

Pathology

Doctor 2017 | Medicine | JU | GI

Number >>

2nd e-lecture

Doctor

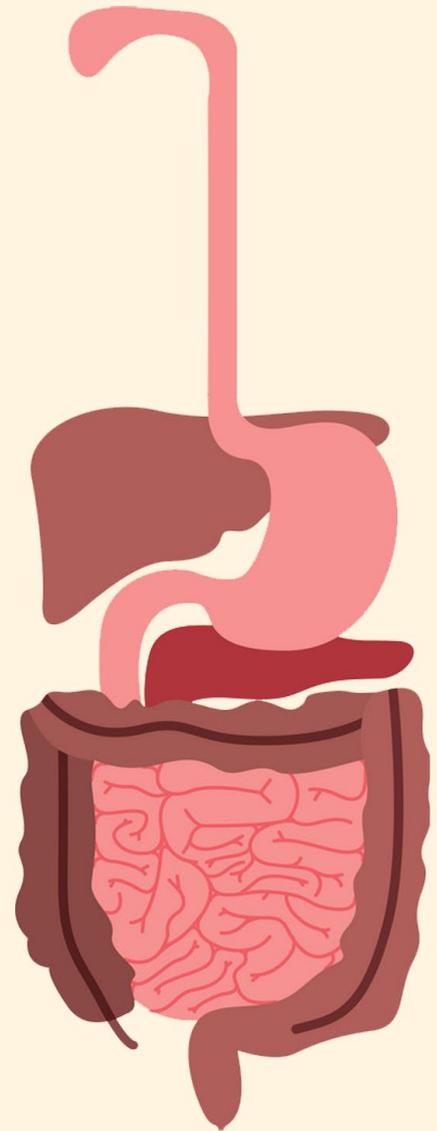
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2nd system - GI



Intestinal pathology

Intestinal obstruction, vascular disorders(hemorrhoids), malabsorptive diseases, infection(microbiology), inflammatory intestinal disease, colonic polyps and neoplastic disease)

Anatomy: small intestine (duodenum, jejunum, ileum),

Large intestine (cecum, ascending, transverse, descending and sigmoid colon)

Normal Histology: like rest of GIT (mucosa, submucosa, muscularis propria, serosa), however this wall is thinner in the small intestine than in the large intestine)

Lumen: small intestine has a narrower lumen than large intestine

-Diseases of the small intestine and colon affect nutrient and water transport and may cause malabsorption and diarrhea

-The intestines provide a site of interface for the immune system and antigens present in the food.

-Note that the colon is the most common site of gastrointestinal neoplasia.

1-intestinal obstruction

The small intestine is the **Most common** site of GIT obstruction, because of its relatively narrow lumen.

Can be mechanical or non-mechanical

Mechanical obstruction

: hernias, intestinal adhesions, intussusceptions, volvulus) →80%

: Tumors, diverticulitis, infarction

Non mechanical obstruction

: Hirschsprung disease

: Neurological Disorders

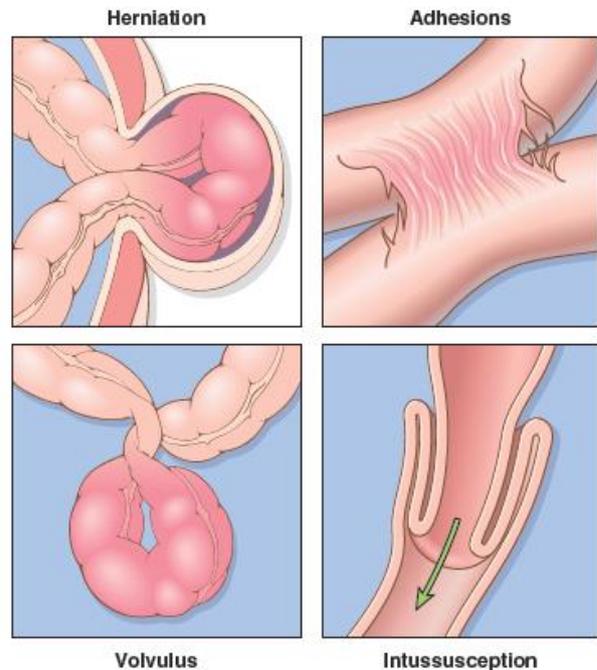
: Drugs

: Paralytic ileus following a surgical operation

Clinical manifestation of intestinal obstruction:

