Is it Gluten Intolerance or is it IBS?

Gerald Holtmann, MD, PhD, MBA
Director of Gastroenterology & Hepatology, Princess Alexandra Hospital
University of Queensland
Associate Dean Clinical
Faculty of Medicine & Faculty and Health and Behavioural Sciences

Aims

• What defines gluten intolerance and IBS
• Pathophysiology
• Diagnostic approaches/therapy
• Future developments & directions

Patient RJW, 34 yrs, female

GI symptoms
- Relapsing abdominal pain,
- bloating,
- Severe postprandial pain, fullness
- Loose stool/diarrhea, occasional constipation
- Symptoms affect normal life, stopped her work as teacher

History
- Cholecystectomy 5 years ago

Extraintestinal
- Recurrent back pain, migraine
- Complains of lack of energy, fatigued

...broad spectrum of gastrointestinal and extraintestinal symptoms...

15 - 40 % of the population experiences digestive symptoms

50% of those with symptoms seek medical attention

50% of those have functional GI disorders
Coeliac disease?  
H. pylori?  
IBD?  
NERD?  
Diverticulosis?  
Postcholecystectomy-syndrome?  
IBS  

If cancer and IBD are ruled out, FGIDs (e.g. FD, IBS, NERD) or a FGID-like disease are the most likely cause for symptoms

Patient RJW, 34 yrs, female

**Laboratory tests**
- FBC, LFT etc.: very mild IDA  
- Stool, no evidence for parasites  
- Glucose breath test (SIBO) negative  
- Stool microbiome: inconclusive  
- *H. pylori* serology: positive  
- tTGA IgA: pending  
- Serum IgA normal  
- Calprotectin normal

Coeliac disease?

What is gluten?

- Gluten is a protein complex  
- 75 to 85% of the total protein in bread wheat  
- Gluten = glutenin molecules cross-link, network attached to gliadin, which contributes viscosity (thickness)
Symptoms of coeliac disease

- Abdominal symptoms, diarrhea, bloating fullness (constipation)
- Weight loss (infrequent)
- Anaemia, usually resulting from iron deficiency
- Loss of bone density (osteoporosis)
- Itchy, blister skin rash (dermatitis herpetiformis)
- Headaches and fatigue
- Nervous system injury, including numbness and tingling in the feet and hands, possible problems with balance, and cognitive impairment
- Joint pain
- Acid reflux and heartburn

Why and how is the gluten sensitive enteropathy linked to a broad spectrum of GI and non-GI symptoms?

Diagnosis of coeliac disease

- Tissue Transglutaminase Antibodies (tTG-IgA) – tTG-IgA positive in about 98% of patients with celiac disease who are on a gluten-containing diet.
- A positive blood test always needs to be followed by a small bowel biopsy to confirm the diagnosis.

Coeliac disease: Marsh Criteria

- Symptomatic Celiac Disease
- Manifest mucosal lesion
- Silent Celiac Disease
- Latent Celiac Disease
- Normal Mucosa

Genetic susceptibility: DQ2, DQ8 Positive serology

Non coeliac gluten sensitivity?
Non Coeliac Gluten Sensitivity

- Symptoms in response to ingestion of foods with gluten and improvement after discontinuation.
- The symptoms may be accompanied with an increase in levels of antibody to gluten. No identifiable structural changes.

Wheat allergy, celiac disease, gluten intolerance

- Differences between Wheat Allergy and Celiac Disease or Gluten Intolerance. A wheat allergy should not be confused with "gluten intolerance" or celiac disease.
- A food allergy is an overreaction of the immune system to a specific food protein. ... People who are allergic to wheat often may tolerate other grains.

Diagnostic approach

- Serology: Tissue Transglutaminase Antibodies (tTG-IgA) while on Gluten diet (if serum IgA normal, if not anti Gliadin ab IgG)
- Endoscopy/histology: verification of inflammatory changes
- Dietary intervention: Improvement of symptoms and inflammatory changes

IBD?

