Non-responsive coeliac disease: next steps for investigation

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• Cases

• Non-Responsive Coeliac Disease
  – Causes
  – Investigation
  – Treatment

• Refractory Coeliac Disease
  – Investigation
  – Management
Case 1

- 27 year old female

- GP referral
  - Lifelong history of GI upset
  - Intermittent diarrhoea and constipation
  - Bloating abdominal discomfort
  - More symptomatic on eating wheat
  - Positive coeliac serology please see and advise
Case 1

• Bloods
  – Anti TTG 36 U/ml
  – FBC/U+E/LFT/CRP/bone profile normal

• OGD
  – “Poorly tolerated” but no mucosal abnormality
duodenal biopsies taken as requested

• Histology
  – Raised IELs and “blunted” villi please correlate with
    serology and clinical picture
Case 1

• Follow up
  – Diagnosed coeliac disease and referred to dietician started on GFD
  – Good adherence with GFD
  – DEXA – normal BMD – lifestyle advice only required
  – 1 year later – after initial improvement ongoing bloating abdominal discomfort GP suggests codeine/loperamide for diarrhoea and fybogel for diarrhoea
  – No weight loss
  – Normal biochemistry
What would you do next?
1. Repeat Serology?
2. Repeat Biopsy?
3. Steroids?
4. Other tests?
5. Discharge back to GP for follow up?
Case 2

• 64 year old female
  – Diagnosed with coeliac disease many years previously in different area but lost to follow up
  – CD diagnosed on background diarrhoea and iron deficiency anaemia
  – Apparent improvement on GFD and managed CD herself so not turned up to follow up
Case 2

- GP referral on 2 week wait
  - Weight loss, diarrhoea, iron deficiency anaemia
  - Seen in surgical clinic gastroscopy and colonoscopy arranged
- Bloods
  - HB 9.7 MCV 73 Ferritin 4
  - Albumin 27 ALT 64 Alk P 189 Bilirubin 18
  - U+Es normal
  - Corrected calcium 2.01
- OGD/Colonoscopy normal – D2 biopsies taken
Case 2

- **Histology**
  - Raised IELs and total villous atrophy “suggest referral to gastroenterology for further advice”
- **Represents to A+E**
  - Tetany and positive chvostek’s sign
  - Corrected ca – 1.45
  - Hb7.4
  - Albumin 17
  - Continued weight loss and diarrhoea
  - Apparently good adherence with GFD
What would you do next?

1. Prescribe calcium supplements and ask to stick to GFD and f/up in clinic?
2. Repeat Serology?
3. Repeat Biopsy?
4. Steroids?
5. Other tests?
Definitions

• Non-Responsive coeliac disease (7-30%)
  Ryan BN et al *Gastroenterology* 2000;119:243-51
  – Failure of symptomatic or histological improvement with a presumed GFD
  – Primary or secondary

• Refractory coeliac disease
  – Persistent malabsorptive symptoms and villous atrophy despite strict adherence to a gluten free diet (GFD) with negative serology for anti-TTG or EMA
Non-Responsive Coeliac Disease (NRCD)

- Has the correct initial diagnosis been made
  - Review supporting evidence – serology, FHx, hyposplenism etc
  - Review biopsies
  - Consider alternative causes of villous atrophy
  - Initial symptomatic response to GFD not necessarily a marker of coeliac
  - HLA DQ2/DQ8
Serology

- Anti-tTG alone
  - 15 U/ml cut off (n=2000)
    - Sensitivity 90.9%
    - Specificity 90.9%
    - Positive predictive value 28.6%
    - Negative predictive value 99.6%
    - Prevalence of tTG negative coeliac disease – 0.4%
  - False positive tTG antibody results may occur in chronic liver disease, myeloma, monoclonal gammopathy, and type 1 diabetes among others

Hopper AD et al. BMJ 2007;335:558-562
• **Marsh stage 0:** normal mucosa

• **Marsh stage 1:** increased number of intra-epithelial lymphocytes, usually exceeding 20 per 100 enterocytes

• **Marsh stage 2:** proliferation of the crypts of lieberkuhn

• **Marsh stage 3:** partial or complete villous atrophy

• **Marsh stage 4:** hypoplasia of the small bowel architecture
Causes of small bowel villous atrophy

- Agammaglobulinaemia or hypogammaglobulinaemia
  - Check immunoglobulins
- AIDS enteropathy – HIV status
- Amyloidosis
- Autoimmune enteropathy – anti enterocyte ABs
- Bacterial Overgrowth – SB aspirate/?H2 breath test
- Collagenous sprue
- Crohn’s disease
- Eosinophilic enteritis
- Giardiasis – Stool OCP/SB biopsy for PCR
- Graft versus host disease
- Intestinal lymphangiectasia
- Intestinal lymphoma
- Ischaemia – CTA/MRA
- Mastocytosis
- Tropical sprue
- Tuberculosis
- Radiation enteritis
- Whipple’s disease – SB biopsy for PCR
- Zollinger Ellison Syndrome

Mooney PD et al. JGLD 2012;21(2):197-203
Adherence to GFD

- No adherence most common cause of NRCD
- Estimated adherence 42-91%
- Check serology – marker of gluten exposure not villous atrophy
- Food diaries
- Dietetics input
- Oats

Other causes for symptoms

• Linked with coeliac disease
  • Microscopic colitis
  • Lactose/fructose malabsorption
  • Small bowel bacterial overgrowth
  • Pancreatic exocrine insufficiency
• Other co-existing conditions
  • IBS
  • IBD
  • Anal sphincter dysfunction
  • Protein losing enteropathies
  • Hyperthyroidism
  • Giardia
Exocrine Pancreatic Insufficiency using FEL-1

\[ p < 0.0001 \]
Response to therapy

Number of bowel motions per day before and after treatment

- Pre-treatment
- Post-treatment

p < 0.0001
Summary of data on exocrine pancreatic insufficiency

• N=259 (50 controls)
• 20/66 CD with diarrhoea had low FPE (30%)
• Stool frequency reduced but no changes in weight
• Creon initially at 10,000 units tds then titrated

What happened with time?
- IBS prevalence: coeliac disease 22%, (n=225)
- Concomitant IBS was associated with reduced SF-36 scores in patients (\(P<0.0001\)).

