Diagnostic and Management Dilemmas in Celiac Disease
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Issues for Consideration
- Approaches for diagnosing celiac disease
- Role of genetic testing
- How to evaluate someone already on a GFD
- What to do with non-responsive celiac disease
- Celiac disease crises
- Refractory celiac disease
- Management of RCD
- Potential new therapies for celiac disease

Definitions and Current Terminology
- Celiac disease (CD): a chronic small intestinal immune-mediated enteropathy precipitated by exposure to dietary gluten in genetically predisposed individuals
- Other terms including celiac sprue, sprue, gluten intolerance and gluten-sensitive enteropathy are no longer recommended
- Classical and non-classical celiac disease
- Asymptomatic or subclinical celiac disease
- Potential celiac disease

Changing Prevalence of Celiac Disease
- Prevalence of up to ~1:100 in most genetically susceptible populations
- Less than 10-15% of current cases of CD have been diagnosed in the US
- CD is 4 to 4.5 times more prevalent than 50 yrs ago
- Cause of “CD epidemic” unknown
  - Dietary – grains with increased gluten, increased wheat in diets worldwide
  - Other environmental factors
  - Microbiota

Changing Picture of Disease
- Classical form less prevalent now
- Average age of diagnosis in 5th decade
- Many are overweight
- Seroprevalence M=F, diagnosis M<F
- Other presentations are being increasingly recognized:
  - Obstetrical problems
  - Neuropsychiatric manifestations
  - Related autoimmune conditions
  - Many others – true associations or chance?

Diagnosis
- Characteristic histological findings
- Clinical, serological, and in some cases, histological response to a gluten free diet
- Rarely necessary to observe clinical and histological response to gluten challenge
- Intestinal biopsies are the only method by which celiac disease can be diagnosed
- However, for dermatitis herpetiformis a classical skin biopsy is sufficient for diagnosis

Rubio-Tapia, A et al, Gastroenterology, 137: 88, 2009
Vieira et al, Scand J Gastroenterol, 44:933, 2009
Ludvigsson, J et al, Gut, 2012
Performance of Diagnostic Tests for Identifying Celiac Disease

- 16 studies included (N=6085 subjects)
- EMA IgA (N=8 studies)
  - Sensitivity 0.90 (95% CI, 0.80-0.95)
  - Specificity 0.99 (95% CI, 0.98-1.00)
- TTG IgA (N=7 studies)
  - Sensitivity 0.89 (95% CI, 0.82-0.94)
  - Specificity 0.98 (95% CI, 0.95-0.99)

TTG IgA and EMA IgA have high sensitivity and specificity for diagnosing celiac disease in adults with abdominal symptoms in primary care or other unselected populations.

Van der Windt et al, JAMA, 203:1738, 2010

Farrell & Kelly, NEJM, 346:180, 2002

Deamidated Gliadin Peptide (DGP) Abs

Serum from celiac with active disease preferentially recognize deamidated gliadin peptides

IgA and IgG antibodies to deamidated gliadin peptides (DGP) are more sensitive and specific tests than IgA and IgG antigliadin antibodies (AGA)

Deamidated Gliadin Peptide (DGP) Abs

Schwertz et al, Clin Chem, 50:2370, 2004
Agardh, Clinical Gastroenterology & Hepatology, 5: 1276, 2007

What are the Best Serological Tests for Screening?

- Depends on prevalence and age of population being examined
- Overall, tTG IgA is the recommended test to screen for disease but sensitivity varies with lower levels (≥90%) reported in routine practice – 1 in 10 false negatives!
- EMA IgA is helpful when positive
- TTG, EMA less sensitive for milder histologic stages
- Traditional AGA no longer used as a first line antibody test except in young children
- Check total IgA for assays with narrow range of normal
- Antibodies to GDP are less sensitive than to tTG

Lewis, NR, Aliment Pharmacol Ther, 31: 73, 2010

? Proposed New Criteria for Diagnosis

“Four out of five” sufficient to diagnose CD?