- Abdominal pain, gaseous distention, vomiting and constipation
- Present either as an acute problem of sudden onset (intussusception, volvulus, infarction) or chronic longstanding problem (Hirschsprung disease, tumors)

Fig. 15.18 Intestinal obstruction
The four major mechanical causes of intestinal obstruction are (1) herniation of a segment in the umbilical or inguinal regions→maybe complicated with infarction (2) adhesion between loops of intestine →usually a complication of a previous inflammatory condition or surgery that led to scarring and fibrous tissue formation (3) volvulus, torsion of intestine→impaired venous drainage ,stasis, edema and congestion→ complicated with infarction and ischemic damage (4) Intussusceptions.



1-Intussusception (mechanical obstruction)

- Intussusception occurs when a segment of the intestine, constricted by a wave of peristalsis, telescopes into the immediately **WIDER** distal segment.
- Once trapped, the invaginated segment is propelled more inside the distal segment with every peristaltic contraction pulling the mesentery along.
- Untreated intussusception may progress to intestinal obstruction, compression of mesenteric vessels, and infarction.
- **Most common cause of intestinal obstruction in children younger than 2 years of age**
- Idiopathic in most cases in infants and young children (<2 years).
- In Other cases, its due to lymphoid hyperplasia which is associated with viral infection and rotavirus vaccines→reactive hyperplasia of Peyer patches. Note that Rota virus is responsible for most cases of gastroenteritis in this age group.
- Also caused by Meckel's diverticulum (congenital diverticulum of the ileum)
- Typically, Reactive hyperplasia of Peyer patches and Meckel's diverticulum can act as the leading edge of the intussusceptions (start of intussusception).

- Atypically, as intussusception is not common in older children and in adults, it indicates that there is another underlying cause such as an intraluminal mass or tumor that serves as the initiating point of traction.

Clinical features

In Children under the age of 2 Abdominal swelling and distention, vomiting, stool with blood and mucus (currant jelly stool), pain expressed by crying.

Management

Contrast enemas are **both** diagnostically useful and effective in correcting early uncomplicated idiopathic intussusceptions in infants and young children.

Contrast enema: injection of contrast material through the rectum to reduce the intussusception.

However, surgical intervention is necessary in complicated cases when an intraluminal mass or tumor serves as the initiating point of traction, in older children and in adults, or when intussusception is complicated by infarction.

That's why early diagnosis is the key to save the patient's life, by decreasing the incidence of infarction and for easier management.

2-Hirschsprung disease (non-mechanical disease)

- Hirschsprung disease stems from a congenital defect in colonic innervation.
- It may be isolated or occur in combination with other developmental abnormalities.
- It is more common in males but tends to be more severe in females.
- Siblings are at increased risk for development of Hirschsprung disease (family history).
- Patients typically present as neonates with failure or delay passing meconium (first stool passed from fetus after delivery) in the immediate postnatal period followed by obstructive constipation.

Pathogenesis

- The enteric neuronal plexus develops from neural crest cells that migrate into the bowel wall during embryogenesis.
- Hirschsprung disease, also known as *congenital aganglionic megacolon*, results when the normal migration of neural crest cells from cecum to rectum is disrupted (Aganglionic: absence of ganglion cells in tissue under the microscope. Megacolon: dilated colon proximal to the aganglionic area).
- This produces a distal intestinal segment that **lacks both the Meissner submucosal plexus and the Auerbach myenteric plexus** ("aganglionosis"), and thus fails to develop coordinated peristaltic contractions leading to constipation.

Underlying Mutations:

- Receptor tyrosine kinase (RET) accounts for the majority of familial cases and 15% of sporadic cases.
- Mutations in other genes, including disease-modifying genes, as well as environmental factors play a role.

