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Coeliac disease in children – an update for general dental practitioners

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Coeliac disease (CD) is an immune-mediated systemic disorder caused by ingestion of gluten found in wheat, rye and barley. It affects around 1% of children but 90% of cases are considered to remain undiagnosed. CD classically presents with gastrointestinal manifestations including diarrhoea, bloating, weight loss and abdominal pain, but extra-intestinal features (including oral and dental manifestations) are increasingly being reported. Dental and oral manifestations such as dental enamel defects, delayed eruption of teeth, recurrent aphthous ulcers are well recognized manifestations of CD. In patients with yet undiagnosed CD, these can sometimes be the only presenting features. Dentists have regular contact with well children, and therefore the visit to the dentist is an opportunity to suspect CD. When CD is suspected, Dental practitioners can liaise with the General Medical Practitioner to organise screening for coeliac disease. Positive serology will prompt onward referral to a paediatric gastroenterologist to confirm the diagnosis. The recent European Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) guidelines have streamlined the diagnostic pathway for faster diagnosis of CD. Management involves strict adherence to a gluten free diet, which should lead to resolution of symptoms, recovery of intestinal mucosa and prevention of long-term complications associated with it. This article aims to describe CD, inform of recent changes to the diagnostic pathway and highlight the dental manifestations of the condition to equip Dental practitioners to aid early diagnosis and initiation of treatment for children with CD.

Introduction and historical perspectives

Coeliac disease (CD) is defined as an immune-mediated systemic disorder elicited by ingestion of gluten and related prolamines in genetically susceptible individuals. CD is characterised by the presence of a variable combination of gluten dependent clinical manifestations, specific antibodies, human leucocyte antigen HLA-DQ2 or HLA-DQ8 haplotypes and enteropathy1,2. Children commonly present with gastrointestinal features such as abdominal pain, bloating, persistent diarrhoea, and weight loss although increasingly extra-intestinal features are being recognised2.

The clinical features of CD were first accurately described in 1887 by Samuel Gee. The role of wheat and rye flour in causing CD was established by William Dicke, a Dutch paediatrician in the 1940’s3. The concept of a gluten free diet (GFD) as a treatment for CD was devised after observing that an improvement in symptoms occurred in CD patients during the Second World War when there was reduced consumption of wheat flour3. The gluten protein in wheat, barley and rye was subsequently identified as the causative agent for CD3.
The revised European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) guidelines published in 2012 forms the current basis for diagnosing paediatric CD in children in Europe. 

Oral and dental manifestations of CD are not uncommon in children with known and undiagnosed CD. The dental manifestations include dental enamel defects and delayed eruption of teeth. Children with CD have a greater prevalence of recurrent aphthous ulceration (RAU) which may cause significant discomfort and impede effectiveness of daily oral hygiene measures. Dentists have regular contact with well children, and therefore the visit to the dentist is an opportunity to raise suspicion of CD. Appropriate referral may allow interception of CD in its subclinical form. It is important to remember that children with undiagnosed CD may have no other symptoms than the oral and dental abnormalities. Early referral and diagnosis of CD is important to prevent associated complications.

This review article highlights the importance of considering CD as a multi-organ disorder and the importance of collaborative working between paediatricians, gastroenterologists and other health professionals, particularly dentists.

**Epidemiology**

Over the last two decades, understanding of CD has changed from an uncommon enteropathy (prevalence of 1 in 2500 to 3000) to a common multi-organ disease with a strong genetic predisposition associated with HLA-DQ2 and HLA-DQ8. The prevalence of CD in children based on a number of paediatric prevalence studies including the confidential Avon Longitudinal Study of Parents and Children (ALSPAC) is around 1%. CD illustrates the ‘tip of the iceberg’ phenomenon as up to 90% of cases of CD still remain unidentified. This was also evident from the ALSPAC study of 5470 children who underwent serological screening at 7.5 years of age; some of whom subsequently got diagnosed with CD.

The overall prevalence of systemic dental enamel defects in CD patients with mixed or permanent dentition ranges from 9.5% to 95.9% (mean 51.1%); the prevalence in the deciduous dentition is 5.8% to 13.3% (mean 9.6%). An Italian study which assessed 166 patients between 2 and 17 years of age, reported the prevalence of RAU as 69% in CD patients versus 43% in the control group which was statistically significant. Interestingly, they reported the similar difference in prevalence of caries and dental abnormalities in both groups.
Pathophysiology of CD

CD is caused by the ingestion of gluten and related prolamines (such as hordein in barley). The toxic component of gluten is contained in gliadin which traverses through the epithelial barrier of the small intestine during periods of increased intestinal permeability\(^3\). In genetically susceptible people, it may result in an inflammatory reaction mediated by the innate and adaptive immune system.