- Typical symptoms of CD
- High titer of serum CD IgA class autoantibodies
- HLA DQ2 and/or HLA-DQ8 genotypes
- Celiac enteropathy by small bowel biopsy
- Response to a GFD

This proposal remains controversial amongst other experts in the field

Sapone, et al, BMC Medicine, 2012

New ESPGHAN Guidelines for the Diagnosis of CD in Children

Children with symptoms of CD
- Symptoms
- Positive serology
- Histology
- If TTG IgA titers > 10X upper limit normal option to diagnose without biopsy but strict protocol of further lab testing recommended (verify TTG with EMA to exclude a false positive, HLA testing)

JPGN, 154:136, 2012

New ESPGHAN Guidelines for the Diagnosis of CD in Children

Asymptomatic children at increased risk of CD
- HLA-DQ2 and HLA-DQ8
- Positive serology (TTG IgA) – confirm low titer TTG IgA elevation (3 times ULN) with EMA
- Histology
  - if EMA negative, repeat serology q 3-6 months on gluten-containing diet

JPGN, 154:136, 2012
Endoscopic Findings in Celiac Disease

- Flattened or absence of folds
- Notching or scalloping of folds
- Fissuring of mucosa

Endoscopic findings are not very sensitive but they are quite specific. If you suspect celiac disease, take biopsies!

Oorenteno, Am J Gastroenterol, 97:933, 2002

Biopsies are the Gold Standard but Have Some Limitations

- False positives
  - Other conditions that cause epithelial changes and/or increased inflammation (peptic duodenitis, bacterial overgrowth, enteric infections, tropical sprue)

- False negatives
  - Subtle findings, insufficient sample, patchy disease, distal disease

Taking ≥4-6 biopsies including at least one from the duodenal bulb increases CD detection rate and using an experienced pathologist minimizes these pitfalls.

Oorenteno, Am J Gastroenterol, 97:933, 2002

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How Well Are Endoscopists Doing When Looking For Celiac Disease?

- Retrospective study using data from a national pathology service in 43 states
- 132,352 subjects without known celiac disease (CD) underwent duodenal biopsies for possible CD
- Rate of diagnosis of CD for ≥4 versus <4 biopsies: 1.8% vs 0.7% (P < 0.0001)
- Rate of ≥4 biopsies in 2006 was 35%, in 2009, 37% and in cases of malabsorption still only 39.5%
- These data and my own experience indicates that there is room for improvement!


HLA DQ Screening Tests

<table>
<thead>
<tr>
<th>Risk of celiac disease and HLA status</th>
<th>DR3-DQ2 or DR5/7-DQ2 – 90-95%</th>
<th>DR4-DQ8 – 5-10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>General population ≤ 1.0%</td>
<td>DQ2 homozygous – 31X</td>
<td>DQ8 homozygous – 10X</td>
</tr>
<tr>
<td>DQ2/DQ8 positive – 14X</td>
<td>DQ2 heterozygous – 10X</td>
<td>DQ8 heterozygous – 2X</td>
</tr>
<tr>
<td>DQ2 and DQ8 negative – &lt; 0.1X</td>
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Only HLA DQ2 or DQ8 positive subjects are at risk of getting celiac disease

Necessary but not sufficient

Helpful test for its NPV


When to Use Genetic Testing

How to test:
- PCR of RNA extracted from cells in a cheek swab or blood sample

Who to test:
- Close relatives of patients with confirmed CD wishing to know if they are at risk of developing CD
- Patients on a gluten free diet who are candidates to undergo a gluten challenge to confirm possible CD
- Equivocal histology and serology findings in which a negative test result would make CD highly unlikely

How often to test: Once in a lifetime

What to Do with the Patient on a Gluten Free Diet without Biopsy?

Celiac disease is possible & patient is willing to undergo gluten challenge?
- Up to 6 to 12 months on "GFD" check serology and consider EGD + Bx
- Challenge if HLA DQ2 or 8 positive
- Check Ab q1-2 months up to 6 months
- No but wants genetic testing for sake of children
- Yes, get genetic testing
- No further evaluation if they will still stay on GFD regardless of evaluation and will not have children tested

Diagnostic Dilemma Case

35 yr old woman with DM type I developed bloating, loose stools
PCP orders serology that includes elevated TTG IgA, patient starts a GFD
Sees me after 5 weeks on diet, TTG level has fallen to 32 (N 20) and DGP Abs also mildly elevated
EGD with biopsies are normal – I advised her to stay on GFD since CD was highly likely

Diagnosing CD by VCE when EGD and Bx were unable to to provide a diagnosis

- 8 cases of patients suspected to have celiac disease
  - 4 with negative EGD & Bx
  - 2 declined EGD & Bx
  - 2 in which EGD & Bx was contraindicated
- In all cases VCE showed mucosal changes of celiac disease
- 7 followed up and all had either serological or clinical improvement on a GFD

