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Adult celiac disease in the elderly

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Abstract

There is an increased awareness that celiac disease may occur in the elderly although presentations with either diarrhea, weight loss or both may be less common causing delays in diagnosis for prolonged periods. Higher detection rates also seem evident owing to active case screening, largely through serodiagnostic measures. In some elderly patients who are genetically predisposed, it has been hypothesized that celiac disease might be precipitated late in life by an antigen, possibly from an infectious agent. As a result, peptide mimicry or other poorly-defined mechanisms may precipitate an autoimmune gluten-dependent clinical state. Although diarrhea and weight loss occur, only isolated iron deficiency anemia may be present at the time of initial diagnosis. In addition, the risk of other autoimmune disorders, particularly autoimmune thyroiditis, and bone disease, are increased. Osteopenia may also be associated with an increased risk of fractures. Finally, elderly celiacs have an increased risk of malignant intestinal disease, especially lymphoma.

Key words: Celiac disease; Elderly; Lymphoma; Silent celiac disease

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INTRODUCTION

Celiac disease has been traditionally recognized in children and young adults, however, in recent years, detection in the elderly population has increased[1]. This is reflected historically in published clinical series from North America and Europe (e.g. about 7% in a Birmingham series were diagnosed after the age of 60 years, similar to a Mayo Clinic series of 4%[2]. Later, studies from the United Kingdom[3] recorded that about 25% were initially diagnosed in their seventh decade. Similar findings were also recorded in the United States[4], Sweden[5], Scotland[6], Ireland[7] and Canada[8]. In each, typical symptoms of impaired intestinal absorption, such as diarrhea or weight loss, while common, were less prominent compared to those with celiac disease diagnosed at a younger age, even though adult celiac disease was reported to be the most common cause of steatorrhea after the age of 50 years[9]. Others, however, have also recently emphasized the need to suspect celiac disease in the elderly, as even classical features of celiac disease may be ignored leading to prolonged delays in diagnosis[10-12].

CLINICAL PRESENTATION

A precise explanation for the apparent paucity of clinical findings in the elderly age group is still required. Firstly, this may be due, in part, to a limited mucosal extent of disease in the proximal duodenum and jejunum. As a result, symptoms and signs, such as diarrhea and weight loss, may be minimized. Instead, isolated deficiencies of specific nutrients, such as iron, may occur. Secondly, a low index of suspicion by the physician for celiac disease may lead to a delay in recognition or a distraction to other sinister disorders. For example, iron deficiency anemia may lead to studies to exclude colon cancer. Thirdly, some patients with elderly celiac disease may have cognitive impairment which makes the definition of some symptoms more difficult[13]. Occasionally, in those treated with a gluten-free diet, cognitive decline may be minimized or may resolve[11]. Finally, and most intriguing, recognition of celiac disease, in some cases, may not be delayed. Possibly, the disease may only be precipitated later in life by some environmental factor, such as a viral agent (e.g. adenovirus) or an as yet unidentified superantigen with a peptide structure that mimics, at a molecular level, the offending gluten peptide[14,15]. Especially intriguing is a recent report showing that in a biopsy-defined population,

celiac disease was more commonly found in the elderly than any other younger age group implying a critical need for active case finding, possibly through serological screening[16]. The reason for this late clinical definition of celiac disease needs to be further elucidated.

ASSOCIATED DISORDERS

A number of disorders have now been recognized in the elderly which might provide a clinical clue to underlying or occult celiac disease. In addition to isolated iron deficiency, folic acid or calcium deficiencies may also occur because the principal uptake site for these nutrients is also the proximal small intestine. Moreover, autoimmune disorders linked to adult celiac disease (and possibly with a similar etiopathogenesis) may be the predominant clinical manifestation of occult celiac disease, such as dermatitis herpetiformis[17,18] or autoimmune thyroiditis[19]. Celiac disease may also be associated with collagenous mucosal diseases (i.e. collagenous colitis)[20], as well as epithelial lymphocytosis of the stomach, colon and biliary tract[21-23]. In some patients, collagenous colitis may be a clue to underlying celiac disease[24], or may complicate celiac disease causing an apparently "refractory" diarrhea, despite a gluten-free diet. Finally, specific malignancies traditionally associated with celiac disease may occur, including lymphoma and small bowel adenocarcinoma[25,26].

Other disorders of the intestinal tract have been recorded. Gastric and duodenal ulcers may occur, but jejunal or ileal ulcers are especially worrying, since these may harbour a malignant small bowel lymphoma[25], especially if the presentation is associated with a free perforation of the small intestine[27]. Also, pancreatic calcification has been described, similar to the calcific pancreatitis noted in autoimmune pancreatitis, protein-energy malnutrition and long-term alcohol abuse[28].

LATENT CELIAC DISEASE

Latent celiac disease has also been documented in some elderly patients with dermatitis herpetiformis. In these patients, initial small bowel biopsies were architecturally normal (suggesting that celiac disease might not be present)[29]. Following a high gluten diet, however, histological changes of variable severity were induced, indicating that the small bowel mucosa was gluten-sensitive. In some biopsies, architectural changes were only mildly or moderately abnormal, but in others, changes were severely ("flat") abnormal. These small intestinal biopsy changes do not occur in normal volunteers fed high gluten-containing diets. Later, improvement in the small bowel biopsies occurred with gluten restriction. Similar changes were documented in serial small intestinal biopsies carried out in an elderly patient with intestinal lymphoma[30].

