Pathology

# Pathology sheet

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Malabsorption

• Malabsorption is characterized by defective absorption of:
  Fats
  fat- and water-soluble vitamins
  Proteins
  Carbohydrates
  Electrolytes
  Minerals
  Water

• presents most commonly as chronic diarrhea

• A hallmark of malabsorption is steatorrhea, characterized by excessive fecal fat and bulky, frothy, greasy, yellow or clay-colored stools.

Malabsorption: defected absorption of any type of nutrients. The malabsorption can be in one nutrient or in multiple nutrients (depending on the defect).
In steatorrhea there is a defect in the absorption of fat so, it will be excreted with stool.

• General symptoms include:
  Diarrhea --- from nutrient malabsorption and excessive intestinal secretion
  flatus, abdominal pain, and weight loss, anorexia, abdominal distention, borborygmi, and muscle wasting
Inadequate absorption of vitamins and minerals can result in:
- anemia and mucositis due to pyridoxine (B6), folate, or vitamin B12 deficiency;
- bleeding, due to vitamin K deficiency;
- osteopenia and tetany due to calcium, magnesium, or vitamin D deficiencies;
- peripheral neuropathy due to vitamin A or B12 deficiencies

Abdominal pain usually happens with flatus.

Weight loss is due to a defect in absorption of nutrients responsible for body building and, fat accumulation in the body.

Borborygmi: when you can hear the sound of the bowel.

Another manifestation of the malabsorption is the defect in a specific nutrient like, the malabsorption of the B12 that will cause a macrocytic anemia.

• Malabsorption results from disturbance in at least one of the four phases of nutrient absorption:
  Intraluminal digestion: in which proteins, carbohydrates, and fats are broken down into forms suitable for absorption.
  Terminal digestion: which involves the hydrolysis of carbohydrates and peptides by disaccharidases and peptidases in the brush border of the small intestinal mucosa.
  Transepithelial transport: in which nutrients, fluid, and electrolytes are transported across and processed within the small intestinal epithelium.
  Lymphatic transport of absorbed lipids.

The digestion happens mainly in the small intestine.

Large molecules are broken to small molecules in the intraluminal digestion (become easier to digest).

• Diarrhea is defined as an increase in stool mass, frequency, or fluidity, typically greater than 200 gm per day.
• **Dysentery**: Painful, bloody, small-volume diarrhea.

The maximum frequency of defecation is three times per day and the minimum is once per three days (if this frequency increases it will cause diarrhea and, if it decreased it will cause constipation.

The dysentery happens from some types of shigella, salmonella or, some types of E.coli.

• Diarrhea can be classified by its mechanism into:

  **Secretory diarrhea** is characterized by isotonic stool and persists during fasting ---- increase in the active secretion -- **cholera toxin** (CL-)

  **Exudative diarrhea**: purulent bloody stools (blood and pus) that continue during fasting ---- IBD, severe infections such as E. coli

  **Osmotic diarrhea** is due to the excessive osmotic forces (water is drawn into the bowels) exerted by unabsorbed luminal solutes. The diarrhea fluid is more than 50 mOsm more concentrated than plasma and abates/relieved with fasting ---- **lactase deficiency**, maldigestion, malabsorption (pancreatic disease) , osmotic laxatives.

In order to diagnose the types of diarrhea you should ask the patient if the diarrhea persists with fasting or not.

Another name for osmotic diarrhea is malabsorptive diarrhea.

  Secretory diarrhea is characterized by increased secretions in the bowel or decreased absorption, and we see it the most in the patients with cholera toxins (that will increase the secretion of the chloride from the epithelium......listen to the record (12:14) )
The mechanism of the exudative diarrhea is the inflammation of the epithelium and, it is characterized by bloody stools.

In the osmotic diarrhea, the patient has malabsorption so, the nutrients will stay in the lumen of the bowel and, it will drive the water in to the lumen of the bowel by osmotic forces.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Intraluminal Digestion</th>
<th>Terminal Digestion</th>
<th>Transepithelial Transport</th>
<th>Lymphatic Transport</th>
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<tbody>
<tr>
<td>Celiac disease</td>
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<td>Environmental enteropathy</td>
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<td>Chronic pancreatitis</td>
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<td>Cystic fibrosis</td>
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<td>Primary bile acid malabsorption</td>
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<td>Carcinoid syndrome</td>
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<td>Autoimmune enteropathy</td>
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<td>Disaccharidase deficiency</td>
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<td>Whipple disease</td>
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<td>Aetalipoproteinemia</td>
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<td>Viral gastroenteritis</td>
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<td>Bacterial gastroenteritis</td>
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<td>Parasitic gastroenteritis</td>
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<tr>
<td>Inflammatory bowel disease</td>
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</table>

+ indicates that the process is abnormal in the disease indicated. Other processes are not affected.

