

## REVIEW ARTICLE

# Coeliac disease in children: the need to improve awareness in resource-limited settings

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### ABSTRACT

Coeliac disease (CD) is an immune-mediated systemic disorder caused by the ingestion of gluten. In children, it may present with intestinal or extra-intestinal manifestations such as diarrhoea, weight loss, iron deficiency anaemia or faltering growth. Diagnosis is confirmed by small bowel biopsies showing histological changes consistent with enteropathy. In 2012, the European Society for Paediatric Gastroenterology, Hepatology and Nutrition revised the CD guidelines and suggested that, in a selective group of symptomatic children, CD can be diagnosed without the need for small-bowel biopsies. Management of CD is through strict adherence to a life-long gluten-free diet (GFD). CD is of great public health significance as its prevalence in developing countries has been found to be similar to that in developed countries. Early recognition and treatment improves prognosis. Patients and families require long term support to enable effective adherence to a GFD lifestyle. This alone can be challenging, but through

support of health professionals and dietitians, can improve patient outcomes. In resource-limited settings medical professionals need to be creative in formulating cheaper and locally sourced gluten free options in close cooperation with the dietitians thereby ensuring availability of gluten free food items at affordable prices. In this paper, we gave an overview of the subject followed by authors' view to emphasize the need for improved awareness in resource-limited settings.

### KEYWORDS

Anti-tTG; Coeliac disease; Enteropathy; DQ2 and DQ8 haplotypes; Resource-limited countries.

### INTRODUCTION

Coeliac disease (CD) is a complex immune-mediated systemic disorder caused by the ingestion of gluten and related prolamines in genetically predisposed individuals. It is characterised by a

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Received: 06 February 2019 | Accepted: 14 April 2019

### How to cite this article:

Paul SP, Stanton LK, Adams HL, Basude D. Coeliac disease in children: the need to improve awareness in resource-limited settings. Sudan J Paediatr. 2019;19(1):6–13.

<https://doi.org/10.24911/SJP.106-1549488256>

range of gluten dependent clinical manifestations, CD-specific antibodies, strong association with human leukocyte antigen (HLA) DQ2 and/or DQ8 haplotypes and enteropathy [1]. The three main gluten containing food groups are wheat, rye and barley [2]. CD classically presents with gastrointestinal manifestations, such as diarrhoea, abdominal pain and weight loss [3]. CD is now increasingly being recognised as a multi-organ condition with serious morbidity [4]. CD has historically been considered a disease of the developed world, where wheat remains the staple diet [3]. In this journal, Suliman and Hassan in 1977 [5] published the first case series of CD from Sudan in four children who had gastrointestinal symptoms, such as diarrhoea, abdominal bloating, constipation, weight loss and steatorrhoea.

## EPIDEMIOLOGY

CD has traditionally been viewed as a disease of the Western world [3,4]. The prevalence of CD has changed exponentially from 1:3,000 (United States of America) [6] to as high as 2.4:100 (Finland) [7]. The current prevalence of CD in children and young people in the UK is 1% [8]. It has been identified from the confidential Avon Longitudinal Study of Parents and Children that 1% of children were IgA based anti-endomysial antibody (EMA) positive by 7 years of age, and therefore likely to have subclinical CD; however, <0.1% were reported to be on a gluten-free diet (GFD) following a histologically confirmed diagnosis of CD [8].

Clear countrywide prevalence data are lacking for the developing countries; however, there are

suggestions that the prevalence of CD may not be dissimilar. A community based cross-sectional study from India with 10,488 participants, found the prevalence of CD to be 1.04% [9].

A Sudanese study where 172 patients with suspected CD were investigated, 128/172 (74%) had confirmed CD and 105/128 (82%) were aged  $\leq 20$  years [10]. 64/105 had gastrointestinal symptoms and the remainder ( $n = 41$ ) had extra-intestinal manifestations, such as stunted growth, bone or joint pain, anaemia, skin manifestations and peripheral neuropathy [10]. Another Sudanese study where 38/60 (63%) were aged  $\leq 20$  years, revealed the most common symptoms as chronic diarrhoea, followed by iron deficiency anaemia, weight loss, abdominal pain, and delayed growth and puberty [11]. A prospective hospital-based Sudanese study looked at 80 children (aged 15 months–18 years) who presented with poor appetite, weight loss, pallor and proximal muscle wasting [12]. 30/80 was deemed strongly suspicious following serological testing and 18/30 got diagnosed with CD following endoscopy and biopsies. The remaining 12 were left undiagnosed as consent for endoscopy was refused by parents/guardians [12].