MORPHOLOGY

- Hirschsprung disease always affects the rectum, but the length of the additional involved segments varies.
- Most cases are rectosigmoid, but severe disease can involve the entire colon.
- The aganglionic region may have a grossly normal or contracted appearance, while the normally innervated proximal colon may undergo progressive dilation as a result of functional distal obstruction (megacolon), just like in achalasia where there is also dilatation of esophagus.

Diagnosis

Made by a combination of clinical features, e.g. failure to pass meconium or chronic constipation with unknown cause. We demonstrate the absence of ganglion cells in the affected segment by either:

1. **Barium enema**
2. **Gold standard diagnoses is a biopsy**, has to be a thorough biopsy in order to proof absence of ganglion cells (deep layers examination), so we keep looking for ganglion cells in Hirschsprung disease suspected cases (abundant eosinophilic cytoplasm with a central nucleus and prominent nucleolus)

Complications

The major threats to life are:

1. Enterocolitis (stasis of stool→infectious enterocolitis).
2. Fluid and electrolyte disturbances (can cause dehydration)
3. Perforation, and peritonitis (due to megacolon)

Treatment

Surgical resection of the aganglionic segment with anastomosis of the normal colon to the rectum is effective, although it may take years for patients to attain normal bowel function and continence.

Fig. Hirschsprung disease.

(A) Preoperative barium enema study showing constricted rectum (*bottom*) and dilated sigmoid colon. Ganglion cells were absent in the rectum, but present in the sigmoid colon.

(B) macroscopic appearance, intraoperative appearance of the dilated sigmoid colon.

3-Ischemic Bowel Disease (vascular disorder)

Ischemic damage to the bowel that results from Loss or decreased blood supply to the bowel, whether acute or chronic, tends to occur in older adults.

4-Hemorrhoids (2nd vascular disease)

Hemorrhoids are dilated submucosal anal and rectal collateral vessels that connect the portal and caval venous systems (portosystemic anastomosis) to relieve elevated venous pressure within the hemorrhoid plexus.

Pathogenesis of these lesions is similar to esophageal varices; hemorrhoids are less severe.

Common predisposing factors

- Chronic constipation and associated straining, which increase intraabdominal and venous pressures.
- Venous stasis of pregnancy
- Portal hypertension.

Hemorrhoids are of two types, external and internal, depending on location:

External hemorrhoids: located below the anorectal line.

Internal hemorrhoids: above the anorectal line.

Histologic examination

Hemorrhoids consist of thin-walled, dilated, submucosal vessels beneath anal or rectal mucosa. These vessels are subject to trauma, which leads to rectal bleeding.

Symptoms

Hemorrhoids often manifest with pain and rectal bleeding, particularly bright fresh red blood seen on toilet tissue.

Complications

Thrombosis and inflammation

5- DIARRHEAL DISEASE

- Diarrhea is defined as an increase in stool mass, frequency, or fluidity
- Painful, bloody, small-volume diarrhea is known as **dysentery**
- Diarrhea is a common symptom of many intestinal diseases, including those due to infection, chronic inflammatory diseases, ischemia, malabsorption, and nutritional deficiency. (underlined are the most common)

Malabsorptive Diarrhea

The chronic malabsorptive disorders most commonly encountered are

1. Pancreatic insufficiency (decreased pancreatic enzymes)
2. Celiac disease (CIBD)
3. Crohn disease.

Other causes:

1. Cystic fibrosis
2. Lactase deficiency
3. An abetalipoproteinemia

- Malabsorption manifests most commonly as **chronic diarrhea**
- Defective absorption of fats, fat- and water-soluble vitamins, proteins, carbohydrates, electrolytes, minerals, and water.
- A **hallmark** of malabsorption is **steatorrhea**, characterized by excessive fecal fat and bulky, frothy, greasy, yellow, or clay-colored stools.

