abnormal phenotype in RCD II.^{95,96} About 5% of celiac patients may develop RCD with the majority of patients belonging to the elderly group. In a study of 57 Mayo Clinic patients, the median (range) of age for RCD diagnosis was 58 (30-76) and 70 (47-76) years for RCD I and RCD II, respectively.⁹⁷ The diagnosis of celiac disease in half of RCD patients was made after 54 (in RCD I) and 61 (in RCD II) years of age. In the same study, the cumulative five-year survival was reported to be 80% in RCD I but just 45% in RCD II patients and the main causes of death were refractory state (in RCD I) and enteropathy-associated T cell lymphoma (in RCD II).⁹⁷ Unfortunately, in those RCD II patients who develop enteropathy-associated lymphoma, the prognosis is very poor.⁹⁸ In the new system proposed for the staging of RCD, the age (greater than 65 years old) was found to be one of the five prognostic factors with negative effect on the survival of RCD patients.⁹⁷

Malignancy

The risk of malignancy is increased in celiac patients, particularly in those with advanced age. The relative risk for the development of intestinal lymphoma in celiac patients is reported to be 5 to 300 in different studies.^{99,100} The incidence of lymphoma is much greater after the 6th decade of life, and it occurs more commonly in patients who were diagnosed with celiac disease between 50-80 years of age.⁹ The enteropathy-associated T cell lymphomas have the strongest association with celiac disease and present with multifocal and ulcerative lesions. This explains the high rate of bowel perforation in these patients which may sometimes be the initial presentation of the disease. There is also a high risk of perforation upon commencement of chemotherapy. Non-Hodgkin lymphomas and adenocarcinomas of gastrointestinal track are also more common in celiac patients than expected.^{48,101} Interestingly, the risk of breast cancer is reduced in celiac patients.^{6,102} Most studies show an increased mortality rate in celiac patients which has not always been attributed to the increased cancer risk in these patients.^{6,7,103} Even asymptomatic patients (silent celiac disease) have a higher mortality rate compared to the general population.¹⁰⁴ A gluten-free diet is shown to have a protective effect on the risk of malignancy in celiac patients.^{101,105}

Management

The treatment of celiac disease relies on the basis of strict adherence to a gluten-free diet. Despite high rate of dietary compliance reported in the elderly celiac patients,¹¹ the management of celiac disease in these patients has some specific challenges. Firstly, patients usually have a life-time of dietary habits that may be hard to break. They may also have limited financial or social resources and limited mobility restricting their ability to travel to gluten-free suppliers. Elderly patients may be residing in assisted living facilities where it may be difficult to provide them with a gluten-free diet. Additional issues relate to poor nutritional intake and impaired vision limiting their ability to read ingredient lists which are often minute in size.

Patients should be encouraged to seek out community support and family members should be recruited and probably should participate in the patient's dietary consultation. Direct communication between the dietician and the director of food services at the patient's institution, if institutionalized, are likely necessary to achieve a gluten-free diet. In the very elderly or debilitated patient who has relatively minor symptoms, consideration of not treating the patient with a gluten-free diet may have some rationale. However, it should be noted that patients can often have a dramatic improvement in chronic symptoms, even non-GI symptoms, after adherence to a gluten-free diet, and the opportunity for this recovery should not be lost.

Patients diagnosed with celiac disease should be referred to a gastroenterologist to ensure optimum management of the disease and its associate complications.³⁶ It is important that patients be investigated for the presence of anemia, calcium and vitamin D deficiency, osteoporosis, and thyroid and liver diseases during the follow-up visits. Calcium and vitamin supplementation should be encouraged in these patients and should be used in conjunction with bisphosphonates if the osteoporosis is present.

Conclusions

Celiac disease is a common disorder, not only in the young, but also in the elderly. It may linger for many years before the diagnosis, causing subtle or quite troubling symptoms and it may present for the first time with serious fatal complications. A greater awareness of the incidence and clinical presentation of celiac disease in the elderly is essential to prevent long delays in the diagnosis. Whilst the treatment for celiac disease is relatively straightforward, the elderly present specific challenges in the management of their celiac disease, particularly in view of making radical changes to diet as well as coping with the complications of longstanding malabsorption. A comprehensive, multidisciplinary approach to management of celiac disease should result in reduced morbidity in these patients. A management approach tailored to the particular challenges presented by elderly celiac patients is crucial to their success.

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Figure 1. Increased in the incidence rate of celiac disease in people older than 60 years of age over a 56-year period in Olmsted County, Minnesota (1950-2006); Incidence rate= new cases of CD per 100,000 person-years, adjusted to the US 2000 white population.

Table 1

Diagnostic Values of Antibody Testing for Celiac Disease in the Adult Population

Test	Sensitivity (%)	Specificity (%)
EMA IgA ⁵⁹	85-100	~100
TTG IgA ^{56,59}	80-100	90-100
TTG IgG ^{56,60}	20-60	>95
DGP IgA ^{60,61}	75-95	>95
DGP IgG ⁶⁰⁻⁶²	65-90	>95
Gliadin IgA ^{56,59}	60-90	80-100
Gliadin IgG ^{56,59,60}	40-80	70-90

The estimated range of sensitivity and specificity for serologic diagnosis of celiac disease based on reports from studies in adult population. The outlier results of some studies are excluded. EMA, Endomysial antibody; TTG, Tissue transglutaminase; DGP, Deamidated gliadin peptides.