Role for Video Capsule Endoscopy

- Meta-analysis of studies that examined accuracy of VCE in diagnosing CD
- 166 individuals included
- 6 studies eligible
- Overall pooled VCE sensitivity compared to biopsy was 98% [95% CI (82-94)], specificity was 95% [95% CI (89-98%)], AUC 0.9584
- Authors conclude VCE not as accurate as pathology but a reasonable alternative

Gluten Challenge

- Gradual increase of gluten in diet up to target (4 slices bread a day - unrestricted)
- Check tTG IgA at 2-6 weeks and at intervals thereafter until positive
- EGD/biopsy if diarrhea develops and/or become seropositive
- Management if still seronegative at 3 to 6 months needs to be individualized

Diagnostic Dilemma Case (2)

Patient returns a few weeks later very frustrated with staying on the GFD
Wants further confirmation that she has celiac disease and no other causes of GI symptoms
Colon and ileal biopsies normal
VCE shows fissuring of mucosa in the proximal jejunal region
Push enteroscopy with biopsies targeted to abnormal mucosa which confirm celiac disease

Evaluating Role of SB Endoscopy

- Assessment of patients undergoing CE, PE, DBE, or IOE in a single center in England since 2002 (CE, PE, IOE) or 2006 (DBE)
- Demand for CE and DBE increased every year
- 1431 CE, 247 PE, 102 DBE, 17 IOE in 93 months
- Diagnostic yields were 34.6%, 34.5%, 43% and 88% respectively. Management altered 25%, 19%, 33%
- Authors conclude that CE as first-line investigation followed by PE/DBE or IOC is potentially less invasive and tolerable


VCE Findings in Celiac Disease (1)

Scalloping of Folds
Mucosal Fissuring

VCE Findings in Celiac Disease (2)

Notching, Layering/Stacking
Villous Atrophy

Non-responsive Celiac Disease

- Usually due to ongoing or recurrent gluten exposure
- Coincident disorders
  - Lactose intolerance
  - Pancreatic insufficiency
  - Small intestinal bacterial overgrowth
  - Microscopic colitis
  - IBS
- Unrelated to celiac disease – incorrect or additional diagnoses
- Complications of celiac disease
  - Refractory celiac disease
  - Malignancy


UVA Study of NRCD

272 with CD (69% F, 96% white)
97 of the 272 had NRCD

32% non-compliance with GFD
21% had IBS
10% microscopic colitis
5% gastroparesis
4% SIBO
3% pancreatic insufficiency
13% RCD

Basile, JM, Hammerle, CW, Crowe, SE. DDW 2011

Evaluating Possible Complications of Celiac Disease

54 yr old male who had been doing well on a GFD.
Develops anemia and abdominal discomfort. EGD unremarkable and duodenal biopsies show mild villous blunting and mild increased IELs.
Colonoscopy normal.
Undergoes VCE for further evaluation.
Capsule Endoscopy in NRCD

- Case-control study of 42 NRCD and 84 age- and sex-matched controls who underwent CE. Also included 30 patients with uncomplicated CD.
- 13/42 of NRCD had macroscopic findings of CD vs 0/84 controls or 14/30 of uncomplicated CD.
- 2 severe complications detected in NRCD.
- Erosions/ulcers in NRCD associated with increased ASA/NSAID use in NRCD but rate of detection of lesions similar in all 3 groups.


VCE Findings in NRCD

Ulcerative Jejunitis

NSAID Erosions


Refractory Celiac Disease (RCD)

Villous atrophy associated with persistent or recurrent malabsorptive symptoms despite strict adherence to a GFD for at least 6-12 months in the absence of other causes of nonresponsive CD or overt malignancy.
- Rare, prevalence low even in major referral centers.
- Primary form – no initial response to GFD.
- Secondary form (more common) - after an initial period of response no longer responds to GFD.
- tTG IgA often normal in RCD if patient is GF.

Rubio-Tapia & Murray, Gut, 59: 547, 2010

Refractory Celiac Disease

- Variants - collagenous, ulcerative, stricturing.
- Risks for RCD:
  - Older age, two DQ2 alleles, untreated or partially treated.
- Two main forms based on T cell TCR:
  - RCD type I – phenotypically normal IEL.
  - RCD type II – associated with clonal expansion of IEL bearing CD3ε but lacking expression of CD4, CD8 and the β-chain of TCR.