IgA-based anti-tissue transglutaminase antibodies (tTG) are CD specific antibodies and form part of the screening test for CD\(^2\). Characteristic small intestinal mucosal changes are villous atrophy with crypt hyperplasia and increased intra-epithelial lymphocytes. These changes hamper absorption of nutrients, fat soluble vitamins and minerals\(^2\).

Clinical presentation

CD is a multi-organ disorder with a variety of manifestations. Children diagnosed with CD may be classified as symptomatic and asymptomatic. Symptomatic children can present with a spectrum of both gastrointestinal and extra-intestinal symptoms from mild to severe.

CD is commonly diagnosed in children by the age of seven years, but can present later in life and in adults as well\(^6\). CD classically presents in young children with gastrointestinal symptoms including diarrhoea, abdominal pain and weight loss. Other gastrointestinal symptoms include bloating, flatulence, vomiting, steatorrhoea, and occasionally constipation\(^11\). Extra-intestinal manifestations include unexplained iron-deficiency anaemia, idiopathic short stature, faltering growth, liver disease, arthropathy, muscle weakness, delayed menarche or delayed onset of puberty and dermatitis herpetiformis\(^1,2,7\).

Oral and dental manifestations of CD

Specific dental and oral manifestations of CD are now increasingly being recognised and are highlighted below\(^12,13\):

- Dental enamel defects
- Delayed eruption of teeth
- Dental caries
- Recurrent aphthous ulceration (RAU)
- Oral manifestations of dermatitis herpetiformis
- Angular cheilitis
- Atrophic glossitis
- Other oral manifestations
Dental enamel defects (DED) (Fig 2) are one of the most common dental manifestations seen in children\textsuperscript{14}. The likely mechanism of development of DED is a combination of immune-mediated enamel damage and nutritional disturbance (e.g. hypocalcaemia)\textsuperscript{15}. In a study of 53 children with confirmed CD (mean age 9.7 yrs) when compared with 28 children (mean age 10 yrs) where CD had been excluded, DED were identified in 29 in CD group against 5 in control group\textsuperscript{16}. ‘Localised’ enamel defects (especially in incisors) were found in 20 children with CD and 1 in control group\textsuperscript{16}. In a Dutch study with 4233 children (median age 6 years and not previously diagnosed with CD), serum samples for tTG-titres were collected along with clinical photographs of clean, moist teeth taken with an intra-oral camera. Children with positive tTG-titres tended to have more DED\textsuperscript{17}. An Egyptian study with 140 children with DED and a control group of 720 children with no DED underwent serological screening for CD; both groups had no other features of CD. CD was diagnosed in 17.86\% with DED in comparison to 0.97\% in the control group\textsuperscript{18}. An Italian study with 603 children with CD, systemic DED was detected in 32.4\% (195/603) in comparison to 0.59\% in healthy controls (52/6949)\textsuperscript{15}. Another Italian study with 72 children with CD and 162 normal healthy subjects, DED was much higher in those with CD (20\%) as compared to the healthy subjects (6.2\%)\textsuperscript{19}.

de Carvalho et al (2015) analysed the chemical composition of the dental enamel of the primary teeth of patients with CD\textsuperscript{20}. They found the Calcium/Phosphorous ratio to be significantly lower in the teeth of the children affected by CD\textsuperscript{20}. The decrease in Calcium/Phosphorous ratio could be explained by the incorporation of carbonate in the tissue structure, which would increase its solubility\textsuperscript{21}.

Fig. 1  Clinical appearance of minor RAU

Fig. 2 - Clinical appearance of DED
The presence of CD when the permanent teeth are developing is a risk factor for DED’s\(^{12}\). These tend to appear symmetrically and chronologically in all 4 quadrants\(^{22}\). Both hypoplasia and hypomineralisation of the enamel can occur. DED may include pitting, grooving and complete loss of enamel. Table 1 highlights DED classification and has been adapted from Aine et al. (1990)\(^{23}\):