## CLINICAL FEATURES

Clinical signs and symptoms of CD can be varied, non-specific and wide-ranging as evident from the discussion above [3,10–13]. The symptoms can be broadly divided into intestinal and extra-intestinal manifestations (Table 1) [1,10–13,17]. A study from India showed that the mean age

**Table 1.** Clinical manifestations of CD.

Intestinal symptoms of CD	Extra-intestinal symptoms of CD
Recurrent abdominal pain	Faltering growth
Abdominal distention (bloated appearance)	Unexplained iron deficiency anaemia
Abdominal cramping	Unexpected weight loss
Persistent or intermittent diarrhoea	Delayed onset of puberty
Constipation	Dental enamel defects
Vomiting	Dermatitis herpetiformis
	Recurrent aphthous stomatitis
	Arthropathy/arthralgia

**Table 2.** Asymptomatic children at high risk of CD.

First-degree relative with CD
Type 1 diabetes mellitus
Down's syndrome
Selective IgA deficiency
Autoimmune thyroid disease
Turner syndrome
Williams syndrome
Autoimmune liver disease

of diagnosis of CD in children presenting with extra-intestinal manifestations was higher ( $6.9 \pm 2.9$  years), compared to diarrhoeal-related CD ( $5.8 \pm 2.8$  years) [14].

However, it is important to note that CD can also be asymptomatic at presentation, especially in children from high risk groups (Table 2) [1,13,16]. In an Asian study where 94 first-degree relatives of index cases of CD were studied, 78/91 had a positive HLA-DQ2/8 haplotype (86%) and 4/91 (4.4%) were confirmed with CD via histological diagnosis [15]. A literature review studying the coexistence of CD and type-1 diabetes mellitus (T-1DM) in children where four African studies were included showed a prevalence of histologically confirmed CD between 4% and 16.4% [16].

There is an increasing interest in the association of CD with neuropsychiatric disorders in children. A Swedish registry-based matched nationwide cohort study with 10,903 children with CD (aged <18 years) and their siblings ( $n = 12,710$ ) reported that children with CD had a 1.4-fold greater risk of developing future psychiatric disorders, e.g., mood disorders, anxiety disorders, eating disorders, behavioural disorders, attention deficit hyperactivity disorder (ADHD), autistic spectrum disorders and intellectual disability [18]. In a small Italian study of 67 ADHD patients (mean age 11.4 years), 10/67 ( $\approx 15\%$ ) were positive for CD who reported significant improvement in their behaviour and functioning after initiation of the GFD [19]. Other larger studies and systematic reviews, however, have not demonstrated a similar increased prevalence of CD with ADHD; hence,

routine screening for neither CD nor empirical initiation of GFD is recommended [20–22].

It is important to consider a set of differential diagnoses in cases where CD is suspected; however, the anti-tissue transglutaminase [anti-tTG] and small bowel biopsies remain inconclusive. Other pathologies to consider include: autoimmune enteropathy, cow's milk protein intolerance, Crohn's disease, wheat intolerance, irritable bowel syndrome, post-enteritis syndrome, environmental enteric dysfunction, giardiasis, Whipple disease, spontaneous intestinal bacterial overgrowth and common variable immunodeficiency [17].

## DIAGNOSIS

Obtaining a focused history and maintaining a suspicion of CD based on symptoms is the first step in diagnosing CD (Table 1). A detailed physical examination should aim to recognise both intestinal and extra-intestinal manifestations. The height and weight of children should be plotted on an appropriate growth chart [4].

Any child displaying signs or symptoms suggestive of CD should undergo screening blood tests with anti-tTG and immunoglobulin A (IgA) levels, as 1.7%–8% of children with CD are known to be IgA deficient [1,13]. The current diagnostic assays for anti-tTG are quantitative and have high sensitivity and specificity. It is now recognised that this reach >98% when the anti-tTG levels are greater than 10-times ( $10\times$ ) the upper limit of normal (ULN) for the assay [1]. The gold standard for diagnosis of CD had been a positive anti-tTG result and small bowel enteropathy identified on endoscopic small-bowel biopsies. The currently agreed international standard for multiple small bowel biopsies are to obtain at least two biopsies from duodenal bulb and four biopsies from second part of duodenum [1,3,23].

