Mucosal immunology and immunopathology (IBD, CD & NCGS)

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Organic - functional

- Common diseases common.
- Medical history
- Look / listen / feel.
- Which laboratory test?
- Supplementary examinations: Which? When?

Opposing views

The endoscopist
- IBD
- Cancer
- Reflux
- Celiac disease
- Ulcus
- Functional disorders

The patient
- Functional disorders
- Reflux (50 % endoscopy neg)
- Celiac disease
- Cancer
- IBD/Ulcus

Simple investigation of GI disorders

- Clinical examination including patient age
- Clinical chemistry
- Coeliac disease?
  - Serology (and possibly endoscopy)
- IBD?
  - Stool calprotectin (and endoscopy)
- Cancer
  - Fecal blood and endoscopy

Immune homeostasis of mucosa

MacDonald and Monteleone, Science 2005

The 64 000 dollar questions

- Why do some but not all DQ2+ and DQ8+ individuals develop celiac disease?
- Why do some but not all individuals inflammatory bowel disease?
- Why not GI cancer in all?
- It is all about immunology and genetics – and maybe some good/bad luck!
GWAS

- Genome wide association studies.
- Usually done on with SNP analysis (single nucleotide polymorphisms)
- Large sample sizes (thousands of patients and controls)
- SNPs are markers for all genes in human DNA
- Most of them regulatory!!!

GWAS and GI disorders

- Several in Inflammatory Bowel Disease
  - Almost 200 genes involved
  - Immune genes, barrier functions, autophagy
- Some in Celiac Disease
  - Almost 50 genes involved
  - Immune genes, T and B cell regulation
- None in functional disorders!!!

Inflammatory bowel disease (IBD)

IBD – endoscopy and histology

Genetics of IBD: 173 confirmed loci
Lymphocytes Are Migratory Cells That Traffic to Specific Tissues

- Intricate system to guide lymphocytes
- Imprinting of activated lymphocytes allows for preferential migration
- α4β7 and MAdCAM-1 adhesion mechanism in lymphocyte trafficking to inflammation in the gut

Vedolizumab blocks gut homing lymphocytes that would contribute to inflammation

- By binding to α4β7, Vedolizumab blocks capture of pathogenic gut homing lymphocytes
- Vedolizumab does not target lymphocytes to other organs

IBD

- Lot of progress in understanding
  - But what is “the point of no return”?
- Several new therapeutic options
  - The old workhorses 5-ASA, steroids and immunosuppression
  - Anti-TNF (infliximab, adalimumab, golimumab)
  - Anti-adhesion (vedolizumab)
  - But several that did not reach the market (anti-IL-17, anti-IFNγ, anti-CD3)
  - Only 50(-70) % of severe cases respond to treatment
Coeliac disease and gluten related disorders

Gluten intolerance
- the broadest term for all aspects of adverse reactions to gluten

Coeliac disease
- a small intestinal enteropathy, usually also typical serology (IgA-tissue transglutaminase)

Wheat allergy
- a rapid, allergic response

Non-coeliac gluten sensitivity
- clinically quite like coeliac disease, but without enteropathy or serology

I have no idea what gluten is either, but I am avoiding it just to be safe”

Gluten – definitions
- Gluten as in
  - Gluten free food
  - The glue-ish mass after washing of flour
  - The gliadin and glutenin proteins in wheat, hordeins of barley and secalin of rye

Willem K. Dicke defined celiac disease a lifelong and gluten induced disease
- Dutch pediatrician
- On track of gluten since 1934, concluded during and after WWII
- Challenge experiments
- Wheat, rye and barley (and oats) responsible

Adult coeliac disease
- Age at which the patients were first seen and diagnosed at the General Hospital, showing the major peak at 25 and 35 years
- Typical histological appearance of the small intestine

Ludvigsson et al, Gut 2012
The CLUE cohort – adults develop coeliac disease!

- 3511 adults followed from 1974 to 1989 (no intervention)
- 1974: Seven with coeliac disease
- 1989: Additional nine with coeliac disease

Catassi et al. Ann Med 2010

Coeliac disease worldwide

- Chronic diarrhoea in India
- 1:40 in Saharawi population in Sahara
- 1:200 – 1:50 in most Western European countries, increasing
- 1:100 in US, increasing, vast majority without diagnosis
- Unknown among most Far Asian, African and native Americans populations. China???