Malabsorption results from a defect in **one or more than one** of the four phases of nutrient absorption:

1. **Intraluminal digestion**, in which proteins, carbohydrates, and fats are broken down into absorbable forms (pancreatic deficiency)
2. **Terminal digestion**, which involves the hydrolysis of disaccharides and peptides by disaccharidases and peptidases, respectively, in the brush border of the small-intestinal mucosa (lactase deficiency)
3. **Transepithelial transport**, in which nutrients, fluid, and electrolytes are transported across and processed within the small-intestinal epithelium
4. **Lymphatic transport** of absorbed lipids

Manifestations

In many malabsorptive disorders, a defect in one of these processes predominates, but more than one usually contributes. As a result, malabsorption symptoms resemble each other more than they differ.

1. Weight loss and anorexia.
2. Flatus, abdominal distention (bacteria act on unabsorbed food producing gases).
3. Borborygmi (sounds due to gas presence in lumen), and muscle wasting.
4. Anemia and mucositis (inflammation of mucous membrane at the angle of the mouth), due to pyridoxine, folate, iron or vitamin B12 deficiency; bleeding due to vitamin K (for thrombosis) deficiency;
5. Osteopenia and tetany due to calcium, magnesium, or vitamin D deficiency
6. Neuropathy due to vitamin A or B12 deficiency (numbness).
7. Endocrine and skin disturbances may also occur (e.g. deficiency of iodine leads to thyroid hormone deficiency)

Cystic fibrosis (as one of the causes of malabsorptive diarrhea)

- Multi organ system disease with genetic bases (affects lungs, pancreas, intestines)
- Mutations are in cystic fibrosis transmembrane conductance regulator (CFTR), which leads to defects in ion transport across intestinal and pancreatic epithelium.
- Thick viscous secretions. (as a result of a defect in sodium transport → water transport defect)
- Mucus plugs in pancreatic ducts >>> pancreatic insufficiency (80% of patients) (pancreatic enzymes do not reach the intestine)
- Defect in intraluminal digestion → Malabsorptive diarrhea

Celiac Disease (as a cause of malabsorptive diarrhea)

- Also called Gluten sensitive enteropathy
- Immune mediated enteropathy
- Sensitivity towards gluten which is present in wheat, rye or barley
- Genetically predisposition: HLA-DQ2 or HLA-DQ8
- Treatment → Gluten free diet, it is hard to follow since gluten is found in almost all of the food we eat.
- **Patients health improve dramatically once they start following a gluten free diet**
- Association with other immune diseases: type 1 diabetes, thyroiditis, and Sjogren syndrome

