MALDIGESTION AND MALABSORPTION:

THE MALABSORPTION SYNDROME

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Maldigestion, malabsorption

Disturbances in the digestion (catabolism) of nutrients

- Gastric disorders (less acid) - carbohydrates, intinsic faktor
- Pancreas (exocrin) - CH, lipids, proteins
- Bile (less bile acid) - lipids, lipidofil molecules
- Motility (mixing and transiting forward)
- Baktérial flora (bacterial overgrowth in small intestine)

Insufficient absorption of elements of the well-catabolyzed nutrients

- decreased surface for absorption (surgery, inflammation, tumor, etc)
- impairment of the absorptive mucosa
  - rarely primary: Whipple, amyloidosis, congenital enzyme loss
  - mostly secondary: inflammation (Crohn), autoimmun (celiac), enzyme deficiency (laktase), infection (any), sarcoidosis, endocrine (diabetes, hypo/hyperthyroid, hyper/hypoparathyroid), circulation problems (arterial or venous or lymphatic), tumors, drugs (non-steroid, laxative, cytostatic), irradiation

Collectively: malabsorption syndrome.

Clinical symptoms of the malabsorption syndrome

Gastrointestinal tract: **diarrhea, steatorrhea, weight loss**

flatulence, abdominal distension and pain
glossitis, cheilosis, stomatitis
ascites, bile stone

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General: physical weakness, tiredness, decreased capacity to load

Skin: acrodermatitis, keratosis, herpetiform or follicularis dermatitis, hyperpigmentation, edema, alopecia, nail deformations

Hormonal: amenorrhea, infertility, decreased libido, hypothyroidism, late menarche, early menopause, sec. hyperparathyroidism, osteoporosis, osteomalacia, cretinism, Addison's disease, diabetes mellitus type-I

Musculoskeletal: inflammation and pain in muscles and joints, bone fracture

Neurology: dementia, neuropathies, funicular myelosis, depression

Hematology: iron-deficient anemia, megaloblastic anemia, coagulopathies, lymphoms, lymphopenia, eosinophilia

Immunology: autoimmune diseases and autoimmune combinations, sarcoidosis

Cardiology: arrhytmias (K, Mg), cardiomyopathies

Urology: calcium-oxalate kidney stone

Ophtalmology: xerophtalmia (dry eyes), night-blindness

Diagnostic approach to the malabsorption

1, **Think** about it ! – not only in case of gastrointestinal symptoms, but in case of other – even distant – symptoms what are not explained by other special diseases

2, Medical history and physical examination – signs pointing to possible causes

3, Laboratory tests

- basic pathologies in the lab report
- functional tests

4, Morphologic examinations

- imaging methods
- endoscopies

5, Histology

6, *Ex juvantibus*: argument (or proof) came from the beneficial effect of a therapy

Basic lab findings for malabsorption

Low levels of:

- iron
- folate
- B12
- calcium
- phosphate
- 25OHD
- magnesium
- albumin
- prothrombin
- carotine

Decideable if there is a deficit of different compounds or not?

Sometimes the cause also can be suggested

Can be high:

- alkaline phosphatase
- parathormon
- TSH

Functional test of the enteral absorption

Oral loading with a material, the effect of which is dependent on its absorption

1, D-xilose test: monosaccharide, passively absorbed in the proximal small intestine, and will be presented in the blood and in urine. The presented amount is dependent on the size of absorbing surface and on functional condition of the absorbing mucosa. Measured variable: xylose level in the blood or the amount of xylose excreted in a 5 hours collected urine. Low value in malabsorption: 25 g loading - < 4.5 g exretion.

2, Disaccharide (lactose, saccharose) test: reflects the hydrolase enzyme activity. Measured variable: blood glucose concentration – in comparison to glucose level in the oral glucose tolerance test. Flat curve in malabsorption.

3, Lactose breath test: in lactase deficiency the lactose will reach the colon where its bacterial digestion produces Hydrogen. The Hydrogen will be expirated and measurable in the exhalated air.

4, Oral iron loading test: 200 mg iron per os, followed by serum iron level in the next 2 hours.

5, Schilling-test: the orally given, radiolabeled cobalamin will be absorbed only in presence of gastric acid and gastric intrinsic factor, moreover, a pancreatic protease split is also needed for the absorption in the ileum. Complex testing of gastric + pancreatic + enteral function.

1. step: saturating the hepatic cobalamin binding sites: im. B12 inj;
2. step: orally giving radiolabelled cobalamin: a succesful absorption will be followed by urinary excretion.

