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ORIGINAL ARTICLE

Coeliac screening in a high-risk population: paediatric type 1 diabetes—a review of current guidelines and practice

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Abstract

Background and aims Coeliac disease (CD) is more common in those with type 1 diabetes mellitus (T1DM) and may be asymptomatic despite the presence of intestinal histological changes. Optimal screening practice guidelines differ internationally. We undertook a retrospective audit to determine the efficacy of current screening practice for CD in T1DM in our centre.

Methods All children and adolescents < 16 years, diagnosed with T1DM in our service and continuing to attend the service in January 2017 were included. Data on CD screening was collected and compared to current NICE, NASPGHAN and ESPGHAN guidelines.

Results Of the 355 patients attending our service, 253 attended from T1DM diagnosis and all had CD screening performed in our centre. In 37 of 253 patients, IgA-TTG was positive, providing a cumulative prevalence of 14.6%. Of these, 31(83.78%) with an elevated TTG on screening had no recorded gastrointestinal symptoms or CD-related clinical signs. Of the 35 TTG plus EMA-positive patients, 22/35 (59.46%) had diagnostic endoscopic biopsy. Nineteen (83.4%) had CD confirmed, 1 (4.54%) had negative biopsy and 2 (9%) had equivocal, non-diagnostic changes.

Conclusions Timely diagnosis of CD can prevent chronic ill health in affected individuals, and in patients with T1DM, CD is an independent risk factor for increased morbidity and mortality. Given the high prevalence of atypical symptoms and silent CD in those with T1DM, in this and other studies, and the benefits of detection and treatment of CD, screening is essential. Large-scale data collection allowing for the development of evidence-based guidelines is required.

Keywords Coeliac disease · Coeliac disease screening · Paediatric type one diabetes mellitus

Introduction

Coeliac disease (CD) is more common in those with type 1 diabetes mellitus (T1DM) [1–3] and may be asymptomatic despite the presence of intestinal histological changes [3, 4]. The benefit of CD screening in T1DM has been proven with adherence to a gluten-free diet associated with improvement in weight and lipid profile, reduction in hypoglycaemia risk and possibly reduction in long-term risk of both retinopathy and chronic renal disease, while the impact of CD diagnosis has been shown to have a limited negative effect on quality of life [5–13]. Screening for CD in this high-risk group is inconsistent across several paediatric guidelines [14–17], with discrepancies between European and American guidelines on optimal screening practice (use of HLA DQ2/DQ8 as an initial screening test, inter-screen interval, need for endoscopic biopsy and recommendations when serological evidence of CD does not correlate with histology). We undertook a retrospective audit to determine the efficacy of our current screening practice for CD in this high-risk population in our centre.

Methods

All patients aged 16 years and under, diagnosed with T1DM in our service and continuing to attend our service in January

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2017 were identified on our diabetes database. A retrospective chart review was conducted to determine age, symptoms of CD, serology screening results and endoscopic biopsy results. Anonymised data with no identifying patient characteristics was collected and analysed using Microsoft Excel and our screening practice was compared to current NASPGHAN, ESPGHAN and NICE guidelines. The study received ethical approval from Children's University Hospital, Temple St.

Results

Of the 355 patients attending our service, 253 attended from T1DM diagnosis and all had CD screening performed in our centre. Total IgA levels were not routinely screened. In all cases, serum IgA-TTG (TTG) was the initial screening test performed. In 37 of 253 patients, TTG was positive, providing a cumulative prevalence of 14.6% (Fig. 1).

Of the 37 TTG-positive patients, 26 (70.3%) screened positive in the first 24 months after T1DM diagnosis. Of these, 31 (83.8%) with an elevated TTG on screening had no recorded gastrointestinal symptoms or CD-related clinical signs. All patients with an elevated TTG also had IgA-EMA (EMA) checked and there was a 94.6% (35/37) concordance with IgA-TTG result. Two of TTG-positive asymptomatic children had negative EMA serology and have planned interval follow-up.

Of the 35 TTG plus EMA-positive patients, 22/35 (59.5%) had diagnostic endoscopic biopsy. Nineteen (83.4%) had CD confirmed, 1 (4.5%) had negative biopsy and 2 (9%) had equivocal, non-diagnostic changes (Table 1).

Table 1 Screen-positive patients $n = 37$

Asymptomatic at screen positive	31 (83.8%)
Positive TTG in first 24 months post T1DM diagnosis	26 (70.7%)
Biopsy confirmed CD after positive TTG and EMA	19 (83%)
Equivocal biopsy after positive serology	2 (9%)
Negative biopsy with positive serology	1 (4.5%)

Discussion

This study confirms the high incidence of asymptomatic CD in a paediatric population with T1DM. Overall, 7.5% (19/253) of our population have biopsy-confirmed CD—a figure comparable to other studies conducted on similar populations [1–4, 13] (Fig. 2).