**Table 1 – Classification of DED\(^{23}\)**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Defects in colour of enamel: single of multiple cream, yellow or brown opacities</td>
</tr>
<tr>
<td>II</td>
<td>Slight structural defects: rough enamel surface, horizontal grooves, shallow pits</td>
</tr>
<tr>
<td>III</td>
<td>Evident structural defects: deep horizontal grooves, large vertical pits</td>
</tr>
<tr>
<td>IV</td>
<td>Severe structural defects: shape of tooth changed</td>
</tr>
</tbody>
</table>

**Table 2 – Few scenarios that may be encountered by a GDP**

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A child presenting with isolated DED or delayed dentition or RAU or dental caries without any other oral manifestations and no history of GI involvement – referral to GMP not indicated</td>
</tr>
<tr>
<td>2</td>
<td>Child presenting with isolated DED or delayed dentition or RAU or dental caries with history of chronic GI symptoms – referral to GMP indicated.</td>
</tr>
<tr>
<td>3</td>
<td>Child presenting with multiple oral manifestations with combinations of DED, delayed dentition, RAU, dental caries etc with no other obvious aetiology – referral to GMP indicated.</td>
</tr>
<tr>
<td>4</td>
<td>Child presenting with DED, RAU with family history of CD in 1st degree relatives – referral to GMP indicated.</td>
</tr>
<tr>
<td>5</td>
<td>Child presenting with DED, RAU in high risk group of CD (Fig. 3) – referral to GMP indicated. *</td>
</tr>
<tr>
<td>6</td>
<td>A child with known CD with any combination of oral manifestations – referral to GMP to explore adherence to GFD.</td>
</tr>
<tr>
<td>7</td>
<td>Child with any of the associated oral manifestations and presence of skin dermatitis herpetiformis – referral to GMP indicated. *GI involvement includes diarrhoea, abdominal pain, bloating, weight loss and faltering growth</td>
</tr>
</tbody>
</table>

*GI involvement includes diarrhoea, abdominal pain, bloating, weight loss and faltering growth

**Delayed dental development/eruption** greater than 2 standard deviations occurs frequently in children with CD\(^4\). An Italian study\(^{24}\) involving 120 female children where 60 children had CD and other 60 served as healthy controls, following were the percentages of children with skeletal and dental age delay - 20% in healthy subjects, 56.7% in CD (23% in children with CD with early diagnosis and in 90% with a late diagnosis [aged >8 years]). In children with a late diagnosis of CD, a difference of 11 months was noted between mean chronological age and mean dental age\(^{24}\). In the absence of any local factors or genetic disorders, CD may be considered the commonest systemic disorder associated with this condition.

**Dental caries** occurs more often in children with CD. In a Turkish study of 64 children (mean age 8.2 years) with CD compared with another 64 age-sex matched control, incidence of caries was higher in CD group at 83% versus 62% in control group\(^{22}\). A similar result with higher incidence of caries was described in another Greek study with 27 children in each arm\(^{25}\). In an Italian study, children (aged 4 – 13 years) with CD (n=300) had higher indexes of caries than healthy subjects (n=300), both in
deciduous teeth (dmft 2.31±1.84 versus 1.42±1.13; \(p=0.021\)) and permanent teeth (DMFT 2.97±1.74 versus 1.74±1.64; \(p=0.0001\))\(^{24}\). However, a different Italian study with 166 children (aged 2 – 17 years) in each arm reported similar prevalence of caries in the two groups (45% versus 45%)\(^{10}\). Another Italian study\(^{26}\) compared the dental enamel fragment analysis of hypoplastic teeth obtained from 10 children with CD and 10 non-CD children who were treated for dental caries, dental extractions for extensive caries lesions or deciduous teeth exfoliation. The morphological analysis at scansion electron microscopy demonstrated that the enamel hypoplasia of deciduous and permanent teeth in CD is highly hypomineralised with shorter prisms, more irregularly distributed and less interprismatic substance than observed in the non-coeliac children\(^{26}\).

**Recurrent aphthous ulceration (RAU)** may be associated with systemic predisposing conditions. A Canadian study with 168 children reported that 16% had mouth (aphthous) ulcers prior to diagnosis of CD\(^{27}\). In a Turkish study with 81 children with CD and 20 healthy controls, RAU was present in 48.1% (n=39) cases with CD as compared to 5% (n=1) in healthy control\(^{28}\). In another Italian study involving 72 children with CD and 162 normal healthy subjects, RAU was slightly higher in those with CD (24/72 [33.3%]) as compared to the healthy subjects (38/162 [23.4%])\(^{19}\).