IBD in coeliac disease

Functional GI disorder?
Rome IV Diagnostic Criteria: IBS

IBS a chronic, episodic disorder characterized by abdominal pain or discomfort associated with altered bowel function and often bloating

- Abdominal pain/discomfort associated with two of three features:
  - <3 bowel movements (BM) per week or >3 BMs per day
  - hard or lumpy stools, or loose or watery stools (stool form)
  - relieved by defecation

Rome IV (2016):

Overlap of symptoms

Dyspepsia

Chronic Constipation

IBS

GERD

There is considerable overlap of extraintestinal symptoms and symptoms of functional gastrointestinal disorders

Gastrointestinal and Extraintestinal Symptoms

Without consultation

Population

GP

Tertiary Center

Intensity of Symptoms

Holtmann et al., EJGH 1994;6:917

* p<0.05

IBS – a psychiatric disease?

IBS/FGID

Organic GI

Why and how is the gluten sensitive enteropathy linked to a brought spectrum of GI and non-GI symptoms?


Why and how is the gluten sensitive enteropathy linked to a brought spectrum of GI and non-GI symptoms?
Post-infectious Irritable Bowel Syndrome - A Meta-Analysis

- Median prevalence of IBS 9.8% (vs. 1.2% in controls)
- Pooled odds ratio 7.3 (95% CI, 4.7–11.1)

Visceromotor reflex after TNB

Infection/inflammation in FGID
a paradigm shift!
Inflammation plays a central role for the manifestation of altered function and central factors modify the effect of inflammation.

Clusters of eosinophils (circled) in the lamina propria adjacent to glands in a subject with functional dyspepsia.


Inflammatory mediators and FGID?

Release of inflammatory mediators significantly increased in patients with IBS & FD.

TNF-α release from PBMCs in FD patients

Liebregts et al AJG 2011

Duodenal eosinophilia in 50% of FD - early satiety

TNF-α release from PBMCs in IBS patients

Liebregts et al Gastroenterology, 2007

HC

TNF-α (pg/ml)

0
50
100
150
200
250
300

M-IBS
C-IBS
D-IBS
[   PI-IBS]

Without LPS

[A]

Release of inflammatory mediators significantly increased in patients with IBS & FD.

TNF-α release from PBMCs in FD patients

Liebregts et al AJG 2011

HC

FD

Release of inflammatory mediators significantly increased in patients with IBS & FD.
...inflammatory mediators and symptoms/function

IBS – a psychiatric disease?

TNF-α and anxiety scores

Anti-TNF-alpha alters GI symptom response to nutrient challenge and the cognitive processing of afferences

Inflammatory mediators closely associated with symptoms in CD & IBS. Driver for immune activation is the MAM
Clinical management

- Establish diagnosis (history, TTT-IgA, endoscopy)
- Define targets of therapy (symptoms vs. structural lesions)
- General measures (concerns of the patient), elimination diet
- Reassurance/Psychological interventions
- Targeted pharmacologic therapy
- Herbal medications
- TCA

Small intestine bacteria – a link to gut-homing markers

Characterisation of Interactions
Brain - Gut - Mucosa Associated Microbiome - Immunity

The most effective drug in IBS

PLACEBO

...The secret of medicine is to distract the patient until nature cures...

Voltaire
Course of disease activity

The most effective drug in functional dyspepsia

The placebo response reflects spontaneous fluctuations of disease activity

Effects of PPI therapy

Improvement after 4 and 8 weeks of therapy: Herbal preparation

Itopride in Functional Dyspepsia

Antidepressants in FGID

In favour of active treatment
Summary

- Functional GI disorders are highly prevalent
- Cause substantial morbidity
- Altered function (sensory) relevant for symptom manifestation
- Significant psychiatric comorbidity
- Minimal inflammation key driver
- Future research in the field of gastrointestinal microbiome

'I have a dream

...we will be able to identify the causes of symptoms in all patients with FGID
...recommend therapies that specifically target the underlying causes
...and may cure (or at least provide symptom control for) all patients with these conditions..

The Future: The Mucosa Associated Microbiome

Fibre / Bulking Agents for IBS

- All have significant methodological flaws
- Psyllium/ispaghula husk (20-30 g/day) improves constipation
- Wheat bran does not appear to be effective
- Data does not support the use of fiber for abdominal pain or diarrhea
- No RCTs have evaluated other laxatives for IBS

A placebo in IBS??
There is no evidence that bulking agents are effective for treating IBS.

There is evidence that antispasmodics are effective for the treatment of IBS. The individual subgroups which are effective include cimetropium/dicyclomine, peppermint oil, pinaverium and Trimebutine.

