Gluten related disorders
and
Microscopic Enteritis

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Outline

• Grains
• Classification of gluten related disorders
• Microscopic Enteritis
History of Grain

The Fertile Crescent >10,000 yrs BC

- Wheat was among the first cultivated crops
With growing of grains, cooking developed

If cooking had not started, it is doubtful the cereal crops would have been of much use to man.

Cooking, the first form of food processing, developed simultaneously with grain agriculture.

It was the Romans who gave us our first “white bread.”
most abundant and diffusely spread dietary components for most populations

In Europe, the mean consumption of gluten is 10 g to 20 g per day, with segments of the general population consuming as much as 50 g of daily gluten or more.
Stone Age

- Human’s body might not be designed to use Grains

- By discovering Grains many disorders developed
  - Palaeolithic diet
  - There were no
    - Obesity
    - COELIAC DISEASE
    - Inflammatory bowel disease
    - Other autoimmune disorders
      - Diabetes Type I/II
Consensus: Gluten related disorders

Coeliac disease

Immune-mediated enteropathy
• caused by a permanent sensitivity to gluten
• in genetically susceptible individuals.

A unique autoimmune disorder:
• environmental trigger (gluten) and the autoantigen (tissue Transglutaminase)
Gluten and Horses

Common in Animals
Recently a sport Horse with symptoms of diarrhoea and weight loss for months was diagnosed with coeliac disease

This was an interesting Horse Model of coeliac disease
Horses eat much more Wheat than in the old days, when had only grass and oats
The Horse had positive antibodies and positive histology for coeliac disease
Sport Horse successfully treated with gluten free diet

Prevalence of celiac disease in Egyptian children disputes the east-west agriculture-dependent spread of the disease.

Epidemiology

Prevalence of autoantibodies or prevalence of coeliac disease?

Non-coeliac GLUTEN SENSITIVITY
ARE YOU 1 IN 10?

Polly J Bingley et al.
Undiagnosed coeliac disease at age seven: population based prospective birth cohort study
BMJ 2004; 328: 322 - 323

The prevalence of CD is increasing directly proportional with identifying non-classic or atypical gluten-sensitive cases.


Clinical presentation

• Historically no relationship between the degree of mucosal damages and malabsorption syndrome

• Recent studies;
  – Malabsorption in cases with microenteropathy

• Atypical predominant

Subclinical celiac disease

Confusing terminologies:
Latent
Potential
Silent

Rostami Nejad et al, Subclinical celiac disease and gluten sensitivity
Nail deformity in coeliac disease

The picture shows onycholysis, ridging, thinning, and nicking associated with red and white bands before treatment that normalized after treatment with gluten-free diet.

Zali MR, Rostami et al. Am J Gastroenterol 2011 106, 2202-2204
Osteoporosis in mild or severe enteropathy
Severe enteropathy and classical CD is still rare

Increased percentage of Overweight and obese CD patients from 2001 – 2009

44% had a BMI of 25 or above
13% had a BMI of 30 or above

E. Tucker, K. Rostami, S. Prabhakaran, D. M. Aldulaimi THE INCIDENCE OF OBESITY AMONG PATIENTS WITH COELIAC DISEASE UEGW 2009
Neurological Disorders and microscopic enteritis

- MS
- Epilepsy with cranial calcifications
- Gluten ataxia
  - Anti-tissue transglutaminase IgA antibodies are present in the gut and brain of patients with gluten ataxia with or without an enteropathy
    - The deposition most pronounced in the
      » cerebellum,
      » pons, and
      » medulla
Inspirational Friendship between Gut and Brain

David Sanders
Gastroenterologist

Coeliac disease
Gluten ataxia

Marios Hadjivassiliou
Neurologist
Clinical presentation in microscopic enteritis (Mic ent, Marsh I) compared to macroscopic enteritis (Mac ent, Marsh IIIa-c) in percentage.

Chronic diarrhea, constipation, failure to thrive, short status

Shahraki T, Rostami K et al, UEGW 2009
Wheat Allergy

Adverse immunologic reaction to wheat proteins

onset: minutes to hours after gluten exposure
Wheat Allergy

Classic food allergy affecting the skin, gastrointestinal tract, or respiratory tract; food-dependent,

Risk Factors:
-associated Asthma
-Hay fever
-Skin abnormalities

Exercise-induced anaphylaxis (FDEIA);
-Occupational asthma (so-called baker’s asthma) and rhinitis; or
-Contact urticaria.

IgE antibodies play a central role in the pathogenesis of these diseases.
Non Celiac Gluten sensitivity (NCGS) was originally described in the 1980s and recently a “re-discovered” disorder characterized by intestinal and extra-intestinal symptoms related to the ingestion of gluten-containing food. Whether non-coeliac gluten intolerance is permanent or in some cases may be transient is not known.

Geoffrey Holmes

Non-coeliac gluten sensitivity (NCGS)

- Is now attracting more and more attention as a common cause of morbidity.

- There is still much to learn and research is likely to focus on obtaining information regarding
  - prevalence,
  - developing simple tests to identify patients,
  - exploring aetiology and uncovering the damaging component of gluten and if other foods contribute to ill health.
This patient reflects on his 20 years of unexplained ill health with multiple symptoms

- he describes how gluten has affected his
  - digestive system,
  - his skin,
  - his nervous system,
  - muscles and joints,
  - sleep, and mood, and even his so called
    - incurable interstitial cystitis.

