INTRODUCTION
Coeliac Disease (CD) is an immune-mediated systemic disorder elicited by the ingestion of gluten and related prolamines in genetically susceptible individuals and characterised by the presence of a variable combination of gluten dependent clinical manifestations, CD-specific antibodies, HLA-DQ2 or HLA-DQ8 haplotypes and enteropathy. Over the last two decades, understanding of CD has changed from an uncommon enteropathy (incidence 1:2500 - 3000) to a multi-organ disease with a strong genetic predisposition associated with HLA-DQ2/DQ8. Based on a number of paediatric studies including the confidential Avon Longitudinal Study of Parents and Children (ALSPAC); prevalence of CD is currently considered to be around 1%. It is no longer considered to be a disease of the developed world and its widespread prevalence has been well documented in studies from developing countries. Greater awareness and easier availability of serological testing has improved identification of CD, however, population studies show that up to 90% cases can remain undiagnosed.

Clinical features: CD can present with wide range of symptoms and can largely be divided into intestinal and extra-intestinal features. Intestinal features include diarrhoea, abdominal pain, bloating, weight loss and constipation. Extra-intestinal features include unexplained iron deficiency anaemia, short stature, faltering growth, constipation, liver disease, arthropathy, mouth ulcers, muscle weakness, delayed menarche or onset of puberty and dermatitis herpetiformis. A number of asymptomatic children will be diagnosed with CD following screening for first degree relatives with CD or for other autoimmune conditions such as type-1 diabetes, autoimmune thyroiditis, autoimmune liver disease, selective IgA-deficiency, and children with raised transaminases without known liver disease. Children with certain genetic conditions such as Down's, Williams and Turner syndromes are also at increased risk of developing CD.

Diagnosis: Until recently, the diagnosis of CD in children has been based on small-bowel biopsies and histology (Marsh histological grading). The modified ESPGHAN guidelines recommend that in symptomatic children with anti-tissue-Transglutaminase (tTG) titre of > 10 times Upper-Limit-of-Normal (ULN), diagnosis of CD can be made without small-bowel biopsies. However, positive HLA-DQ2/DQ8 serotype and anti-Endomysial Antibodies (EMA) are necessary. Studies from resource-limited countries have demonstrated applicability of the ESPGHAN guidelines for serological diagnosis of CD. CD should not be diagnosed on the basis of a single high tTG-titre. Small-bowel biopsies are necessary for diagnosing CD in asymptomatic children and those with tTG-titre < 10 x ULN. Management of CD needs lifelong gluten free diet.
CD was reported in another study from Pakistan with 49 children. It is important to understand that a significant proportion of normal population has positive HLA-DQ2/DQ8 serotype and if they do not have symptoms of CD along with a normal IgA titre, they do not have CD.3

The new ESPGHAN guidelines have been found to be applicable in low-resource settings when compared with very high IgA titres and histological grading of biopsies were made in studies from Iran (pre-publication of ESPGHAN guidelines) and from India (post-publication of ESPGHAN guidelines).12,15 Although anecdotal, our limited experience in managing children from South-East Asian background were similar to that of European children where IgA titres > 10 x ULN co-related well with a positive diagnosis of CD.

The authors, therefore, suggest that in low-resource countries, symptomatic children with IgA titres > 10 x ULN and positive Anti-Endomysial Antibodies (EMA) can be diagnosed and managed as a case of CD. The joint ESPGHAN and Coeliac UK guidelines adapted from the 2012 ESPGHAN guidelines suggest that in centres where EMA is not available, a second IgA titre may be used as an alternative while the child still remains on a gluten-containing diet;1 the repeat IgA titre also needs to be > 10 x ULN.1 This is also supported by a study from India with 333 children where IgA titre was found to be a highly sensitive and specific serologic marker.16 The authors also suggested that as IgA titre analysis is technically simpler and has high concordance with EMA, it can be used as an alternative to EMA in developing countries.16 Attempt should be made to send a HLA DQ2/DQ8 sample, applicability and usefulness of which has previously been established in a study from Pakistan.14