NORMAL MUCOSA

- gluten

- gluten

autoantibodies to tissue transglutaminase (TG2)

CELIAC DISEASE MUCOSA

The celiac lesion

Blue: Epithelium
Green: T cells
Red: Plasma cells

Courtesy of dr. Beitnes, CIR

The immune reaction in CD

Sollid/Lundin, Mucosal Immunology 2009, modified

CD increases in Scandinavia

Dydensborg, Acta Paed 2011

Iversson, J Int Med 1999

Lohi, Aliment Pharmacol Ther, 2007


Beitnes & Stordal et al, unpublished 2012
The changing clinical presentation

Diagnostic challenge
- Aim: Diagnose CD correctly, economically, definite
  - Leading to lifelong treatment (that precludes later re-diagnosis)
  - Leading to improvement of symptoms (that can be vague and “atypical”)
- In many cases simple
- But
  - false pos / false neg serology is not infrequent
  - Biopsy sampling / interpretation / cut-off may be problematic

Management and follow-up
- Diagnosis based on combination of
  - clinical signs, serology (IgA-TG2, IgA-DGP, IgG-DGP), duodenal biopsy (1-2 from bulb, 4 from duodenum)
  - HLA? (very good neg predictive value)
- Refer to Clinical dietician (gluten free diet)
- Follow up by gastroenterologist once (?)
  - Clinical signs, serology, biopsy not needed (?)
  - Bone densitometry, clinical chem (Fe, folic acid, B12)
- Later follow-up by GP

Potential therapeutic targets
- Inhibit TG2
- Block HLA-DQ2
- Knock out pathogenic T cells

IgA-Transglutaminase (TG2)
- untreated CD
- before challenge
- during challenge
- after challenge
- disease controls

Sulkanen et al. Gastroenterology 1998
Gluten-free market Europe vs US

US consumption of gluten-free food USD 5-10 000 000 000

US trends 2004-2011

Sapone et al. 2012

Pressure from celebrities

Lady Gaga
Kim Kardashian

Tried gluten free food/diet in 2013?

<table>
<thead>
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<th>Percentage</th>
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<tbody>
<tr>
<td>All</td>
<td>17 %</td>
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<tr>
<td>Females</td>
<td>21 %</td>
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<tr>
<td>Men</td>
<td>14 %</td>
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<tr>
<td>15-24 years</td>
<td>32 %</td>
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<tr>
<td>25-45 years</td>
<td>17 %</td>
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<tr>
<td>46 + years</td>
<td>14 %</td>
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General public - Norway

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<th>2006</th>
<th>2012</th>
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<tbody>
<tr>
<td>I try to get a more fit body</td>
<td>55 %</td>
<td>77 %</td>
</tr>
<tr>
<td>I avoid food with a lot of sugar and fat</td>
<td>64 %</td>
<td>81 %</td>
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<tr>
<td>I am not so concerned about my body</td>
<td>24 %</td>
<td>10 %</td>
</tr>
<tr>
<td>I do not consider much what I eat</td>
<td>20 %</td>
<td>14 %</td>
</tr>
</tbody>
</table>

Volunteers for a GFD?

- Gluten free not always tasty!
- But can be!

Price for one (1) bread: USD 15
3-500 customers every day
Opposing views

• NCGS is due to a specific reaction to gluten or “something else” in wheat, rye and barley
• NCGS is due to a reaction to FODMAP

The FODMAP concept

• Fermentable Oligo-, Di-, Monosaccharides And Polyols (FODMAP)
• Colonic fermentation of poorly digestible carbohydrates
  • “Invented” by Gibson and Shepherd in Australia

Oslo work on NCGS

• Celiac disease is rare among NCGS “individuals” recruited from general population
  – 130 responded, 35 were DQ2+, 3 had CD
    • endoscopy and a “HLA-DQ2-gliadin peptide tetramer test”
    – Brottveit et al Am J Gastro 2011
• No signs of psychosomatic disorder
  – Brottveit et al Scand J Gastro 2012
• Increased levels of IEL in NCGS and activation of IFN-γ after challenge with bread
  – Brottveit et al Am J Gastro 2013

The placebo problem

• Traditional placebo
  – Capsules with flour or decoy capsules
  – Poor performance
  • Lundin and Alaedini 2012
• Most studies not well described
• Pioneer work from Gibson group
  – Quinoa based müsli bars spiked with gluten
  – Complete meals

Concluding remarks

• Glutenfree diet and living
  – Has reached considerable proportions
  – NCGS lacks strict diagnostic criteria
    • Placebo-controlled blinded or open challenge?
    • Availability of proper placebo?
    • Treshold for diagnosis?
    • Biomarkers of limited value (but being over-used)
• No signs of “hard end points” for NCGS
• Huge public pressure