Coeliac disease- Paediatric perspective

Dr Dharam Basude
Consultant Paediatric Gastroenterologist
Bristol Children’s Hospital; Bristol Paediatric Gastroenterology
Definition and Prevalence of Coeliac Disease

- Immune mediated systemic disorder caused by ingestion of gluten and related prolamines (Wheat, Rye and Barley).
- Genetically susceptible individuals (mainly HLA DQ2, DQ8 haplotypes)
- Gluten ingestion related manifestations
- CD specific antibodies – Anti tissue transglutaminase (tTG), Endomysial antibodies (EMA), Deamidated Gliadin peptides (DGP)
- Small bowel Enteropathy
- Estimated prevalence UK 1:100 (including Bristol ALSPAC study)
- Approximately 90% still undiagnosed in childhood
Pathogenesis of Celiac Disease

- Loss of villi
- Increased IELs
- Increased mitosis
- Crypt elongation

Gluten → Gliadin

- Deamidated gliadin
- Tissue transglutaminase (tTG)
- IFNγ

- APC
- HLA (DQ2 or DQ8)
- T cell receptor
- Anti-gliadin
- Anti-endomysium
- Anti-tTG

- MIC-A
- IL-15
- NKG2D

- B cell receptor
Symptomatic children

- Persistent diarrhoea
- Faltering growth, idiopathic short stature
- Abdominal pain, vomiting, abdominal distension
- Constipation
- Dental enamel defects
- Recurrent aphthous stomatitis

- Delayed menarche
- Unexplained anaemia or iron deficient anaemia unresponsive to treatment
- Unexplained liver disease
- Lassitude/weakness
- Dermatitis herpetiformis
- Osteoporosis/pathological fractures
Asymptomatic but with associated condition (estimated lifetime prevalence)

- Type I diabetes (≥ 8%)
- Selective IgA deficiency (1.7%–7.7%)
- Down (5%–12%), Williams (8.2%) and Turner (4.1%–8.1%) Syndromes
- Autoimmune thyroiditis (~15%)
- Autoimmune liver disease
- Unexplained raised transaminases without known liver disease

- Intussusception
- Dermatitis herpetiformis
- Relatives of coeliac patient:
  - First-degree relative (~10%)
  - HLA-matched sibling (~30%–40%)
  - Monozygotic twin (~70%)
Serological tests

- Requires adequate Gluten consumption for period >6 weeks
- Total IgA in normal range
- IgA based
  - Anti tTG:
    - Qualitative: Positive or negative not good enough
    - Quantitative >95% specific and sensitive at higher titres. Almost 100% for >10 times the upper limit
  - Anti EMA: >95% - dilution matters
- Ig G based tTG and EMA about 70% specific only
Genetic test- HLA DQ2, DQ8

- Positive – propensity to develop CD only
- Up to 40% Caucasian may have HLA DQ2 or DQ8
- About 98% association with CD
- Helpful in specific situations only
Endoscopic diagnosis

- Patchy disease
- Multiple duodenal biopsies
- 2\textsuperscript{nd} or 3\textsuperscript{rd} part of duodenum and now 1\textsuperscript{st} part of duodenum
- Villous atrophy, crypt hyperplasia and increased intra epithelial lymphocytes
- Marsh grading 1-3 c
Guidelines for diagnosis and management

- Updated ESPGHAN 2012 – after nearly 20yrs
- Updated BSPGHAN 2013
- BSG 2013
- NICE 2015
- Coeliac UK
Diagnostic criteria for symptomatic children
Diagnostic criteria Asymptomatic children

Asymptomatic children with associated conditions

With: Type 1 diabetes, selective IgA deficiency, Down, Williams, Turner syndromes, autoimmune thyroiditis, autoimmune liver disease, unexplained raised transaminases, first degree relative of coeliac patient.

INITIAL SCREENING:
Check HLA-DQ status and IgA tTG.

1. IF HLA-DQ2/ DQ8-ve.
   Coeliac disease very unlikely - no biopsy required.

2. IF DQ2 or DQ8+ve but tTG -ve.
   Coeliac disease unlikely - unless IgA deficient or inadequate gluten intake. Still potential to develop CD in the future. Thus test again in 3 years or if becomes symptomatic.

3. IF DQ2 or DQ8+ve and tTG positive, <3 x upper limit of normal.
   Check EMA on second sample.
   If negative, maintain on normal diet but follow up serological testing required.
   If positive, perform duodenal biopsy.

4. IF DQ2 or DQ8 positive and tTG positive, >3 x upper limit of normal.
   Perform duodenal biopsy (although it may be reasonable to restart in 3-6 months and proceed to biopsy if tTG persists at this level or increases).
Simplified pathway for diagnosis of CD in children

Suspicion of CD in children (both symptomatic/asymptomatic)

Serological screening with tTGA-titre, IgA levels. Advise the child to continue a normal (gluten) containing diet

- tTGA-titres <10xULN (symptomatic) and asymptomatic child with +ve IgG titre
  - Endoscopy & small-bowel biopsy
    - Positive histology, diagnosis of CD confirmed
    - Start Gluten-free diet, follow-up with paediatricians and paediatric dieticians.

- tTGA-titres >10xULN, child symptomatic
  - Use new diagnostic pathway, obtain further blood samples for EMA and HLA DQ2/DQ8 typing. If EMA not available, take a 2nd sample for tTGA.