Any deviation from the established ESPGHAN guidelines along with reasons for non-adherence (e.g. non-affordability of HLA DQ2/8 serotype testing) should be clearly documented in patient notes. It is also necessary to explain that CD is a lifelong condition and strict adherence to GFD is necessary to remain symptom-free and prevent complications. A (paediatric) dietician should be involved in explaining the diagnosis, need for continuing lifelong GFD and monitoring the adherence to GFD.1 There is need to ensure that clinical review post-diagnosis of CD confirms resolution of symptoms once GFD is commenced and that coeliac serology (i.e. IgA titres) returns to normal thus confirming the diagnosis especially if serological pathway was used to diagnose CD.3 Time taken for normalization of the IgA titre depends on the initial level and is achieved within 12 months of starting GFD.1,2

Studies from low-resource countries have proved that the modified 2012 ESPGHAN guidelines are applicable and useful for serologically diagnosing CD in children. The ESPGHAN guidelines for serologically diagnosing CD in other published studies,8-11 including experience from our own centre (unpublished data, Thomas and Dodd 2013).

A change in clinical practice (i.e. serologically diagnosing CD) even in context of developing countries should be evidence-based. CD is a diagnosis which needs commitment and adherence to lifelong Gluten-Free Diet (GFD); this is neither economical nor easily available in developing countries. It is, therefore, important to make the initial diagnosis of CD with reasonable certainty and the modified ESPGHAN guidelines (Figure 1) may be used in selective symptomatic patients with IgA titres > 10 x ULN.2 It is important to note that different laboratories have different normal ranges for IgA titres and this should be taken into account while deciding the value corresponding to > 10 x ULN.

It is important to understand that the modified ESPGHAN guidelines are currently not applicable to asymptomatic children (irrespective of IgA titres) or other symptomatic children with IgA titre < 10 x ULN.2,3 These children will need endoscopy and small-bowel biopsies for a diagnosis of CD.2 An isolated low-grade rise in IgA titre can be found in conditions un-related to CD, such as viral infections (Coxackie virus, Epstein-Barr virus), giardiasis, cow’s-milk protein allergy, autoimmune diseases, autoantibody syndrome, tumours, liver disorders, inflammatory bowel diseases, myocardial damage, and psoriasis.12

A French study13 reported that the association between positive HLA-DQ2/DQ8 and serologic testing for CD has a high predictive value. Less than 1% of CD patients have negative HLA DQ2/DQ8 serotype and these children will need small-bowel biopsies for a diagnosis of CD.13 Similar genetic predisposition of HLA-serotype to CD was reported in another study from Pakistan with 49 children.14 It is important to understand that a significant proportion of normal population has positive HLA-DQ2/DQ8 serotype and if they do not have symptoms of CD along with a normal IgA titre, they do not have CD.3

The authors, therefore, suggest that in low-resource countries, symptomatic children with IgA titres > 10 x ULN and positive Anti-Endomysial Antibodies (EMA) can be diagnosed and managed as a case of CD. The joint ESPGHAN and Coeliac UK guidelines adapted from the 2012 ESPGHAN guidelines suggest that in centres where EMA is not available, a second IgA titre may be used as an alternative while the child still remains on a gluten-containing diet;1 the repeat IgA titre also needs to be > 10 x ULN.1 This is also supported by a study from India with 333 children where IgA titre was found to be a highly sensitive and specific serologic marker.16 The authors also suggested that as IgA titre analysis is technically simpler and has high concordance with EMA, it can be used as an alternative to EMA in developing countries.16 Attempt should be made to send a HLA DQ2/DQ8 sample, applicability and usefulness of which has previously been established in a study from Pakistan.14

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Studies from low-resource countries have proved that the modified 2012 ESPGHAN guidelines are applicable and useful for serologically diagnosing CD in children. The ESPGHAN guidelines for serologically diagnosing
symptomatic children with tTG titres > 10 x ULN without a biopsy is evidence-based and has produced persistently good sensitivity and specificity values in multiple settings. It is also cost-effective and likely to reduce the diagnostic time.

REFERENCES


