A Cohort Study of Comorbidities in Celiac Disease from a Single Tertiary Paediatric Center

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Abstract

Celiac Disease (CD) is an autoimmune disease with a broad spectrum of clinical disorders and associated comorbidities. In many cases, patients have no gastrointestinal disorders and are referred to paediatric gastroenterologist due to combined endocrinological disorders. We aimed to identify children with CD and determine the prevalence of paediatric endocrinologists’ referrals due to positive anti-tTG antibodies and coexisting T1D, thyroid disease or Down syndrome. A total of 62 patients [48 females (77.4%), 13 males (20.9%)] were retrieved. The median age at diagnosis was 9 years (range 2-17). The most common clinical presentations were short stature (27.4%), failure to thrive (19.3%), anaemia (9.7%) and abdominal pain (8%). Associated comorbidities included autoimmune gastrointestinal disorders and are referred to paediatric gastroenterologist due to combined endocrinological disorders. We aimed to identify children with CD and determine the prevalence of paediatric endocrinologists’ referrals due to positive anti-tTG antibodies and coexisting T1D, thyroid disease or Down syndrome.

Introduction

Celiac Disease (CD) is an immune-mediated enteropathy that develops in genetically susceptible individuals in response to the consumption of gluten [1]. As other autoimmune disorders, the aetiology of CD is multifactorial with complex genetic pathogenesis and variable co-morbidities. CD can present with a wide spectrum of clinical manifestations. The typical disease is characterized by chronic small intestinal inflammation and malabsorption, as well as various symptoms that can potentially affect any organ system [2]. More frequently, CD presents with a non typical or even silent clinical course. This can result in late diagnosis of affected individuals, delay of treatment onset and increased risk of subsequent long-term complications. However, CD is a unique example of autoimmunity, since early serological diagnosis and dietary treatment can reverse the autoimmune process preventing its severe, sometimes life threatening complications [3]. The diagnosis of CD relies on both serologic and histological exams, as well as, on response to gluten-free diet (GFD). A significant number of asymptomatic patients with CD are also diagnosed through serologic screening of high-risk populations [1,4]. Currently, various assays are available in order to detect antibodies associated with CD, such as antibodies against deamidated gliadin peptide, the tissue transglutaminase (tTG), and the endomysium.

The autoimmune disorders associated with CD can be: 1) organ-specific, in which the auto-antibodies are specifically directed against antigens localized in a particular organ and are often detected in circulation, such as the Hashimoto thyroiditis and Type 1 Diabetes (T1D), or 2) non-organ-specific, characterized by the presence of auto-antibodies directed against ubiquitous antigen, including the Systemic Lupus Erythematosus, the Juvenile Idiopathic Arthritis (JIA), the Sjogren’s syndrome and scleroderma [5,6]. Non-autoimmune diseases linked to CD include the Down and Turner syndromes, as well as certain neurological disorders, such as the attention deficit hyperactivity disorder (ADHD)’[7]. High-risk groups include family members of an affected patient and patients with autoimmune disorders associated with CD, such as T1D. Recent studies have provided some evidence of a potential need for routine screening of the general population due to the significant proportion of under-diagnosed patients and the frequency of non-gastrointestinal symptoms of CD at disease onset.

We aimed to identify children with CD in our Tertiary Paediatric Department and determine the prevalence of paediatric endocrinologists’ referrals due to positive anti-tTG antibodies and coexisting T1D, thyroid disease or Down syndrome.

Methods

Children diagnosed with CD in the Paediatric Gastroenterology Outpatient Clinic of the General University Hospital “Attikon” were included in the study. Data were retrospectively reviewed. An a priori hypothesis was used testing for diseases putatively associated in
the literature with CD. These include: T1D, autoimmune thyroiditis, thyroid disorders, selective IgA deficiency, Down syndrome, psoriasis, inflammatory bowel disease, dermatitis herpetiformis, Turner syndrome, alopecia areata, ADHD, systemic lupus erythematosus, autoimmune hepatitis, and sarcoidosis.

**Results**

A total of 62 patients [48 females (77.4%), 14 males (20.9%)] were retrieved. The median age at diagnosis was 9 years (range 2-17). The most common clinical manifestations were short stature (27.4%), failure to thrive (19.3%), anaemia (9.7%) and abdominal pain (8%). Associated co-morbidities included autoimmune thyroiditis [8 (12.9%)], T1D [9 (14.5 %)], Down syndrome [2 (3.2 %)] and JIA [2 (3.2%)]. Among 62 included patients, 25 (40%) were referred from a Paediatric Endocrinologist. All children with T1D, abnormal anti-tTG IgA underwent esophagogastroduodenal endoscopy with Marsh classification consistent with CD. The percentage of biopsies with a Marsh score greater than IIIB was 42%, whereas 3 (4.8%) patients were also diagnosed with eosinophilic esophagitis (EoE).

**Discussion**

Paediatric patients with short stature referred from paediatric endocrinologists should be closely monitored for CD in order to allow early diagnosis and treatment onset with GFD [8]. CD is a well-known co-morbidity with T1D in individuals with similar genetic predisposition. Patients with T1D and CD often have concurrent silent CD [8]. Thus, screening for CD should be part of the routine investigation in children with T1D due to the high prevalence and potential benefits of treatment with GFD. This includes control of symptoms, stabilization of diabetes and prevention of complications associated with CD [4].

JIA in CD patients has been examined on a limited number of paediatric patients [9]. Consistent with published literature are the results of our cohort, identifying a small number of children (N=2) with concurrent JIA and CD. Limited studies show an increased prevalence of CD in children with JIA, but not the opposite. EoE and CD are considered distinct immunological diseases of the gastrointestinal tract with specific clinico-pathogenetic characteristics [10]. The potential association of EoE with CD is not well established. In our study, only 3 patients had coexisting EoE and CD. In all children undergoing upper gastrointestinal endoscopy for suspected CD, coexistence of EoE should be considered.

**Conclusion**

A large number of patients with CD still remain undiagnosed. Future studies are warranted in order to further elucidate the association of several controversial co-morbidities of CD, including EoE and ADHD. Recommendations for screening considerations for this disorder amongst CD patients in a cost effective, timely, and efficient manner is deemed necessary as to optimize the prognosis of the disease. Especially, it could be recommended to follow-up children with EoE more closely for CD.

**References**