In 2012, the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) critically reviewed and acknowledged the changing scenario in epidemiology and improvements in diagnostic modalities and suggested a non-biopsy pathway

(NBP) for diagnosis of CD provided following criteria are fulfilled [1,13]:

- Symptoms attributable to CD.
- Anti-tTG titre  $>10\times$  ULN.
- Positive EMA or a second anti-tTG  $>10\times$  ULN (if EMA is not available).
- Positive HLA-DQ2 and/or HLA-DQ8 haplotype.

There are a number of studies from Europe which confirm that the NBP provides a secure pathway for diagnosis. An Indian study also showed that of the 51/176 children who had anti-tTG  $>10\times$  ULN, all had a confirmed histological diagnosis of CD [23], highlighting the applicability of this criteria in resource-limited settings. However, anti-tTG titres vary dependent on the assay used [24]. It is important that anti-tTG assay available from a particular laboratory is compared with retrospective histological data of confirmed CD patients for that specific centre, to ensure its specificity remains high [1].

The role of HLA-DQ2/DQ8 assay in supporting the NBP has been questioned [25]. This is because approximately 30%–40% of the Caucasian population are HLA-DQ2 haplotype positive and only 1% develops CD [1]. A small Libyan study with 31 children with CD (median age 9.2 years) and 156 healthy controls (median age 10.9 years) confirm that although the presence of HLA-DQ2/DQ8 haplotype is similar in CD patients to that in Italy; however, the controls had higher positive HLA-DQ2/DQ8 when compared to Italian populations studies [26]. Routine HLA-DQ2/DQ8 genotyping is not indicated for CD screening even in children from high-risk groups (Table 2).

HLA-DQ2/DQ8 testing may, however, have a role in situations when the diagnosis is uncertain as a negative test renders CD highly unlikely [1]. Examples of such situations are:

- Negative CD specific antibodies and mild infiltrative changes in small-bowel biopsy specimens.
- Mildly raised anti-tTG levels with minimal or no symptoms and no histological changes suggestive of CD on small bowel biopsy specimens.

## MANAGEMENT

A lifelong strict GFD is the only treatment currently available for CD [1,4,13]. Serological re-testing in 6–12 months is required as normalisation of anti-tTG levels indicates a good response and adherence to the GFD [1,13]. Cross reactivity with gluten free (GF) oats is reported in 5% and hence is best introduced after normalisation of the anti-tTG levels [13]. Regular paediatric and dietetic review is required for clinical and serological follow up, to reinforce compliance and for monitoring response to the treatment [1,13] and correction of specific nutrient deficiencies (iron, vitamin D, folic acid, etc.) [4]. Annual review allows monitoring of growth and development and detection of other developing associated autoimmune conditions (e.g., T-1 DM, hypothyroidism) [1,13].

GF products are defined as food items containing less than 20 parts per million (ppm) of gluten, i.e., 20 mg of gluten per kilogram of food [27]. GF products are now easily available in the developed countries at higher costs. These include similar alternatives as traditional food items, e.g., pasta, bread and cereals in GF options but these do not have the same nutrient value compared to their gluten-containing counterparts [28]. A GF checklist is available for free from the Coeliac UK [29]. However, several recent studies show that food items labelled as GF and available from supermarket shelves or purchased in bakeries may not maintain the strict GF food standards:

- Italian study: 9% of the 200 products tested contained  $>20$  ppm of gluten [30].
- Australian cross-sectional study: 300 food items labelled GF identified 2.7% of those products were above the threshold of  $>20$  ppm of gluten [31].
- Brazilian study of 25 bakeries found that of the 130 samples taken, 21.5% were above the threshold of  $>20$  ppm of gluten [32].

In resource-limited settings, the clinicians and dietitians need to provide families with effective and innovative solutions to sustain a lifelong GFD. Locally produced alternatives, such as non-gluten cereals (rice and corn), psuedocereals (quinoa and buckwheat) and minor cereals (millet and teff) are good examples [33].



Children and families should be counselled by a paediatric dietitian or dietitian with experience in managing paediatric CD, to gain an understanding of the importance of adhering to a GFD [1,4,13,17]. It is important that the dietitian understands the culture-specific dietary needs, and counselling about GFD be tailored to suit that and provide advice on substitute food items to ensure good adherence [17,33]. Families need to be informed that separate toasters, chopping boards, cooking utensils, knives, baking trays, butter dish and freezer compartments should be used to avoid cross-contamination of gluten-containing foods within households and specific precautions is needed to check the constituents of a dish when eating-out [17]. Cross-contamination of food is a major challenge for the families and often leads to the whole family maintaining a GF environment.