Morphologic and histologic examinations

Imaging methods:
- tradidional X-ray, native or with contrasting material
- ultrasound
- CT
- MR

Can be tested: the size and shape of the gastroenteral tube,
normal and abnormal connections,
foreign bodies inside or outside, the motility,
partly the thickness and condition of the enteric wall

Endoscopies: can be tested the size and shape of the tube,
the width and the stenosis,
condition of the wall and mucosa, foreign bodies,
bleeding – ability for interventions

Histology: sample taking by endoscopy,
or transdermal (directed by US/CT/MRI)

Celiac disease – gluten sensitivity

The celiac disease (gluten-sensitive enteropathy):

a systematic autoimmune disease

developing under the effect of gluten

in genetically predisposed people.

Frequency: 1 % of the population. 2/3 of patients are women.

Starting in any age – peaks in infants, in puberty, and in young adults.

Many forms – from classic to potential.

Celiac disease – in genetic predisposition

Poligenic disease
Familiar predisposition: in near relation 10-20%, identical twins 80%.

Supreme determinant: the Human Leucocyte Antigen system:
ONLY that gliadin can provoke the reaction of T-lymphocytes which is bound to cells containing HLA-DQ2 (95%) or HLA-DQ8 (5%) alléle.

115 further, non-HLA gene is also involved in celiac disease:
- most of them are immune-regulating genes
- they determine the combination with other autoimmune diseases.

<u>Environmental factors are essential</u> to developing the disease
- mainly gastrointestinal infections in the infants (viruses, Lamblia, Campilobacter).
- trigger role: without these infections the genetic predisposition rarely produce celiac disease

Celiac disease – under the effect of gluten

Gluten: a storage protein in the cereals.

Gluten = glutenin + prolamin

Prolamin: rich in prolin and glutamin,
resistant to digestion = the intact polypeptide will reach the enteric mucosa

In:	wheat	- gliadin
	barley	- hordein
	rye	- secalin
	oats	- avenin – low prolin content = less toxicity

Gliadin – strong immune effects
- cytotoxic
- immunmodulant
- increases permeability

Celiac disease = gluten + autoimmunity

Gliadin - goes to mucosa without digestion, enters in lamina propria,
- deamination by a tissue-transglutaminase enzyme (activation),
- deamination augments affinity to cell surfaces with HLA-DQ2/8.

Cellular immune reactions

The HLA-connected peptide aktivates the CD4+ T-lymphocytes:
- it causes a T-cell-mediated tissue damage in lamina propria,
- cytokins induce inflammation – desintegrates villous structure.

Cytotoxic fragments of gluten provoke cellular stress in mucosal cells:
- IL-15 will be produced, what activates the intraepithelial lymphocytes – transforming to killer cells.

Humoral immune reaction: activation of B-lymphocytes:
- IgA autoantibodies against gliadin and tissue-transglutaminase.

The transglutaminase-antibody blocks the TGF-beta production:
- TGF is needed to the regeneration of tissue damages and to tissue maturation
- without TGF the pathologic process forms selfsupporting circles

Clinical forms of celiac disease

Classic form: a standard malabsorption syndrome

Infants: diarrhea, steatorrhea, distension and flatulence, loss of appetite, vomiting, weight loss, lack of growth, anemia, muscle atrophy, hair loss, exsiccosis, elektrolyte disturbances, rarely an acute celiac crisis.

Children: the mentioned problems in less severity, diarrhea can be missing, late puberty, thin/small body.

Adults: mild symptoms, tiredness, abdominal pain/distension, diarrhea and weight-loss can be missing – sometimes even obese

Atypic form: there is no any of the classic symptoms.

The diagnosis will be cleared during a search of another disease, what frequently combines to celiac disease.

Diseases – frequently combined to celiac

- Psoriasis
- Atopic dermatitis
- Sjögren, rheumatoid arthritis
- Vasculitis
- IgA nephropathy
- Addison’s disease, Hashimoto’s thyroiditis
- Amenorrhea, infertility, repeated abortions
- Myasthenia gravis, ataxia, epilepsia
- Myocarditis, pericarditis, dilatatíve cardiomyopathy
- Thromboembolism, idiopathic thrombocytopenic purpura
- Sarcoidosis, pulmonary haemosiderosis
- Inflammatory bowel diseases, recurrent pancreatitis
- Peripheral neuropathies
- Recurrent stomatitis aphtosa
- Increased risk: to lymphoproliferative diseases,
  T-cell lymphomas or carcinomas in small bowel

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Silent (symptom-free) celiac disease: found in screening programs, no symptom, but villous atrophy + autoantibodies are found.

