SOME IMMUNOLOGICAL ASPECTS...

Australasian Gastrointestinal Pathology Society AGM
28 oct 2016

Andrew McLean-Tooke
SCGH, Princess Margaret Hospitals and PathWest
Wheat and gluten

- Gluten is a protein mixture found in wheat
- Complex mixture
  - α/β-, γ- and ω-gliadins
  - HMW and LMW glutenins
- Relatively resistant to digestive enzymes
So what happens in CD?

- CD due to immune response to gluten
- Environmental and genetic risk factors
- Activation of immune cells in small bowel
- Malabsorption results in clinical symptoms
- Only known treatment is gluten avoidance
Enterocytes

IELs

Gut lumen

Lamina Propria
Gliadins and glutenins

Proteases

‘Gluten’

Gut lumen

Lamina Propria
Gut lumen

Gliadins and glutenins

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'tTG

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APC

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CD4 T cell

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Tissue Damage

Tissue Damage

APC

CD4 T cell

tTG

Th1 Cytokines

Lamina Propria
Role of HLA

- HLA-DQ molecules are critical in developing CD
- Certain HLA-DQ genetic variants almost invariably present
- These variants critical for response to gluten
- At least 41 non-HLA loci contribute to risk
HLA molecule capable of recognising gluten peptides
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Tye-Din et al. Int Med J 2015;45:441

Pie chart showing the distribution of HLA-DQ2.5 and variants among 1008 individuals:

- 88% express HLA-DQ2.5 (or a variant) and/or HLA-DQ8
- 4% express HLA-DQ8 (DQA1:03, B1:03:02)
- 6% express HLA-DQ2.2 (B1:02+)
- 1.6% express HLA-DQA1*05 (A1:05+)
- 0.4% express HLA-DQ2.5 (A1:05, B1:02)
- Other (99.6%)
• Frequency of HLA-DQ2 haplotype

• Frequency of HLA-DQ8 haplotype

Abadie et al. Ann Rev Imm 2011;29:493
Modification of gluten peptides
Tissue Transglutaminase (tTG)

- Ubiquitous enzyme
- Cross links peptides
- Involved in tissue repair, ECM stabilisation, cell adhesion
- Also catalyses other reactions including deamidation

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Sollid et al. Immunogenetics 2012;64:455
Gliadins and glutenins

Tissue Damage

tTG

CD4 T cell

Th1 Cytokines
Serological diagnosis of CD

- Serological assessment
  - Anti-EMA antibodies
  - Anti-tTG antibodies
  - Anti-DGP antibodies
DGP specific B cell

Deamidated gluten peptide

TTG specific B cell
DGP specific B cell

- Immunoglobulin/antigen complex internalised and broken down

TTG specific B cell

- Peptides presented on surface with HLA Class II
• Gluten specific T cells “see” the gluten peptides

• Provide ‘help’ to B cells activating them
Deamidated gluten peptide

DGP specific B cell

CD4 T cell

Antibody secreting B cells

TTG specific B cell

TTG antibodies

Antibody secreting B cells

CD4 T cell

DGP antibodies
Endomysial antibody
TTG antibodies

- Identified as major target of EMA antibodies
- Allowed development of ELISA based systems
- IgA tTG antibodies mainstay of many algorithms
DGP antibodies

- Gliadin peptides antibodies poor specificity
- Abs to deamidated gliadin peptides a higher specificity systems
- IgG to DGP better than IgG to tTG
- Benefit in children <2yrs
Revised ESPGHAN Guidelines 2012

European Society for Pediatric Gastroenterology, Hepatology, and Nutrition Guidelines for the Diagnosis of Coeliac Disease


Journal of Pediatric Gastroenterology and Nutrition 2012;54: 136–160
Child / Adolescent with Symptoms Suggestive of CD

Anti-TG2 & total IgA*

Anti-TG2 positive

Anti-TG2 negative

Not CD

Consider further diagnostic testing if:
IgA deficient
Age: < 2 years
History: - low gluten intake
- drug pretreatment
- severe symptoms
- associated diseases

Transfer to Paediatric Gastroenterologist
Paed. G1 discusses with family the 2 diagnostic pathways and consequences considering patient’s history & anti-TG2 titers

Positive Anti-TG2 >10x normal

Positive Anti-TG2 <10x normal

EMA & HLA testing for DQ2/DQ8

Not available

EMA pos
HLA pos

EMA pos
HLA neg

EMA neg
HLA neg

EMA neg
HLA pos

Not available

OEGD & biopsies

Marsh 0-1

Marsh 2 or 3

Unclear case
Consider:
false pos. serology
false neg. biopsy or potential CD
Extended evaluation of HLA/serology/biopsies

CD+
Letter to the Editor

Am J Gastroenterol 2015; 110:1504–1505; doi:10.1038/ajg.2015.242

Should ESPGHAN Guidelines for Serologic Diagnosis of Celiac Disease be Used in Adults? A Prospective Analysis in an Adult Patient Cohort With High Pretest Probability

Emilia Sugai PhD1, Hui J Hwang MD1, Horacio Vázquez MD1, María L Moreno MD1, Florencia Costa MD1, Gabriela Longarini MD1, María I Pinto-Sánchez MD1,2, Sonia Niveloni MD1, Edgardo Smecuol MD1, Roberto M Mazure MD1, Elena F Verdu MD2, Eduardo Mauriño MD1 and Julio C Bai MD1,2