CD patients are also recommended to receive the pneumococcal vaccination [13]. First-degree relatives should also undergo screening for CD due to its increased prevalence within this high-risk population group [1,13,15].

## PROGNOSIS

The outlook for children with CD is generally good if strict adherence to a GFD is maintained. Within a few months of commencing the GFD, patients should see an improvement in both gastrointestinal and extra-intestinal symptoms, including corrections of nutrient deficiencies, alleviated fatigue and reduced arthralgia [1,2,13]. A prospective study, undertaken in Delhi, of children diagnosed late with CD (aged 2.25–10 years) found adherence to a GFD, over a 4-year period, led to a normalisation of body mass index and a significant improvement in height-for-age Z score [34]. However, a lack of diagnosis or failure to follow a strict GFD can result in long-term adverse health outcomes, such as persistent gastrointestinal symptoms and a predisposition to complications, including: impaired nutrition and growth, disordered progression of puberty, infertility, osteoporosis, pathological fractures or small bowel lymphoma [1,4,10,13].

## AUTHORS' VIEW

As highlighted above, studies from developing countries show that the prevalence of CD

is almost equal to that of the Western world [35]. CD should always be considered in the differential diagnosis in children presenting with any single or combination of the features (Table 1), such as diarrhoea, weight loss, faltering growth or anaemia. Early recognition, diagnosis and treatment with a GFD are associated with better outcomes [3], including symptom resolution, correction of nutritional deficiencies and reduction in long-term complications.

A major hindrance to a confirmatory diagnosis in resource-limited settings is likely to be the limited availability of standardised anti-tTG assays, paediatric endoscopic facilities and anaesthetists with expertise to administer general anaesthesia to children [4,36]. The 2012 ESPGHAN guidelines recommending the option for NBP in a selective group of symptomatic children whose anti-tTG is  $>10\times$  ULN, may prove beneficial for a large number of children in these settings. Although the ESPGHAN guidelines suggest the need for HLA-DQ2/8 testing for diagnostic confirmation via the NBP, a recently published multi-national study (ProCeDE) with 645 children, suggested that HLA analysis is not necessary for an accurate diagnosis of CD [25]. It is hoped that the next revision of the ESPGHAN guidelines will suggest making a diagnosis of CD via NBP based on anti-tTG  $>10\times$  ULN alone in symptomatic children, without the need for HLA testing. This will enable its wider usage, especially in resource-limited settings.

Unfortunately, adherence to the GFD can be challenging in resource-limited settings, where gluten-containing foods form a staple part of patients' diets, and finding an equivalent GF substitute may prove difficult through their extra expense and limited availability [1,2]. Problems can also occur due to a lack of information surrounding gluten-containing products and ways in which gluten contamination can occur during cooking, storage and serving [2]. It is important that medical professionals in resource-limited settings work closely with their dietitian colleagues to formulate good quality GF food items, which then can be produced locally, in bulk, to bring down the production costs and enhance easier availability of these to the local communities at a cheaper price.

Although GFD is beneficial to those with CD, it needs to be highlighted to the general population that a GFD is not necessarily a healthy lifestyle choice, and can have a negative impact, including undesirable weight gain, unbalanced diet, causing social restrictions and long-term health issues in adult life [2,37]. Parents need to make the dentist aware of their child's diagnosis of CD as case studies have highlighted the use of gluten containing materials in dental treatment which may cause an inadvertent but on-going exposure to gluten causing deleterious effect on the child's health [38].

It is important to support children diagnosed with CD by providing repeated counselling and advice regarding how to overcome the challenges associated with a GFD, the onus of which may often lie with primary care health professionals in the developing countries [2]. Advice can be given surrounding which foods to avoid, where to locally source affordable GF food substitutes and how to avoid accidental gluten contamination when eating-out (e.g., school meals, restaurants, weddings and festivals). These supportive management strategies are likely to reciprocate the findings of a study from India where the adherence to GFD improved from 53% to 92% after 6 months of intensive counselling [39].

## CONCLUSION

CD is now a common condition in both developed and developing world with significant burden to the health systems and families. It can be a challenging condition to diagnose and manage due to resource limitations and its wide-ranging symptoms. Health professionals have an important role in identifying and securely confirming the diagnosis of CD. The NBP provides a less expensive option to confirm diagnosis of CD; however, its implementation needs to be very carefully considered in resource-limited countries. A greater challenge in this setting is maintaining strict adherence to a GFD with innovative use of locally produced resources, on-going counselling and health education.

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