There is good evidence that antidepressants are effective for the treatment of IBS. The subgroup analyses for SSRIs and TCAs are unequivocal and their effectiveness may depend on the individual patient.

Dietary advice? FODMAP

Antibiotic therapy?

Other measures?
**Meta analysis: psychological interventions**

- 4 trials
- Various interventions (psychotherapy, relaxation, cognitive behavioral, psychodrama)
- All suggested benefit (12 months)
- Baseline adjusted outcome measurements, drop out rates

=> Insufficient evidence to confirm efficacy of psychological interventions

Soo et al Cochrane Database Syst Rev. 2004

**Ingredients and potential effects of STW5 (Iberogast®)**

- *Iberis amara* 15% - tonicising, anti-inflammatory
- *Celandine* 10% - prokinetic, tonicising, cholekinetic
- *Liquorice* 10% - spasmolytic, anti-inflammatory
- *Lemon balm* 10% - spasmolytic, anti-inflammatory
- *Chamomille* 20% - spasmolytic, anti-inflammatory
- *Angelica* 10% - spasmolytic, acid inhibition
- *Milk thistle* 10% - anti-dyspeptic, spasmolytic, cytoprotective
- *Caraway* 10% - spasmolytic, bacteriostatic
- *Peppermint* 5% - spasmolytic, anti-emetic

**Herbal medicine: Shotgun approach**

**Experimental design**

What about relapse rates?
Experimental design

Screening, recruitment

Randomisation

Placebo

STW5 20 drops bd

Esomeprazole 20 mg bd

STW5 plus Esomeprazole

Placebo

Esomeprazole 20 mg bd

STW5 20 drops bd

Esomeprazole 20 mg bd

STW5 plus Esomeprazole

Placebo

0% 10% 20% 30% 40% 50% 60% 70%

% Treatment withdrawal

Placebo STW5 PPI PPI + STW5

‘Active’ treatment withdrawal relapse rates (% of responders)

Placebo withdraw relapse rates

% Placebo withdrawal

Placebo STW5 PPI PPI + STW5

Results

Increase of cytokine secretion in FD and FD/IBS patients

Peripheral blood

Flow cytometry

Cell culture

Small intestinal biopsies

T-cells phenotyping, qPCR, imaging, inflammatory markers

Microbiome

Histology

Gene expression
Increase of cytokine secretion in FD and FD/IBS patients - GI symptoms

T-cells subpopulations - inflammatory marker expression and patient's symptoms

Small gut-homing T-cells: a4+b7+CCR9+

Relation between Circulating T-cells and Lamina propria T-cells

T-cells in FD duodenum lamina propria – relation to GI symptom

Small intestine bacteria – a link to gut-homing markers
Current data – Coming research plan

Granulocytes - FD & FD/IBS patients

Association of Granulocyte responses to symptoms

Prof. Gerald Holtmann group
Dr Anh Do
Dr Erin Shanahan
Dr Yuwen Li
Miss Teresa Hansen
A/Prof. Linda Fletcher

NHMRC Grant

Thank you for your attention

What we have known?

- Local immune activation
  - Focal aggregate of T-cells
  - Increase macrophage/eosinophil counts in FD and mast cell in IB

- Systemic inflammation
  - Increased circulating lymphocyte
  - Elevated systemic pro-inflammatory cytokine levels

- Microbiota – symptomatics
  - Correlation b/w anxiety score and inflammatory cytokine level

- Gut-brain axis
  - Correlation b/w anxiety score and inflammatory cytokine level

What we want to know?

- Whether immune activation is a target for therapeutics?
  - Targeting immune activation improve symptoms?
    - Diversity of FGIDs
    - What immunological factors – what symptoms?

Need to define the true target and strategy for therapy

- Directly suppress specific immune marker - Risk level required medication?
  - Indirectly via targeting the microbes?
Designing the research

Patient recruitment: FD and FD/IBS
- Structural assessment GI symptoms
- Nepean Dyspepsia index
- Depression and anxiety score (HADS)

Clinical test:
- Nutrient challenge test
- Gastric emptying test

Sample collection
- Blood
- Endoscopy
  - Eosophageal, gastric, duodenal biopsies


Heres in perfect health, which is fine, is an empty sign of somethingbiologically wrong