1Small Bowel Section, Department of Medicine, Dr. C. Bonorino Udaondo Gastroenterology Hospital, Buenos Aires, Argentina
2Farncombe Family Digestive Research Institute, McMaster University, Hamilton, Ontario, Canada
3Universidad del Salvador, Buenos Aires, Argentina

Correspondence: Julio C. Bai, MD, Small Bowel Section, Department of Medicine, Dr. C. Bonorino Udaondo Gastroenterology Hospital, Av. Caseros 2061, Buenos Aires (1264), Argentina. E-mail: bai@intramed.net
The presence of anti-endomysial antibodies and the level of anti-tissue transglutaminases can be used to diagnose adult coeliac disease without duodenal biopsy

R. Tortora\textsuperscript{1,}\textsuperscript{*}, N. Imperatore\textsuperscript{1}, P. Capone\textsuperscript{1}, G. D. De Palma\textsuperscript{2}, G. De Stefano\textsuperscript{1}, N. Gerbino\textsuperscript{1}, N. Caporaso\textsuperscript{1} and A. Rispo\textsuperscript{1}

Version of Record online: 28 SEP 2014
DOI: 10.1111/apt.12970

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Identification of a serum transglutaminase threshold value for the noninvasive diagnosis of symptomatic adult celiac disease patients: a retrospective study

Authors

Marco Di Tola, Mariacatia Marino, Simone Goetze, Rossella Casale, Sara Di Nardi, Raffaele Borghini, Giuseppe Donati, Antonio Tiberti, Antonio Picarelli

Original Article—Alimentary Tract
First Online: 29 February 2016
DOI: 10.1007/s00535-016-1188-y

Cite this article as:
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Marsh 2 or 3

Unclear case
Consider:
false pos. serology
false neg. biopsy or
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Extended evaluation of
HLA/serology/biopsies

CD+

Consider false neg. HLA test
Consider biopsies

Consider false pos. Anti-TG2 test
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<td>292</td>
<td>12-4</td>
<td>1-4</td>
<td>45-3</td>
<td>72%</td>
<td>28%</td>
</tr>
<tr>
<td>Inova</td>
<td>29</td>
<td>25-5</td>
<td>8-8</td>
<td>45-3</td>
<td>96-6%</td>
<td>3-4%</td>
</tr>
<tr>
<td>Phadia 250</td>
<td>165</td>
<td>12-1</td>
<td>1-4</td>
<td>17-4</td>
<td>96-6%</td>
<td>3-4%</td>
</tr>
<tr>
<td>Orgentec</td>
<td>42</td>
<td>6-0</td>
<td>3-3</td>
<td>9-4</td>
<td>10-3%</td>
<td>90-7%</td>
</tr>
<tr>
<td>Euroimmun</td>
<td>19</td>
<td>14-0</td>
<td>10-0</td>
<td>44-5</td>
<td>0-0%</td>
<td>100-0%</td>
</tr>
<tr>
<td>Phadia Varelisa</td>
<td>24</td>
<td>8-7</td>
<td>3-4</td>
<td>18-2</td>
<td>27-2%</td>
<td>72-8%</td>
</tr>
<tr>
<td>Aesku</td>
<td>13</td>
<td>13-5</td>
<td>1-9</td>
<td>24-4</td>
<td>69-2%</td>
<td>30-8%</td>
</tr>
</tbody>
</table>
Distribution 115

$n=269$
All-laboratory mean = 3xULN
6% of laboratories report > 10xULN

Distribution 121

$n=299$
All-laboratory mean = 8.4xULN
22% of laboratories report > 10xULN

Distribution 122

$n=292$
All-laboratory mean = 12.4xULN
72% of laboratories report > 10xULN
IgA TTG level correlates with histology
IgG DGP level correlates with histology
IgA TTG lower in single site positive
IgG DGP lower in single site positive
Common Variable Immunodeficiency (CVID)

- Relatively common immunodeficiency with variable levels of immunoglobulins and clinical course between patients
- Most frequent clinically symptomatic PID
- Prevalence between 1:10,000 and 1:50,000
- Some genes have been identified but most cases remain unidentified
CVID definition

- Low immunoglobulins of at least 2 isotypes (IgG and either IgA or IgM)
- Associated with poor specific antibody responses:
  - Poor antibody response to vaccines and/or absent isohaemagglutinins
- Disease onset may occur at any age – most in adulthood
CVID definition

- Infections – most common (90%) with sinopulmonary, ear and gastrointestinal infections
- GI (up to 50%) – chronic diarrhoea, malabsorption
- Lymphophadenopathy or splenomegaly (50%)
- Autoimmunity (30%)
- Granulomas (10-30%) – lungs, liver, other
- Malignancy – increased incidence of lymphoma and gastric cancer
CVID enteropathy

- Seen in up to 10-30%
- Associated with atrophic gastritis 80%
- May have distinctive features:
  - Absence/paucity of intestinal plasma cells
  - Diffuse follicular lymphoid hyperplasia
  - GVH-like crypt apoptosis
  - Neutrophil infiltration
  - IEL infiltrate CD8+ T cell enriched

Malamut et al. Am J Gastro 2010; 105:2262-75
CVID enteropathy

- Serologic studies are not helpful
- May be presenting feature
- Small numbers improve on GFD
- Patients with severe disease may benefit from Budesonide