Kamran Rostami, Sabine Hogg-Kollars Non-coeliac gluten sensitivity A Patient’s Journey BMJ 2012;345:e7982
Histopathology of coeliac disease

History

Original Classification Marsh MN, 1990-92

Modified Marsh Classification 1998-9, Rostami et al

Modified Marsh Classification 1999, Oberhuber et al

Corraza-Villanacci

Rostami-Villanacci
Modified Marsh classification, Rostami et al 1998-9

Rostami, Mulder et al. American J Gastroenterol 1999;94:888-894
Oberhuber


• 40 IEL/100EC
Microscopic Enteritis

- **Definition:**
  - Sub-microscopic (Marsh 0)
  - Microscopic presentation (Marsh I-II)

- **Characteristics:**
  - Sub-microscopic
    - Alteration of enterocytes,
    - Microvilli atrophy
    - Increased $\gamma/\delta$ TCR
History

(A) alterations of the enterocyte, significant reduction of the microvillous height

(B) normal enterocyte and microvillous ultrastructure at TEM.

(C) brush border in a group A patient;
(D) brush border in a group B patient;
(E) severe enterocytic lesion in a patient with Pierre–Robin syndrome;
(F) normal brush border from a control patient.

7 +Ve EMA, 4/7 abnormal TEM of intestinal absorptive surface. 10.000

Inspiration

Rostami K, Villanacci V. Microscopic Enteritis
Dig Liver Dis. 2009 Apr;41(4):245-52
Microscopic Enteritis
Differential diagnosis

Non-specific
• Coeliac disease with milder enteropathy Marsh 0-II
• Non-coeliac Gluten sensitivity
• Gluten allergy
• IBS
• Idiopathic enteropathy
• NSAIDs related
• Parasitic Bacterial/viral enteritis
  • H Pylori
  • Bacterial overgrowth
• Inflammatory bowel disease
Microscopic enteritis spectrum

- Coeliac Dis
- IBD
- Bacterial OG
- IBS
- Gluten S
- NSAID
- H Pylori
Idiopathic enteropathy

• A subgroup of patients reported with Marsh I-II no clear etiology in several studies

• F Biagi et al  *J. Clin. Pathol.* 2008;61;1116-1118;
Severe enteropathy

- Severe enteropathy like Marsh IIIb-c
  - Mainly Coeliac disease
  - Tropical sprue
  - Enteropathy Associated With Olmesartan
Alberto Rubio-Tapia, Joseph A. Murray et al.
Severe Sprue-like Enteropathy Associated With Olmesartan

**FIGURE.** Photomicrographs showing reversible sprue-like enteropathy associated with olmesartan. (hematoxylin-eosin, original magnification 100). A, Duodenal biopsy specimen obtained while the patient was taking olmesartan shows total villous atrophy and intraepithelial lymphocytosis. B, Biopsy specimen obtained 6 months after withdrawal of olmesartan and initiation of a gluten-containing diet shows recovery of villi on duodenal mucosa.
What is the patho-mechanism of Malabsorption in ME?
• 4-40% Microcytic anemia CD
  – Caused by inflammation

• Megaloblastic/Macrocytic anemia – folate is absorbed primarily in the proximal third of the small intestine (location of folate hydrolases)

• Vitamin B-12 deficiency occurs

• Cytokines involvement

Most common non-GI manifestation in adults and elderly
Gluten

T-cell receptor

Plasma cells

Antibodies; tTG, AGA

Cytokines; IFNγ; IL4; TNFα

Lymphocyte T NK B

Damage enterocytes

Inhibition of Hepc

Inhibition of NaPi-IIb expression

Patho-mechanism of Malabsorption

Malabsorption caused by inflammation

- Intestinal phosphate absorption mediated by NaPi-IIb protein is reduced in colitis.
- This inhibition is mediated by the proinflammatory cytokine TNF-alpha

Diagnostic pitfalls

- Clinical
- Serological
- Endoscopy
- Histological

Serology sensitivity

Rostami, Mulder et al. American J Gastroenterol 1999;94:888-894
• Looking normal in most cases

• Abnormal in severe mucosal changes

• Segmental biopsy would be required

Including Bulb

Kate E Evans, David S Sanders et al.
A Prospective Study of Duodenal Bulb Biopsy in Newly Diagnosed and Established Adult Celiac Disease The American Journal of Gastroenterology 2011:106, 1837-1742
Most celiac patients present with atypical form with milder enteropathy.

Relative discriminative ability of tests for celiac disease

- BSG _OSLO

Not celiac disease

Increasing certainty of CD
Diagnostic accuracy measures at different thresholds:

A) Serology defined as low: negative/low positive, moderate (3x above normal value), high >10x above normal value
B) Histology defined as low: (Marsh 0-II), moderate (Marsh IIIa), high (Marsh IIb-c),
C) HLA defined as low (negative) moderate (positive DQ8) and high (positive DQ2)
D) Combination:
Depression

All investigation negative
It doesn’t matter as long as you don’t have cancer
Learn to live with it
I can’t help you!
Summary

• Presentation with milder enteropathy like Microscopic Enteritis is very common

• There isn’t such thing as non-specific

• Milder abnormalities should be reported accurately
Art of vision

VISION
IS THE ART OF SEEING
WHAT IS INVISIBLE
TO OTHERS

Jonathan Swift
Any Question?