Current European and American guidelines do not specify optimal timing for first CD screening after initial T1DM diagnosis and the optimal time interval for subsequent screening of asymptomatic individuals [13, 15, 16]. As the majority of our patients had positive screens soon after T1DM diagnosis (26/35 (70.3%), within 24 months), it seems reasonable to begin screening in the 6–24 months post T1DM diagnosis. The optimal time interval for subsequent re-screening remains unclear. In this cohort, 11/35 or 30.4% who screened positive for CD at the second screening did so on average 34 months after T1DM diagnosis. Other studies have reported the diagnosis of CD in T1DM patients may be delayed to 5 and 10 years post initial diabetes diagnosis, with the risk of seroconversion increasing with length of time post diabetes diagnosis, emphasising the importance of continued interval CD screening [13].

An alternative screening strategy to antibody testing is to screen for human leukocyte antigen (HLA) types DQ2 and DQ8, heterodimers necessary for CD but present in 40% of the general population [18]. ESPGHAN guidelines recommend HLA testing as a first-line screening test if available, with the absence of DQ2 and DQ8 rendering further CD screening unnecessary. NASPGHAN and NICE guidelines, in contrast, recommend use of HLA testing only in situations of diagnostic doubt, such as serology and histology mismatch. These tests are not in routine use in our clinic and are expensive and the cost

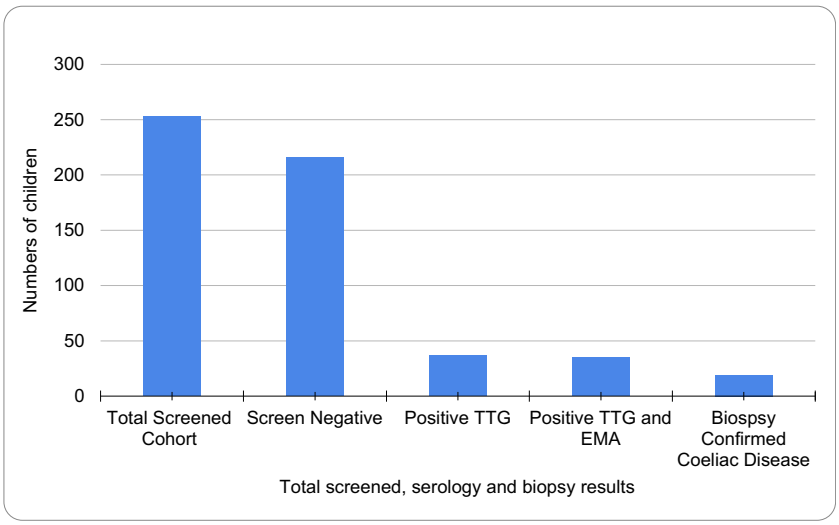

Fig. 1 Total screened, serology and biopsy results

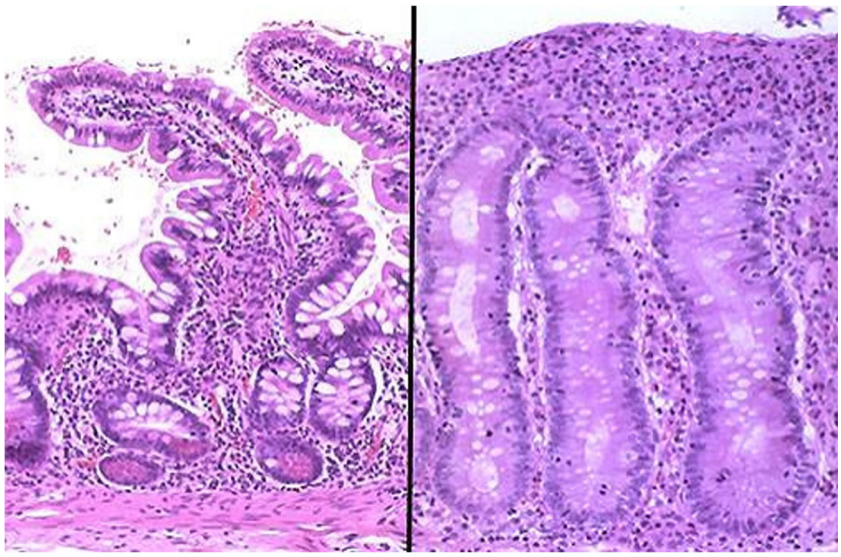

Fig. 2 Pathology photograph examples of normal duodenum on the left vs confirmed CD on the right

effectiveness of once in a lifetime screening for CD in high-risk groups has not been established [13, 19].