  - If EMA +ve (or 2nd tTGA >10xULN) and either DQ2/DQ8 positive, CD is confirmed
  - If HLA DQ2/DQ8 negative, continue normal diet. Perform endoscopy & small-bowel biopsies
Issues with implementing correct CD diagnosis
Wide variation of Anti-tTG testing and values

Barriers to implementing the revised ESPGHAN guidelines for coeliac disease in children: a cross sectional survey of coeliac screen reporting in laboratories in England;

Siba Prosad Paul, Sophie Louise Harries, Dharamveer Basude; ADC Online First, published on May 8, 2017 as 10.1136/archdischild-2016-312027
Figure 1: Flow chart of the recruitment and results of the survey. (*3 laboratories did initial screening for positive samples only and send their positive samples to a specialist laboratory for further testing and confirmation of values).

154 Acute NHS Trusts

139 with paediatric services, 134 included in study

15 Acute NHS provided no paediatric services and were excluded

5 labs did not respond

83 labs have on-site anti-tTG testing

51 labs send their coeliac serology samples away

EMA testing

68 labs do EMA on-site

15 labs outsource EMA

Total IgA Testing

24 labs reported IgA levels automatically

56 labs reported IgA levels on request

1 BMS did not know

2 labs outsourced this test after the initial anti-tTG screen
Fig 2 – Number of laboratories in England performing on-site anti-tTG titre testing

NI – Number of labs interviewed in that region
NP – Number of labs performing anti-tTG titres
RT – Range of anti-tTG titres in the region
Figure 3: Number of laboratories using each tTG values

Upper limit of normal for tTG values (IU/ml)
Understanding of Diagnostic pathway

- Awareness of ESPGHAN guidelines on coeliac disease amongst general paediatricians in Southwest England

Although the consultant general paediatricians are aware of the current ESPGHAN guidelines, full understanding of diagnostic pathways may be lacking.

Confusion surrounds particularly regarding implementation of non-biopsy pathway, timing of commencing GFD, appropriate use of HLA-DQ2/DQ8 and diagnosis of asymptomatic children with high anti-tTG.
HLA typing – is it appropriately used

- Upto 40% Caucasian population are positive

- For non-biopsy diagnosis
  - At risk children needing regular screening
  - To help clarify when diagnosis unclear despite tTg and duodenal biopsies.

- HLA DQ2/8 genotyping should not be requested by primary care physicians for screening/diagnosing coeliac disease in children
Asymptomatic children

- Evidence supporting serology based pathway for diagnosing coeliac disease in asymptomatic children from high-risk groups.
- All the 84 asymptomatic children with anti-tTG titre of >10xULN who had undergone endoscopic small bowel biopsies, had histological changes (MO 3a – 3c) consistent with a definitive diagnosis of CD.
- The serological pathway for symptomatic children can be safely applied to asymptomatic children.
- The guidelines may be modified in future.
Management

- Strict Gluten free diet
- Cross contamination – school, home and restaurants
- Pet and toy handling
- Await Normalisation of tTG about 6 months
- GF Oats introduced after tTG normalises
- Screen other family members
- Pneumococcal vaccine This is now recommended for patients with CD (Coeliac UK guidelines)
Management: Benefits of GFD

- Symptomatic children
  - Reversed bone demineralisation.
  - Resolution of micronutrient deficiencies and likely better height gain.
  - Decreased rate of delayed puberty, menstrual problems, subfertility, spontaneous abortions and low birth weight babies.
  - Decreased rate of some intestinal cancers to normal population levels.
  - Possible prevention of onset of other autoimmune conditions (evidence conflicting).

- Asymptomatic children
  - Likely to reverse covert micronutrient deficiency and optimise bone mineralisation.
  - Unclear whether diabetes control improves.
  - No studies on long-term outcomes of GFD in children with associated conditions.
Some intricate details

- Sensitivity to gluten and acknowledgment of symptoms after ingestion is variable between patients.
- Small amounts of gluten ingested regularly can cause mucosal changes even if patient feels asymptomatic.
- From 2012, only foods that contain 20 ppm or less can be labelled as gluten-free.
- Oats are safe for most patients with CD, although around 5% of patients will be sensitive to oats. These will be labelled gluten-free.
- Most coeliac patients tolerate Codex wheat starch and barley malt extract.
- Lactose-free diet is very rarely needed.
Gluten Re-challenge

- Routine re-challenge is not required if diagnosis is secure.
- Three months gluten challenge prior to testing is advised if asymptomatic with option to expedite blood testing when patient develops symptoms.
- A minimum duration of 4–6 weeks for those with symptoms during gluten challenge is recommended to maximise the likelihood of clear diagnosis.
- Perform at age 6–7 years or when pubertal growth is complete.
- This is best managed by reintroducing a normal diet with adequate gluten content
Summary

- CD prevalence is about 1:100
- Primary care has Key role in early identification and prompt diagnosis
- Maintain normal diet until diagnosis securely established
- Symptomatic Children with Anti-tTG >10 ULN can be diagnosed without duodenal biopsies
- There are some issues in implementing revised guidelines
- No real indication for HLA typing in primary care
- GFD now labelled only if less than 20ppm in UK.
- Most associated risks reduced only if strictly on GFD
Q&A