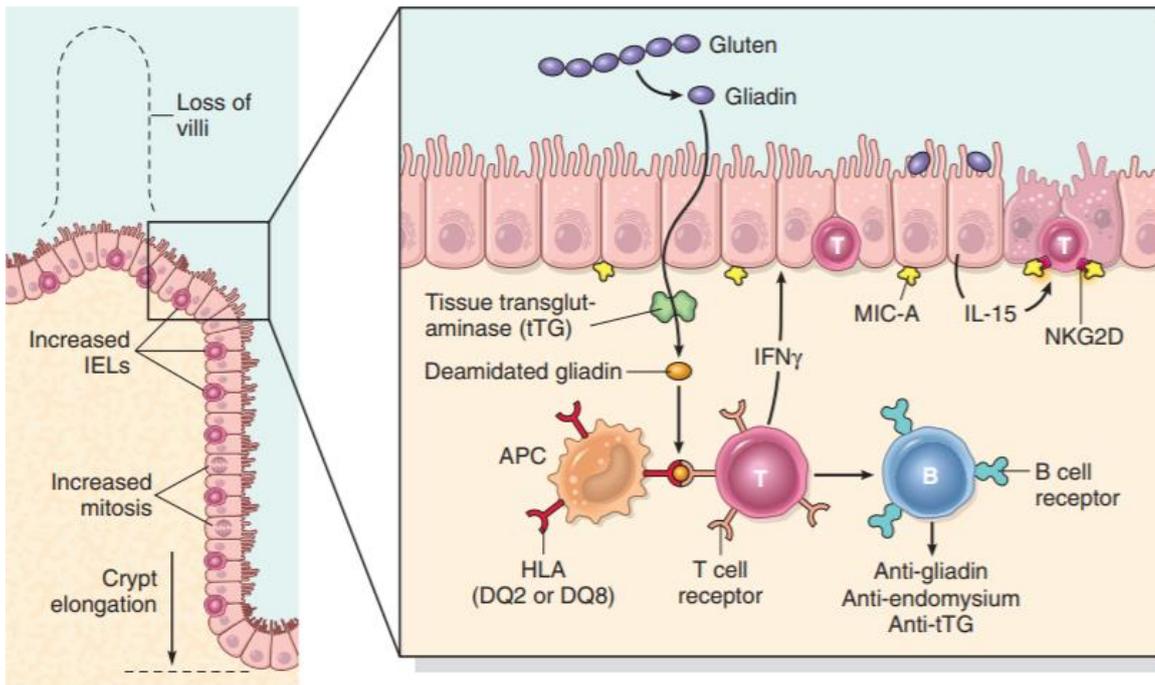
Pathogenesis

- Gluten >> gliadin >> react with HLA-DQ2 or HLA-DQ8 on antigen-presenting cells >> CD4+ T cells activation >> cytokines >> tissue damage.

Steps:

1. Celiac disease is an intestinal immune reaction to gluten, the major storage protein of wheat and similar grains.
 2. Gluten is digested by luminal and brush border enzymes into amino acids and peptides, including gliadin peptide (a short highly resistant peptide)
 3. Gliadin is resistant to degradation by gastric, pancreatic, and small-intestinal proteases.
 4. Gliadin is deamidated by tissue transglutaminase enzyme and is then able to enter the lamina propria and interact with HLA-DQ2 or HLA-DQ8 on antigen-presenting cells and be presented to CD4+ T cells.
 5. These T cells in lamina propria are now activated and produce cytokines that contribute to the tissue damage and characteristic mucosal histopathology of celiac disease
 6. CD4+ cells activate CD8+ that play an ancillary role in causing tissue damage, activation and proliferation of CD8+ intraepithelial lymphocytes that then become cytotoxic and cause more tissue damage
- Main tissue damage is loss of villus architecture, and loss of epithelial cell lining the mucosa → decreased surface area for absorption → malabsorption
 - Degree of loss or shortening of villi is related to severity of disease
 - Note that CD4+ are present in the lamina propria and CD8+ are in the intraepithelial space
7. An antibody response follows (serology): This includes production of AB by B-cells:
 - Anti-tissue transglutaminase antibodies,
 - Anti-gliadin antibodies,
 - Anti-endomysial antibodies
- Note that these AB are not elevated in all patients of celiac disease whether these antibodies contribute to celiac disease pathogenesis or are merely markers of immune activation remains controversial, however, they are diagnostically useful and are effective in monitoring effectiveness of a gluten free diet (level of AB titer expected to fall after 3-6 months of a gluten free diet)

Note: If there is no genetic disposition (HLA-DQ2 or HLA-DQ8 → there will be NO celiac disease



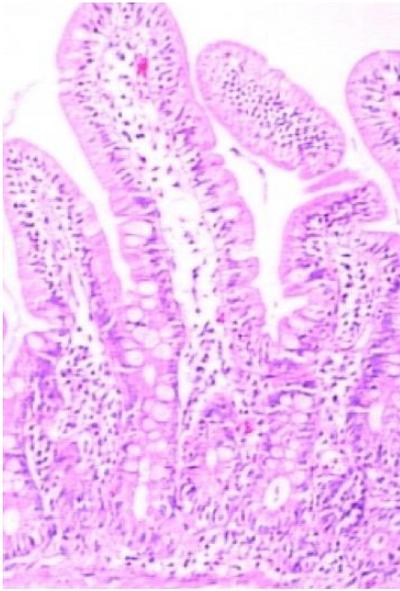
Use diagram to better understand steps of pathogenesis