Latent form: transient mucosal pathologies in a healthy adult. Cause?

Potential celiac disease: HLA and autoantibody positivity, but normal mucosal structure in histology.

High-risk groups for developing celiac disease

- Near relatives of a celiac patient
- Dermatitis herpetiformis
- 1.Type diabetes mellitus
- IgA deficiency
- Hashimoto’s thyreoiditis
- Autoimmune liver diseases (prim biliary cirrhosis, immunehepatitis)
- High transaminase avtivity of unknown origin
- Metabolic bone disease of unknown origin
- Growth-deficiency or pubertas tarda of unknown origin
- Therapy-refracter iron-deficient anemia of unknown origin
- Down or Turner syndrome
- Early menopause of unknown origin

Diagnosis of celiac disease

Examinations always with gluten-exposition!

Histology: standard diagnostic proof

- duodenal biopsy: bulbus 1 + deep duodenum 4 samples
- Marsch-classification: villous atrophy
  crypta hyperplasia
  intraepithelial lymphocyte number
  > 40 / 100 mucosal cell

Serology: autoantibodies, in new US Guideline – first tool and proof

- tissue transglutaminase antibody: IgA és IgG
  first test, very sensitive, false-positive: card. decomp.
- endomysium antibody: IgA
  very specific, evaluation is subjective
- deaminated gliadinpeptid antibody: IgG
  in children and in IgA-defiicit

Genetics: HLA-DQ2/8 is presented in 1/3 of the population = non-diagnostic.
Used, if other methods are blocked of any reason.
Usable in gluten-free condition as well.

The treatment of celiac disease

Glutén-free diet - a really hard work!

- to be avoided: all foods containing cereals
  except: oats, in small amounts
- prohibited: beer, whisky, instant drinks and soups, pies, frozen ready-foods, canned meats, fruit-yoghurts – Terrible!
- permitted: corn, panicfrench wheat, rice, soy, meat, egg, glucose, vegetables, honey, jam, milk, natural milk-proiducts, wine

Improvement
- symptoms: couple of days or weeks
- antibodies: some months
- histology: 1-2 years, or never completely …

Compliance: control by antibody testing

Prognózis: good.

Future therapies in research:

- genetically modified wheat (bad bread quality)
- immunsuppression (pl. antiTNF)
- immun modulation (vaccines, parasites?)

Gluten-sensitivity – without celiac disease

Non-Celiac Gluten Sensitivity – NCGS

If 3 conditions are together:

1, Glutén consumption

- provokes typical abdominal symptoms (pain, distension, diarrhea)
+ many more symptoms (tiredness, muscle pain, tingle, migrene),
+ symptoms disappeare if avoiding gluten

2, No diagnostic signs of celiac: no antibodies
no villous atrophy

3, Simple wheat-allergy is excluded

Laktóz intolerantia

Laktáz: membránenzim a kefeszegélyben
laktózból glukóz + galaktóz
gyermekkorban sok van, korral folyamatosan csökken

Genetika: laktáz génben 13910. bázispárban Timidin vagy Citozin
TT allél: laktáz aktív marad (evolúciós előny állattenyésztő népnek)
TC allél: időskorra elfogy a laktáz, jön az intolerantia
CC allél: már fiatal korban intoleráns
Ritkán veleszületett laktázhiány – autosomális recesszív

Kórélettan: bontatlan laktóz a colonban bakteriálisan erjed,
tejsav, zsírsav, hidrogén, metán, széndioxid keletkezik

Tünet: tejféle után fájdalom, puffadás, görcs, hasmenés

Dg: - H2 kilégzési próba, laktóz fogyasztás után
- vércukor mérés, laktóz fogyasztás után
- laktázgén C/T polimorfizmus kimutatása
- vékonybél biopsia

Th: tej mellőzendő – de fermentált tejtermék mehet
kalciumot másból pótolni (dió, mogyoró, bab)

Másodlagos laktázhiány

Vékonybél károsodáskor a legsérülékenyebb enzim, sokszor véglegesen

- Gastroenteritis
- Coealiakia
- Éhezés (fehérje és kalória hiány)
- Immunhiány állapotok
- Baktériumok túlszaporodása a vékonybélben
- Crohn
- Lambliasis
- Belek lymphomája
- Kemoterápia, irradiáció