Celiac Disease

• also known as celiac sprue or gluten-sensitive enteropathy.

• It is an immune-mediated enteropathy triggered by the ingestion of gluten-containing foods, such as wheat, rye, or barley, in genetically predisposed individuals.
• Celiac disease has an overall worldwide incidence of 0.6% to 1%.

• Pathogenesis:
  Celiac disease is triggered by ingestion of gluten, which is the major storage protein of wheat and similar grains. The alcohol-soluble fraction of gluten, gliadin, contains most of the disease-producing components. Celiac disease is not allergic.

• **Gluten** is digested by luminal and brush-border enzymes into amino acids and peptides, including a 33-amino acid α-gliadin peptide that is resistant to degradation by gastric, pancreatic, and small intestinal proteases.
  • Some gliadin peptides may induce epithelial cells to express **IL-15**, which in turn triggers activation and proliferation of CD8+ intraepithelial lymphocytes.
  • These lymphocytes express NKG2D, a natural killer cell marker and receptor for MIC-A.
  • Enterocytes that have been induced to express surface MIC-A, in response to stress, are then attacked by NKG2D-expressing intraepithelial lymphocytes.
  • The resulting epithelial damage may enhance passage of other gliadin peptides into the lamina propria where they are deamidated by tissue transglutaminase.
  • These gliadin peptides interact with HLA-DQ2 or HLA-DQ8 on antigen-presenting cells and, in turn, can stimulate CD4+ T cells to produce cytokines that contribute to tissue damage.

If the patient didn’t have a HLA-DQ2 or HLA-DQ8 the reaction will not happen.

Deamination: erasing an amino acid
The CD4+ T cells will activate the B cells to produce antibodies. The most important cytokine is interferon-gama which contributes for tissue damage.

While nearly all people eat grain and are exposed to gluten and gliadin, most do not develop celiac disease. Thus, **host factors determine whether disease develops.** Among these, HLA proteins seem to be critical, since almost all people with celiac disease carry the class II HLA-DQ2 or HLA-DQ8 allele.

However, the HLA locus accounts for less than half of the genetic component of celiac disease. Remaining genetic factors may include polymorphisms of genes involved in immune regulation and epithelial function.

There are types of the HLA including, type 1 which is found on all cells, type 2 mainly in APC cells and, type 3 in the complement system.

These genetic variables may also contribute to associations between celiac disease and other immune diseases, including type 1 diabetes,
thyroiditis, and Sjögren syndrome, IgA nephropathy, as well as neurologic disorders, such as ataxia, autism, depression, epilepsy, Down syndrome, and Turner syndrome.

• This loss of mucosal and brush-border surface area probably accounts for the malabsorption.

• In addition, increased rates of epithelial turnover, reflected in increased crypt mitotic activity, may limit the ability of absorptive enterocytes to fully differentiate and express proteins necessary for terminal digestion and transepithelial transport. Affect mainly carves and proteins.

• The combination of histology and serology, therefore, is most specific for diagnosis of celiac disease.

• Adherence to a gluten-free diet typically results in resolution of symptoms, decreasing titers of anti-tissue transglutaminase or other celiac disease-associated antibodies, and restoration of normal or near normal mucosal histology within 6 to 24 months.
Clinical Features:

In adults:
celiac disease presents most commonly between the ages of 30 and 60.

**silent celiac disease**: defined as positive serology and villous atrophy without symptoms.

**latent celiac disease**: in which positive serology is not accompanied by villous atrophy.

Celiac disease may be associated with chronic diarrhea, bloating, or chronic fatigue, but is often asymptomatic. These cases may present with anemia due to chronic iron and vitamin malabsorption.

In adults, celiac disease is detected twice as frequently in women, perhaps because monthly menstrual bleeding accentuates the effects of impaired absorption.

One of the most important histologic manifestations of the celiac disease are, blunted villi (can be mild to severe, so the surface
will be flat like the colon), and the second manifestation is the increased intra epithelial lymphocytes due to the activation by the interleukin 15, so there will be hyperplasia in the crypts to compensate the damaged surface.

• **Pediatric celiac disease:**
  affects males and females equally.
  may present with malabsorption or atypical symptoms affecting almost any organ.
  In those with **classic symptoms**, disease typically begins after introduction of gluten to the diet, between ages of 6 and 24 months, and manifests as irritability, abdominal distention, anorexia, chronic diarrhea, failure to thrive, weight loss, or muscle wasting.
  Children with **nonclassic symptoms** tend to present at older ages with complaints of abdominal pain, nausea, vomiting, bloating, or constipation.
  Common **extraintestinal complaints** include arthritis or joint pain, aphthous stomatitis, iron deficiency anemia, delayed puberty, and short stature.