MORPHOLOGY

The second portion of the duodenum or proximal jejunum are the most affected segments of the GI tract, which are exposed to the highest concentrations of dietary gluten, biopsies from these two regions are generally diagnostic in celiac disease. (multiple biopsies recommended)

The histopathology is characterized by a triad:

1. Increased numbers of T lymphocytes (CD8+), with intraepithelial lymphocytosis (earliest manifestation)
 2. Crypt hyperplasia, due to increase in the damage and turnover of the epithelial cells
 3. Villous atrophy of variables degrees, ranging from just shortening of the villi, to subtotal villous atrophy and even total villous atrophy with flattening of the mucosa which leads to the loss of mucosal and brush-border surface area exposed to the absorption of the nutrients.
- Another feature is increased numbers of lymphocytes (CD4+), plasma cells, mast cells, and eosinophils, especially within the upper part of the lamina propria.
 - It should be noted that intraepithelial lymphocytosis and villous atrophy can be present in other disorders, including viral enteritis. Therefore, a combination of histologic and serologic findings is the most specific diagnosis of celiac disease.



Normal histology

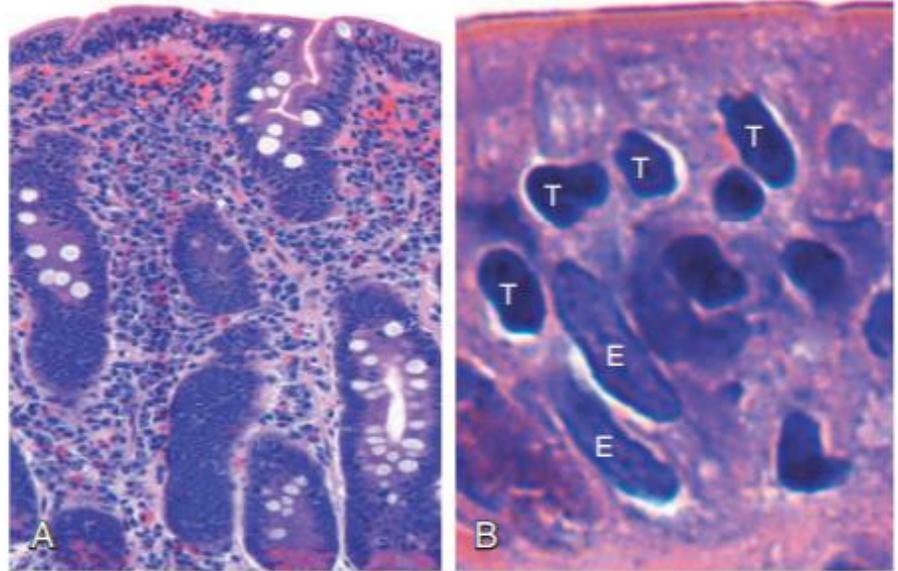


Fig. 15.22 Celiac disease. (A) Advanced cases of celiac disease show complete loss of villi, or total villous atrophy. Note the dense plasma cell infiltrates in the lamina propria. (B) Infiltration of the surface epithelium by T lymphocytes, which can be recognized by their densely stained nuclei (labeled T). Compare with elongated, pale-staining epithelial nuclei (labeled E).

Clinical Features

- Can affect adults and children.
- Pediatric (age of 6-24 months) celiac disease, occurs after introduction of food and cereals to children, is of two types: **classical** and **non-classical**.
Classical symptoms: irritability, abdominal distention, anorexia, diarrhea, failure to thrive, weight loss, or muscle wasting.
Non-classical symptoms: tend to present at older ages with complaints of abdominal pain, nausea, vomiting, bloating or constipation rather than diarrhea (diarrhea is the typical manifestation)
- A characteristic pruritic, blistering skin lesion, **dermatitis herpetiformis**, is also present in as many as 10% of patients (adults or children) (looks like herpes virus)
- In adults, celiac disease manifests most commonly between 30 and 60 years of age.
- The typical presentation of adult celiac disease is malabsorption, leading to anemia due to iron deficiency (because duodenum and proximal jejunum are main sites for iron absorption), less commonly, B12 and folate deficiency → absorbed in ileum which is unaffected here.