SPECIAL PROBLEMS IN ELDERLY CELIAC DISEASE

Anemia and abnormal laboratory tests

Up to 80% of elderly patients with celiac disease in a British series had anemia[31]. Iron deficiency was usually the cause but other nutrients may be deficient, such as folic acid, sometimes producing a dimorphic peripheral blood smear (if combined with iron deficiency). In these elderly patients, concomitant hypoalbuminemia with peripheral edema and ascites may also occur with hypocalcemia and hypomagnesemia[8]. Others may have liver chemistry test changes[23], initially believed, in some cases, to be related to alcohol overuse. In these patients, a hepatocellular injury profile may normalize with gluten restriction. In others with a cholestatic injury profile, lymphocytic sclerosing cholangitis or primary biliary cirrhosis may be present, but these do not improve with a gluten-free diet.

Bone disease and fractures

Bone disease may develop with few clinical features of malabsorption. Decreased bone mass is the most common form of metabolic bone disorder in celiac disease. Up to 70% of adult and elderly patients with celiac disease have a bone mineral density that is less than one standard deviation below normal controls (osteopenia)[32,33]. Men and post-menopausal women are affected more often than pre-menopausal women[33]. Reduced bone mineral density may also occur in treated patients with celiac disease[33,34].

The mechanism for osteopenia in celiac disease may be related, in part, to calcium malabsorption causing increased secretion of parathyroid hormone. Increased bone turnover leads to cortical bone loss. Impaired absorption of vitamin D may also occur. Pro-inflammatory and anti-inflammatory cytokines are believed to play an active role in the pathogenesis of osteopenia in celiac disease. Although celiacs may improve their bone mineral density with a gluten-free diet, the bone mass increment is limited in elderly patients and may be incomplete.

A higher prevalence of fractures also occurs in the peripheral skeleton of elderly celiacs. Most fractures occur before the diagnosis of celiac disease is initially defined and commonly occur in those with poor diet compliance. Most believe that a gluten-free diet is the most important factor providing protection from the risk of fracture. In a recent population-based study on long-term fracture risk[35], celiac disease was linked to an increased fracture risk before and after diagnosis. Appendicular and axial fractures were more common supporting a rationale for earlier detection of celiac disease and active management of bone disease before bone effects, specifically fractures, occur[35].

Recurrent or refractory disease

In well-defined celiac disease, recurrent diarrhea or malabsorption may occur. In an elderly celiac, this may be particularly disconcerting since the number of potentially serious disorders that may complicate the clinical course of celiac disease is significant[36]. In most, limited compliance to the gluten-free diet or inadvertent consumption of gluten remains the most common cause. Ubiquitous sources of gluten include the fillers in pill capsules, a particularly critical issue in this age group. In others, diarrhea or weight loss may be related

to another cause with no specific relationship to celiac disease (e.g. ischemic bowel disease, infectious diarrhea, colonic malignancy). Alternatively, other superimposed small intestinal histological changes may be present which could be related to impaired absorption of a specific nutrient (e.g. folic acid deficiency). In others, an associated cause, such as pancreatic exocrine insufficiency, may be present. Re-evaluation of the original diagnosis may be necessary to ensure that a separate diagnosis has not been overlooked. Sometimes, an associated complication may be responsible, e.g. collagenous or lymphocytic colitis, or a more serious complication may supervene, e.g. lymphoma[36].

In elderly patients with established celiac disease, a rare disorder, collagenous sprue, may develop[36]. In most of these patients, severe pan-malabsorption may occur with recurrent diarrhea, progressive weight loss and significant nutritional and electrolyte deficiencies. IgA-endomysial antibodies may also be detected in collagenous sprue, further evidence for an etiopathogenetic link with celiac disease[37]. In addition, collagenous sprue may be complicated by lymphoma[38]. Collagenous mucosal changes may also concomitantly occur in the colon, and rarely, these may completely disappear with treatment[39]. Most intriguing was the finding of complete histopathological resolution of collagenous small bowel and colonic involvement after resection of an unrelated colon cancer, suggesting the possibility of a paraneoplastic phenomenon[40].

Occasionally, no specific cause for persistent or refractory symptoms can be documented. Some have a poorly understood syndrome characterized by recurrent or persistent small bowel changes of variable severity, splenic hypofunction and cavitation of mesenteric lymph nodes. This disorder may also be complicated by lymphoma[41]. Others in this heterogeneous group remain severely symptomatic with malabsorption and profound wasting despite a gluten-free diet. Some may have a "clinically-resistant" form of celiac disease. Interestingly, a recent report documented persistent changes in elderly celiacs on a gluten-free diet and suggested that follow-up biopsies be done only after two years on a gluten-free diet to document histological recovery[42]. This suggests that the label of "refractory" may only be applied after an extended period of time. Others will be eventually proved to have a difficult-to-diagnose intestinal lymphoma[36].

CONCLUSION

Despite a paucity of symptoms, such as diarrhea and weight loss, celiac disease is becoming increasingly recognized in the elderly. Especially intriguing is a recent report which suggests that celiac disease occurs in the elderly more often than in any other age group, possibly related to serological screening. Other presentations in this elderly age group include iron deficiency anemia (often refractory to oral iron), other autoimmune disorders (dermatitis herpetiformis, thyroiditis), osteopenic bone disease, including fractures, and malignant intestinal disease, especially lymphoma. Diagnosis may be delayed due to limited symptoms, a low index of suspicion or diagnostic difficulties related to cognitive impairment. Conversely, celiac disease may not develop in the genetically predisposed until late in life, possibly being precipitated by an environmental factor. Finally, celiac disease diagnosed late in life is more often associated with recurrent or refractory disease and the appearance of lymphoma.

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