Children with CD have a higher prevalence of RAU compared to unaffected children\(^{10}\). RAU in association with CD is predominantly of the minor variant with the average ulcer size being 5 mm with a non-keratinised mucosal distribution\(^5\). Clinically indistinguishable ulceration can be associated with conditions other than CD such as immunodeficiency states and Crohn’s disease. However, children most commonly develop RAU in the absence of any disease or deficiency (idiopathic). While the exact cause of RAU in CD remains unknown; it may be potentially related to nutrient deficiencies associated with low serum iron, folic acid and vitamin B12\(^5,12,29\). RAU often regresses with the implementation of a GFD\(^{29}\).

**Dermatitis Herpetiformis (DH)** is a rare skin condition with clear association with CD. It has an annual reported incidence of 0.56 per 100,000\(^{30}\). The skin lesions typically present as rashes affecting elbows, knees and buttocks\(^{30}\). It is important to note that DH can present with oral mucosal erythema and vesiculobullous lesions which rupture immediately to form shallow painful ulcers. Gingival erythema may manifest as a patchy or diffuse erythematous or desquamative gingivitis. Oral lesions have been reported 6 months prior to onset of skin lesions in DH. Histopathological diagnosis and screening for CD may be useful when suspicion arises\(^{31-33}\). DH resolves when the child with CD commences strict GFD.
Other oral/ perioral manifestations such as atrophic glossitis and angular cheilitis, may arise secondary to the development of nutritional deficiencies or anaemia in association with CD. Atrophic glossitis arises secondary to selective depapillation with atrophy of filiform papillae resulting in the clinical appearance of a smooth shiny tongue and has been reported as the only manifestation of CD in published case studies.

Diagnosis

Diagnosis of CD in children is usually made by a paediatric gastroenterologist or paediatrician based on symptoms, signs, serological screening with tTG-titres and typical histological features on small bowel biopsies. Whilst the medical history within this context at primary care may be presented by the parents to their general medical practitioner, it is not unreasonable to expect a general dental practitioner (GDP) to probe into the symptoms during a dental consultation where appropriate. Table 2 highlights a few situations which a GDP may come across and where a referral to the general medical practitioner (GMP) is indicated.

Certain groups of children are at higher risk of developing CD and therefore the dentists needs to be aware of the high risk groups which are listed in Figure 3. Any suspicion of CD in such groups should also be followed up by an appropriate referral.

<table>
<thead>
<tr>
<th>First degree relatives of CD patient</th>
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</thead>
<tbody>
<tr>
<td>Type 1 diabetes mellitus</td>
</tr>
<tr>
<td>Selective IgA deficiency</td>
</tr>
<tr>
<td>Down’s, Williams and Turner Syndromes</td>
</tr>
<tr>
<td>Autoimmune thyroiditis</td>
</tr>
<tr>
<td>Autoimmune liver disease</td>
</tr>
<tr>
<td>Unexplained raised transaminases without known liver disease</td>
</tr>
<tr>
<td>Dermatitis herpetiformis</td>
</tr>
</tbody>
</table>

The referral to the GMP should prompt serological screening with tTG-titres. A raised tTG-titre warrants onward referral to the paediatric services (paediatrician or paediatric gastroenterologist if direct access available) for confirmation of a diagnosis of CD. The paediatrician will review the history again, plot the height and weight of the child on an age and sex appropriate growth chart and elicit signs of anaemia, jaundice, mouth ulcers, skin rashes, distended abdomen etc. This will be followed by blood investigations (including a full blood count, liver function tests, urea and electrolytes, blood glucose, vitamin D level, thyroid function), particularly due to the association of CD with other
autoimmune conditions (such as diabetes and hypothyroidism)\textsuperscript{11}. The paediatric gastroenterologist confirms the diagnosis of CD based on serology and endoscopic small bowel mucosal biopsies.

The ESPGHAN guidelines for diagnosing CD in children recommend that in symptomatic children with tTG-titres of >10 times of the upper limit of normal (>10xULN), CD can be diagnosed without need for small bowel biopsies provided they have a positive HLA-DQ2/DQ8 haplotype and a positive anti-endomysial antibody (EMA) result\textsuperscript{1,2}. Small bowel biopsies are still required in all other cases as highlighted below while the child remains on a normal non-restrictive gluten containing diet [initiation of GFD leads to recovery of intestinal mucosa resulting in negative small bowel biopsies]\textsuperscript{1,2,7}:

- Symptomatic children with a positive tTG--titre of <10xULN.
- Symptomatic children with a positive tTG-titre of >10xULN but with a negative HLA DQ2/8 status.
- Asymptomatic children (see Fig 3) with a positive tTG-titre (irrespective of the actual tTG value)

**Management**

CD is a lifelong condition and time initially spent on detailed counselling and educating the child and family goes a long way. The only treatment currently available is strict adherence to a lifelong GFD. It is important that any nutrient deficiencies (e.g. vitamin-D deficiency, iron-deficiency anaemia) detected at initial diagnosis are corrected\textsuperscript{36,37}. Intestinal mucosa and tTG-titres will return to normal once GFD is initiated, this can however take up to a year depending on the initial level of tTG-titre\textsuperscript{1}.