Rubio-Tapia & Murray, Gut, 59: 547, 2010

VCE Findings in RCD

EATL

Persistent Enteropathy

Rubio-Tapia & Murray, Gut, 59: 547, 2010
Diagnostic Yield of CE in RCD

- Retrospective study of 9 patients with symptomatic CD, 11 with RCD I, 18 RCD II and 45 without CD who were investigated by both CE and upper endoscopy or enteroscopy
- Concordance of CE with histology for villous atrophy was better than optical endoscopy
- 3 cases of overt lymphoma detected by CE in follow-up
- Authors conclude that CE may predict type of RCD and allow early detection of lymphoma

Differential Diagnosis of RCD

- Adult-onset autoimmune enteropathy
  - Anti-epithelial antibodies (enterocyte, goblet cell)
- CVID
  - Absent plasma cells on biopsy, reduced serum Ig
- Tropical sprue
- Collagenous sprue
- Eosinophilic gastroenteritis
- Crohn disease

Study of Non-celiac Enteropathy

- Reviewed all cases of duodenal villous atrophy
- 30 cases of non-celiac enteropathy (NCE)
  - 24 of these were HLA DQ2/DQ8 negative
  - 26 negative for TTG IgA
  - 10 had no increased IEL
- 21 misdiagnosed as CD, 1 gluten intolerance - no response to a GFD, no biopsy improvement
- Most common diagnosis was unspecified immune enteropathy (10)

Refractory Celiac Disease Prognosis

- Poor prognosis – 50% of RCD type II die within 3 to 10 years usually due to:
  - Lymphoma, intractable diarrhea, severe infections
- 5 yr survival rates for RCD II - 40-58%
- Better prognosis for RCD I but higher mortality than uncomplicated CD

Experience with RCD at UVA

- 19 of 97 with NRCD had RCD (20%)
  - 3 type I
  - 14 type II
  - 2 untyped
- All had evidence of malabsorption
- 17 (89%) received steroids, 14 (74%) thiopurines
- 11 received temporary enteral and/or parenteral nutrition
- 2 died of celiac disease associated process
  - EATCL
  - Inflammatory neurological disorder

References:

- Cellier, C, and colleagues, Am J Gastroenterol, in press 2012
- Alumut, Am J Gastroenterol, 2010 in press
- Cellier, Clin Gastro & Hepatol, 4: 1320, 2006
- Basile, JM, Hammerle, CW, Crowe, SE. DDW 2011
Treatment Options for RCD

- Corticosteroids including budesonide
- Immunosuppressives
- Infliximab
- Mesalamine (Pentasa)
- Hypoallergenic-elemental enteral feeds
- Parenteral nutrition
- Cladribine, alemtuzumab
- Hematopoietic stem cell transplantation
- Anti-IL-15

Rubio-Tapia & Murray, Gut, 59: 547, 2010
Cellier, Clin Gastro & Hepatol, 4: 1320, 2006

Celiac Disease Crisis

- Acute onset of severe dehydration, renal dysfunction, electrolyte disturbance and weight loss
- Can be the initial presentation of celiac disease
- Can complicate refractory CD or CD with lymphoma
- Requires hospitalization, IV fluids, often requires steroid therapy, sometimes TPN
- One case series of 11 patients reported from Beth Israel-Deaconess Hospital
  - All had ≥ Marsh 3 stage enteropathy, 1/3 with TVA

Jamma, S, Leffler, DA, & colleagues, Clin Gastro & Hepatol, 8:587, 2010

Management

- Goal: Return to normal health and prevent complications of untreated celiac disease
- Life-long gluten free diet
- Low lactose diet initially
- Nutritional supplements if deficient
  - Calcium, vitamin D, iron, folate and other nutrients
- Refer to a knowledgeable dietitian
- Encourage patients to join local chapters of various celiac organizations, gain knowledge


Take Home Messages

- Increased prevalence of celiac disease
- Increased reporting of gluten sensitivity without celiac disease
- Diagnostic tests perform well but have some limitations, growing role for HLA DQ testing
- Role of biopsy is now being challenged
- Emerging role for VCE in celiac disease
- Gluten free diet remains treatment mainstay
- Potential new therapies being investigated