Barratt SM et al. *Eur J Gastroenterol Hepatol* 2011;23:159-165

- Adult coeliac patients on GFD (n=51) still have more GI symptoms than healthy controls (n=182)

Barratt SM et al. *Gut* 2010;59:suppl1 A94
Bacterial overgrowth in coeliac disease

• N=15 with persisting GI symptoms
• lactose malabsorption (n=2), inadvertent gluten exposure (n=1), giardia (n=1), ascaris (n=1),
• 10 had a positive lactulose H2 breath test and responded symptomatically to rifaximin 800mg/day (1 week)
• Difficulties with H2 breath tests in CD?  

• 50 patients with NRCD randomised to Rifaximin or placebo
• No difference in GI symptoms following 10/7 Rifaxmin
• ?actual numbers of pts with SBBO
  Chang MS et al Dig Dis Sci 2011;56:2939-2946
NRCD

Review original diagnosis: biopsy, HLA, serology, FHx

Dietary review

• Repeat gastroscopy with biopsy and aspirate
• Colonoscopy and biopsy
• Faecal elastase
• Stool culture
• Bloods inc inflammatory markers, thyroid function

Exclude other causes:
• SBBO
• PLE
• Fructose intolerance

Lactose intolerance
• Consider FODMAP's

Consider RCD?

No coeliac disease

Gluten contamination

• Microscopic colitis
• Exocrine pancreatic insufficiency
• Giardiasis
• Hyperthyroidism
• Rare cause of NRCD unknown true incidence? 1.5%
• Diagnosis of exclusion
• Persistent changes of CD despite strict adherence to GFD
• Pre-malignant condition
• Type 1 – polyclonal expansion of IELs and villous atrophy
• Type 2 – includes ulcerative jejunitis, clonal expansion of aberrant IELs (CD8+ TCR γ δ cells)
• Enteropathy Associated T-cell Lymphoma (EATL)
Refractory coeliac disease

• Symptoms
  – Persistent malabsorptive symptoms should prompt re-evaluation
  – Diarrhoea/steatorrhoea
  – Iron deficiency
  – Weight loss
  – Micronutrient loss - Zn, Cu, Se etc
Investigation

• Rule out malignancy – EATL/adenocarcinoma/other
  – ‘B’ symptoms?
  – Abdominal pain
  – GI bleeding
  – Obstructive symptoms
  – EATL most commonly affects proximal jejunum

• Consider CT/PET-CT, small bowel imaging (MR/Ba/capsule etc)

• DBE
• OGD – multiple bx strategy - discussion with tertiary centre – Histology for IEL population analysis (PCR/immunohistochemistry)
  – Caveat 1: Study of asymptomatic coeliac patients only 17.5% had achieved complete histological response at 2 years (Bardella et al. Histopath. 2007;50:465-471)
  – Caveat 2: Changes are well recognised to be patchy in some patients (Hopper et al. Endoscopy 2007;39:219-224)
  – Caveat 3: Recent evidence has shown that the presence of an aberrant immunophenotype and monoclonality do not definitively confer a diagnosis of RCD – can be seen in uncomplicated coeliac disease (Liu et al. Gut 2010;59:452-460)
Management

- Nutrition, nutrition, nutrition
- Gluten free diet
- Enteral vs PN
- Micronutrients
- Re-feeding
Management

- Steroids – budesonide/prednisolone?
- 5-ASA?
- Azathioprine?
- Cladribine?
- Stem cell transplant?
- Infliximab? Why not...
- IL-15? Enhances anti-tumour immunity in CD8+ T-cells
Prognosis

- **Type 1**
  - 90-100% 5 year survival
- **Type 2**
  - 50% 5 year survival
- **Ulcerative jejunitis**
  - Dismal
- **EATL**
  - 20-30% 2 year survival
  - 50 times more common in someone with coeliac disease, the annual incidence is low (0.5-1 per million people)
- **Not necessarily a linear progression**
Cases
Case 1

- 27 year old female with persistent GI symptoms despite apparent adherence to GFD

What would you do next?

1. Repeat Serology?
2. Repeat Biopsy?
3. Steroids?
4. Other tests?
5. Discharge back to GP for follow up?
Case 2

- 64 year old female with symptoms of severe malabsorption and weight loss on background of coeliac disease
- What would you do next?
  1. Prescribe calcium supplements and ask to stick to GFD and f/up in clinic?
  2. Repeat Serology?
  3. Repeat Biopsy?
  4. Steroids?
  5. Other tests?
Case 2

- Given IV calcium, IV iron
- Senior dietician review – apparent adherence to GFD, BMI dangerously low – NG feeding commenced
- Anti TTG – normal
- Immunoglobulins – IgA low
- CT chest abdo pelvis – oedematous small bowel, scattered lymphadenopathy but not significant by size criteria
- Referred to surgeons for laparoscopy/LN biopsy – no evidence of lymphoma
Case 2

- Unable to tolerate NG feeding and TPN commenced
- Commenced on prednisolone and slowly starts to put on weight and taken off PN
- Starts to tolerate oral intake and meeting nutritional requirements
- Unfortunately develops Hospital Acquired Pneumonia and rapidly deteriorates – Despite ICU input dies 3 days later
On-going Research at the Royal Hallamshire Hospital