• A characteristic itchy, blistering skin lesion, **dermatitis herpetiformis**, can be present in as many as 10% of patients.
  Dermatitis herpetiformis was named because blisters that come with it looks like the blisters of the herpes virus.

• the only treatment currently available for celiac disease is a gluten-free diet. While adhering to this diet can be challenging, it does result in symptomatic improvement for most patients.

• **A gluten-free diet may also reduce the risk of long-term complications including anemia, female infertility, osteoporosis, and cancer.**
Noninvasive serologic tests are generally performed prior to biopsy: The most sensitive tests are the measurement of IgA antibodies against tissue transglutaminase. IgA anti-endomysial antibodies can also be present. IgG anti-tissue transglutaminase antibodies may be detected in patients with IgA deficiency. The absence of HLA-DQ2 and HLA-DQ8 is useful for its high negative predictive value, but the presence of these alleles is not helpful in confirming the diagnosis.

If the antibody test for the IgA was negative, that doesn’t mean that the patient doesn’t have celiac disease, because a lot of celiac disease patients have IgA deficiency, so we do the IgG test. Taking biopsy and see the histologic changes is also a good test.

Individuals with celiac disease have a higher than normal rate of malignancy: enteropathy-associated T-cell lymphoma
Small intestinal adenocarcinoma
when symptoms such as abdominal pain, diarrhea, and weight loss develop despite a strict gluten-free diet, cancer or refractory sprue, in which the response to a gluten-free diet is lost, must be considered.

The T-cells will become clonal and, mutation that will transform to lymphoma.
The adenocarcinoma can happen in the enterocytes.

Environmental Enteropathy

referred to as tropical enteropathy or tropical sprue.
It is a disorder prevalent in areas and populations with poor sanitation and hygiene, such as those in developing countries.
Affected individuals often suffer from malabsorption and malnutrition and stunted growth.

The underlying causes of environmental enteropathy are unknown, but defective intestinal barrier function, chronic exposure to fecal pathogens and other microbial contaminants, and repeated bouts of diarrhea within the first 2 or 3 years of life are likely involved.

Many pathogens are endemic in these communities, but no single infectious agent has been linked to environmental enteropathy.

The relatively high oral vaccine failure rates in regions where environmental enteropathy is endemic has been proposed to be due to defective mucosal immune function.

Autoimmune Enteropathy

• X-linked disorder
• Characterized by severe persistent diarrhea and autoimmune disease that occurs most often in young children.

• **IPEX**: A particularly severe familial form due to a germline mutation in the FOXP3 gene, which is located on the X chromosome. FOXP3 is a transcription factor expressed in CD4+ regulatory T cells. Net result: defects in regulatory T cell function.

I: immune dysregulation  
P: polyendocrinopathy  
E: enteropathy  
X: X-linkage

Here the patient has autoimmune disease and malabsorption.

Lactase (Disaccharidase) Deficiency
•The disaccharidases, including lactase, are located in the apical brush-border membrane of the villus absorptive epithelial cells. Because the defect is biochemical, biopsy histology is generally unremarkable.

•Lactase deficiency is of two types:

  **Congenital lactase deficiency:**
  - autosomal recessive disorder.
  - caused by a mutation in the gene encoding lactase.
  - The disease is rare and presents as explosive diarrhea with watery, frothy stools and abdominal distention upon milk ingestion.
  - Symptoms abate when exposure to milk and milk products is terminated, thus removing the osmotically active but unabsorbable lactose from the lumen —— osmotic diarrhea.
  - Congenital lactase deficiency was often fatal prior to the availability of soy based infant formula.

The congenital lactase deficiency is autosomal recessive disorder, where the lactase is not present at all, because of a mutation in the gene encoding it and, they will have diarrhea upon ingestion of cow milk.

Death in the prenatal period happen in the infants with congenital lactase deficiency.

•Acquired lactase deficiency:
  - caused by down-regulation of lactase gene expression.
  - Can develop following **enteric viral or bacterial infections** and may resolve over time.
  - Symptoms of acquired lactase deficiency, including abdominal fullness, diarrhea, and flatulence, due to fermentation of the unabsorbed sugars by colonic bacteria, are triggered by ingestion of lactose-containing dairy products.
Abetalipoproteinemia

• rare autosomal recessive disease

• characterized by an inability of enterocytes to secrete triglyceride-rich lipoproteins. caused by a mutation in the microsomal triglyceride transfer protein (MTP). This results in intracellular lipid accumulation.

• Patients also have a complete absence of all plasma lipoproteins containing apolipoprotein B.

• The malabsorption of abetalipoproteinemia is therefore a failure of intraepithelial processing and transport.

• presents in infancy and the clinical picture is dominated by failure to thrive, diarrhea, and steatorrhea.