- Main classical symptoms in an adult are diarrhea, steatorrhea, gaseous distention, bloating, fatigue, weightloss, muscle wasting
- However, many cases escape clinical attention (asymptomatic) for extended periods because of atypical presentations. Some patients have **silent celiac disease**, defined as positive serology and villous atrophy without symptoms, **or latent celiac disease**, in which positive serology is neither accompanied by villous atrophy nor symptoms.
- Both silent and latent can develop into full blown out celiac disease.

Dermatitis herpetiformis.



Celiac disease	silent	Latent
Histology	Positive	Normal
Serology	Positive	Positive

- Celiac disease patients have Higher risk of developing **enteropathy-associated T cell lymphoma** and **Small-intestinal adenocarcinoma**

Diagnosis

Good clinical history → physical examination → diagnostic evaluation like lab results, imaging and histopathology

The diagnosis of celiac disease is of **two types**:

- **Non-invasive serologic tests** (generally performed before biopsy).

Most sensitive, but less specific:

- Anti-tissue transglutaminase antibody, IgA
- Anti-deamidated gliadin antibodies, IgA & IgG

Most specific, but less sensitive:

- Anti-endomysial antibody.
- A combination of serology is recommended

- **Invasive**

Upper endoscopy and small bowel biopsy (2nd part of duodenum and jejunum), triad findings.

Treatment

- Gluten free diet → reversal of entire disease
- Relapses can happen if patient is not adherent to this diet

-However, despite a strict gluten-free diet, patient might develop resistance to the gluten-free diet, leading to refractory symptoms, such as abdominal pain, diarrhea, and weight loss. Then we must consider **lymphoma or adenocarcinoma transformation**

Lactase (Disaccharidase) Deficiency, a cause of malabsorptive diarrhea

- Lactase normally found at apical brush border membrane, but because of deficiency → Lactose remains in the gut lumen and attracts water.
- Osmotic diarrhea
- Normal biopsy findings. (it's an enzymatic deficiency at the biochemical level)
- **Two types:**
 1. Congenital: Autosomal recessive, genetic mutation in lactase enzyme, rare, explosive diarrhea, watery, frothy stools & abdominal distention, after milk ingestion.
 2. Acquired: Common, follow viral or bacterial enteritis, either due to damage to brush border epithelium and hence damage to lactase enzyme, or due to downregulation of gene, after childhood, because it is not needed as much anymore.
- **Treatment**
lactose withdrawal from diet

Abetalipoproteinemia as a cause of malabsorptive diarrhea

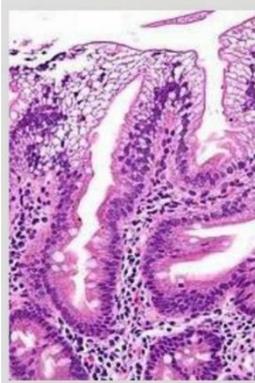
- Autosomal recessive, rare.
- Absence of beta lipoproteins due to lack of absorption of fat and fat-soluble vitamins

Pathogenesis

Inability to secrete triglyceride-rich lipoproteins due to trans epithelial transport defect of TG and FAs. TG and FAs enter the cells of the GI; however, they cannot be transported to the blood. Thus, leading to deficiency of these TG and FAs and fat-soluble vitamins in the body. Body won't be able to synthesize the lipoprotein. Monoglycerides and triglycerides accumulate in epithelial cells, which can result in the typical

microscopic appearance of fat globules seen in the epithelial cells of the small intestine in these patients.

Patients are usually infants and the present with failure to thrive, grow, and gaining of weight, as well as diarrhea, and steatorrhea.



Micrograph showing enterocytes with a clear cytoplasm (due to lipid accumulation) characteristic of abetalipoproteinemia.

As you can see in the picture, the cells are characterized by clear cytoplasm due to lipid accumulation in the surface epithelial cells.