IgA-TTG is the antibody screening test with the most sensitivity, specificity and cost effectiveness for CD screening and is the screening test of choice in most paediatric guidelines [15–18]. Testing must be performed while on a gluten-containing diet to avoid false negatives; however, the exact duration and amount of gluten required for diagnostic certainty has not been established with current NICE guidelines suggesting gluten in more than one meal for at least 6 weeks and NASPGHAN guidelines suggesting daily consumption of 10 g of gluten for 8 weeks [17, 20]. In our study, 26 of 253 (10.3%) patients were TTG-positive within 24 months of T1DM diagnosis with 7.5% of the cohort having biopsy confirmed CD at this time. The discrepancy between serology and histology may reflect the reported transient mild positivity of TTG in association with autoimmunity (such as in the early stages of T1DM), with most guidelines suggesting further screening with EMA rather than proceeding directly to biopsy where TTG level is ≤ 3 times the upper limit of normal (ULN) [13, 15, 16, 21].

If TTG level is greater than 3 times ULN, both ESPGHAN and NASPGHAN guidelines suggest proceeding to biopsy rather than further testing for EMA. No definitive data exists on absolute antibody titre or duration of positive antibodies that should prompt biopsy in asymptomatic individuals. Factors such as dual EMA and TTG positivity, high antibody titres and family history of CD are suggested as considerations to guide decision to biopsy [13]. In our study, we tested EMA in TTG-positive patients and found a 94.6% (35/37) concordance between the two tests. The two patients (5.4%) who tested positive for TTG and negative for EMA had low TTG titres.

IgA deficiency is more common in CD than that in the general population and may cause false-negative results when testing for IgA antibodies [18]. Testing for total IgA in the initial screening test is recommended across most current guidelines [15–17] but the cost effectiveness of this additional step has not been proven [22]. IgA-deficient individuals require IgG antibody screening. An important consideration in this setting is the lower specificity and sensitivity of these serological tests compared with their IgA counterparts. Patients found to be IgA-deficient and therefore TTG IgA-negative, in whom a strong clinical suspicion exists for CD, warrant referral for biopsy in order to conclusively test for presence of coeliac-associated enteropathy [15]. Currently, total IgA is not routinely measured in our practice on initial screening. IgA levels were only checked in patients noted to have undetected IgA-TTG. Despite this, 2.8% (7/253) of all individuals screened for CD in this study were found to be IgA-deficient, far in excess of figures seen in similar studies and further validating total IgA as an important initial screening test [21, 22]. We have amended our screening recommendations to include baseline IgA level check.

Individuals with positive serology generally undergo intestinal biopsy to confirm the diagnosis of CD. Overall, 8.7% (22/253) of patients in our study underwent intestinal biopsy following positive CD serology, and in 83.4% (19/22) of cases, CD was confirmed. Current ESPGHAN and NAPSGHAN guidelines recommend obtaining a minimum of 5 tissue samples during endoscopic biopsy for CD due to the potentially patchy distribution of disease in the duodenum—at least one from the duodenal bulb and four from the distal duodenum [15, 16]. The high (3/22 or 13.6%) frequency of serology-positive histology-negative patients seen in our study may be explained by previous practice of two site endoscopic biopsies. Where negative histology is obtained in adequate endoscopy tissue samples in patients consuming a gluten-containing diet prior to biopsy, evidence-based practice guidelines are lacking. One small study suggested that symptomatic individuals found to be EMA-positive but biopsy-negative benefited from a gluten-free diet [23], while other

studies have shown that individuals found to be serology-positive and biopsy-negative but asymptomatic have a high chance of reverting to serology-negative status without the introduction of a gluten-free diet [24].

Of the 35 (35/253, 13.8%) participants in our study who tested positive for both TTG and EMA, 2 (2/35, 5.7%) became symptomatic in the interval between screen and endoscopy and opted to forgo endoscopic biopsy and move to a gluten-free diet without documented histological evidence of CD. Discordance currently exists between ESPGHAN and NASPGHAN guidelines on the diagnosis of CD in the absence of histological evidence at biopsy. ESPGHAN allow for CD diagnosis in symptomatic individuals in whom serum TTG is found to be greater than 10 times the ULN, EMA is positive from a separate serum sample, HLA type tests as DQ2 and/or DQ8 and patients show response to gluten-free diet—without the cost or risk associated with endoscopic biopsy. NASPGHAN guidelines recommend that all patients obtain a histological diagnosis for a variety of reasons including lack of standardisation of serological tests for CD and the potential for missing other comorbidities that can be diagnosed during biopsy such as *H. pylori* gastritis [15, 16]. Currently, it is our practice to recommend biopsy for all patients as HLA typing is not routinely performed.

Timely diagnosis of CD can prevent chronic ill health such as osteoporosis, infertility and small-bowel cancer [17] in affected individuals and has additional benefits in patients with T1DM with CD as an independent risk factor for increased morbidity and mortality in T1DM [13]. However, screening and diagnosis of CD adds to the burden of care for patients and their families. A lack of consensus on optimal CD screening practice in this high-risk population reflects the lack of evidence for the various screening options. Given the high prevalence of atypical symptoms and silent CD in those with T1DM, in this and other studies [3, 4], and the benefits of detection and treatment of CD, screening is essential. Large-scale data collection allowing for the development of evidence-based guidelines is required.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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