Non-Invasive Monitoring of Intestinal Permeability and Inflammation in a Prospective Serological Diagnosis Study of Pediatric Celiac Disease

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Disclosures

None relevant

Celiac Disease (CD)

- Gluten sensitive autoimmune enteropathy
- Gluten found in wheat, barley and rye
- 1% prevalence worldwide
- Treatment: Lifelong Gluten Free Diet (GFD)
Gene Associations

- HLA-DQ2 & HLA-DQ8 predispose to CD
- Genes are necessary but not sufficient
- Both present in 30% of the population
- HLA-DQ2 is found in 95% of CD patients
- HLA-DQ8 is usually present in 5-10% of CD patients

Celiac Screening

- Serological screening
  - Anti-tissue Transglutaminase (aTTG)
    - 90-98% Sensitivity, 94-97% Specific
  - Anti-endomysial antibody (EMA)
    - 85-98% Sensitivity, 97-100% Specific
    (Husby et al. Ann / Gastro-2011)
- Genetic Screening
  - Tests the potential of having CD
  - Absence of DQ2 and DQ8 excludes diagnosis of CD
    - Negative predictive value of nearly 100%

European Guidelines

- 2012 – ESPGHAN initiated a serological route for diagnosis
  - Symptomatic presentation
  - aTTG 10x upper limit of normal
  - Confirmatory testing (anti-endomysial antibody)
  - Confirmatory genetics
- European Guidelines recommend Genetic screening for:
  - High risk groups
  - Districts of conundrums (negative antibodies, Marsh 3)
  - Symptomatic children where biopsy is not desired
    (Husby et al. JPGN 2012)
Diagnostic Controversy

Current North American gold standard is biopsy
Is it being followed?

- Our local laboratory data suggests 17% children <18 yo have positive serology but no biopsy
- 2/3 of those not biopsied had aTTG <150 U/mL
  (Saginur M et al. Pediatrics & Child Health 2012)
- In Europe 13% of surveyed Pediatric GI doctors would prefer to omit biopsy in symptomatic patients
  (Ribes-Koninckx et al. JPGN 2012)

Serological Diagnosis

Accuracy of serological tools raises the questions:
Is serology sufficient to diagnose CD?

- Retrospective studies show aTTG >200 U/mL positive predictive value (PPV) approaching 100%
  (Mubarak et al. JPGN 2011, Barker et al. Pediatrics 2005,
- Our own local study showed aTTG >200 U/mL PPV 100%
  (Saginur et al. Paediatr Child Health 2013)

Aims

To prospectively pilot serological diagnosis (SD) at our local center

1. Monitoring baseline and follow up aTTG;
   permeability and fecal calprotectin given serological (SD) vs endoscopic (ED)
2. Assessing if either diagnostic strategy impacted adherence to the GFD
3. Assessing patient and family preference for SD vs ED
Methods
- Recruitment at Stollery CD Clinic – 3-17 year olds without co-morbid diagnosis (e.g. IBD, T1DM)
- Consented to:
  - SG: aTTG ≥ 200 U/mL, positive for HLA DQ2 or DQ8
  - ED: aTTG > 7 U/mL, positive Marsh 1-3 biopsy findings
- Baseline & Follow up at 12 months:
  - Symptoms, height, weight, aTTG
  - Urine L/M and %Sucrose excretion as permeability markers
  - Stool FC marker as inflammation marker

Mucosal Permeability
- Sugar probes: secreted in urine show intestinal leaky
- L/M ratio shows damage throughout the whole gut
  - Estimated 96-100% sensitive (Catassi et al. Gut 1997.)
- Sucrose shows proximal intestinal damage
  - Sensitivity 75%, specificity 92% (Simecek et al. Am J Gastroenterol 1999.)
- Increased L/M ratio and FeSucrose in CD patients and recovery to normal levels after GFD

Mucosal Inflammation
- Fecal Calprotectin - Calcium binding protein and marker for inflammation
- FC is increased in disorders with mucosal inflammation (Costa et al. Dig Liver Dis 2003.)
- FC increase in children with CD related to Marsh score and normalizing with GFD
Mean (SD), Significance was shown through T-tests and Mann-Whitney tests (p<0.05).

Baseline Demographics

<table>
<thead>
<tr>
<th>Baseline Diagnosis</th>
<th>Serum Diagnostics</th>
<th>Biopsy Diagnostics</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>0.5 (3.4)</td>
<td>3.9 (3.5)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>14:18</td>
<td>16:27</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>131.2 (21.4)</td>
<td>131.6 (21.1)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>31.0 (15.0)</td>
<td>31.6 (16.1)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>aTTG (U/mL)</td>
<td>193.8 (28.4)</td>
<td>517.0 (250.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GI symptoms</td>
<td>18.4%</td>
<td>16%</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Growth Concerns</td>
<td>46.9%</td>
<td>38.6%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Behavioral Symptoms</td>
<td>46.9%</td>
<td>46.5%</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Anemia/Fatigue</td>
<td>39.4%</td>
<td>53.5%</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>CNS</td>
<td>37.5%</td>
<td>41.9%</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Other</td>
<td>32.5%</td>
<td>33.6%</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Family History</td>
<td>46.9%</td>
<td>45.2%</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

*Note: (SD), Significance was shown through T-tests and Mann-Whitney tests (p<0.05).

12 Month Demographics

<table>
<thead>
<tr>
<th>Follow-Up</th>
<th>Serum Diagnostics</th>
<th>Biopsy Diagnostics</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>9.5 (3.5)</td>
<td>10 (3.2)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>14:18</td>
<td>16:27</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>136.1 (21.3)</td>
<td>140.5 (20.1)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>34.0 (17.7)</td>
<td>37.6 (16.7)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>aTTG (U/mL)</td>
<td>9.4 (1-56)</td>
<td>3.8 (1-420)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>% aTTG Decline</td>
<td>98.5 (67-99.9)</td>
<td>91.4 (368-99.9)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Note: (SD), Significance was shown through T-tests and Mann-Whitney tests (p<0.05).
Conclusions

1. Higher aTTG group had increased abnormalities in mucosal permeability and inflammation at baseline
2. Both CD groups showed improved intestinal permeability
3. There was no difference in adherence or symptom improvement between the diagnostic groups

Clinical Relevance

- Prospective study designed for the local setting
- Serological diagnosis **did not** disadvantage patients in regards to mucosal healing or adherence to GFD
- Families appreciated having the option of diagnosis route
- Engages family and child early in disease management

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[Logos]