Children should continue to be seen by the paediatrician or paediatric gastroenterologist initially at 3 – 6 monthly intervals post diagnosis of CD and then annually\textsuperscript{2}. Children are assessed for their growth and development, adherence to GFD and for early detection of other autoimmune associations such as diabetes and hypothyroidism\textsuperscript{11}. Dietitians are invaluable particularly in explaining the role of GFD in managing CD, risk of non-adherence to GFD and avoiding cross contamination. Dietitians ensure that the child is provided with a nutritionally balanced diet and make the family aware of how to cater for a culturally appropriate GFD, suggesting nutritional supplements where necessary and monitor growth when commenced on a GFD.

Families should be encouraged to join the charity Coeliac UK (\texttt{www.coeliac.org.uk}) as they can provide authentic information on CD along with comprehensive food and drink information and also has an expert helpline. GMPs play an important role in supporting the child with CD in the community and prescribe appropriate gluten-free food to maximise adherence to the GFD. GMPs also facilitate serological testing of first degree relatives (even if asymptomatic), after adequate counselling\textsuperscript{11}. The pneumococcal vaccine is now recommended for patients with CD; many children will have received this as part of their routine immunisation program\textsuperscript{2}.
The diagnosis of CD should be communicated to the child’s dentist as they can play an important role in managing and monitoring children with CD\textsuperscript{12}. Children who have persistence of DED or RAU post diagnosis of CD, suspicion regarding poor adherence to GFD should be raised and communicated to the child’s paediatrician. Dentists may also detect DED, RAU, etc. in first degree relatives or in children from high risk groups (table 2) and a suspicion of CD should be raised and highlighted to the GMP for serological screening\textsuperscript{12}. Furthermore, patients detected with DED at diagnosis of CD will require regular monitoring by dentists and adherence to GFD is likely to improve the symptoms\textsuperscript{18}. Dentists also need to be aware of the different compounds that they use when carrying out various dental procedures, such as equipment’s, dental fillings or retainers to ensure that they do not contain gluten. A case study highlighted a 9 year old girl with CD who continued to be symptomatic despite strict adherence to GFD and this was later found to be exposure to gluten from her orthodontic retainer that contained a plasticised methacrylate polymer\textsuperscript{38}. Although anecdotal, we have managed children who were asymptomatic at diagnosis of CD and subsequent poor adherence to GFD has led to development of DED and other oro-dental symptoms\textsuperscript{39}.

**Prognosis**

Patients who adhere to a strict GFD, the prognosis of CD are generally good and will not develop further complications. Strict adherence to a GFD allows for healing of the intestinal mucosa. Symptomatic children often feel much better within a few weeks of excluding gluten and are likely to appreciate the advantages of the GFD. In children with ongoing symptoms including new onset dental manifestations\textsuperscript{39}, cross-contamination should be considered. Adherence to a GFD in children diagnosed when asymptomatic often needs more support for long-term adherence.

Missing a diagnosis of CD or non-adherence to GFD can lead to persistence of gastrointestinal symptoms, impaired nutrition, impaired growth and delayed onset or progress of puberty. Long-term risks include osteoporosis and low bone mineral density, increased risk of pathological fractures, bowel cancer, unfavourable pregnancy outcomes, low birth weight in offspring, spontaneous abortion and development of other autoimmune conditions\textsuperscript{2,7}.

**Conclusion**

CD is a lifelong condition caused by an immune-mediated reaction to the ingestion of gluten. Improved sensitivity and specificity of serological screening and increased awareness of the condition has led to improved identification of the disease. The recent ESPGHAN guideline should streamline the diagnostic pathway and allow faster diagnosis of CD in children. Dentists should be aware of the oral presentation of CD including DED and RAS and make an early referral where
suspicion of CD is raised. GFD is the only management available and strict adherence such a diet will lead to resolution of symptoms and likely complications.

References


