# GIS 5 online

## PATHOLOGY


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- During this lecture we will discuss **intestinal pathology.**
  - The small and large intestine are formed histologically from the same tissue layers.
  - They are formed of the mucosa, submucosa, muscularis propria and serosa.
  - The wall of the large intestine is thicker than small intestine. However, the lumen of small intestine is narrower than the lumen of large intestine.

So, we have a long list of diseases that can affect the intestine and they are subdivided into these subcategories:

**1-Intestinal obstruction**
**2-Vascular disorders**
**3-Malabsorptive diseases and infections**
**4-Inflammatory bowel disease**
**5-Polyps and neoplastic diseases**

## Intestinal obstruction:

It is subdivided into mechanical and non-mechanical obstruction according to the underlying cause

**Mechanical obstruction** is caused by:

- Intussusception.
- Hernias.
- Adhesions.
- Volvulus

→ 80% of cases.

- Tumors, diverticulitis and infarction.

**Non-mechanical obstruction**

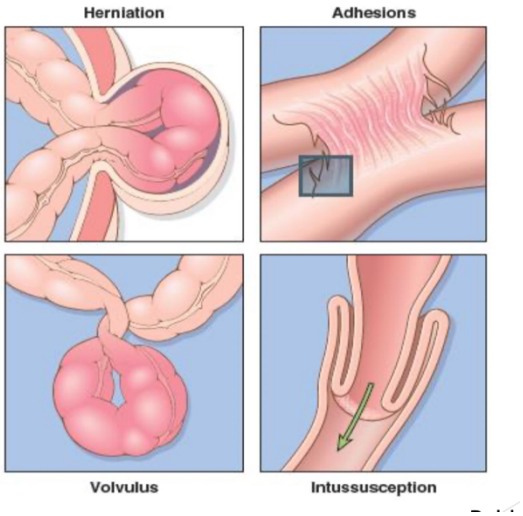
- **Hirschsprung disease**
- **Neurological disorders**
- **Drugs**
- **Paralytic ileus:** it is an obstruction of intestine due to paralysis of intestinal muscle caused by surgical procedures**.**

## Clinical picture of intestinal obstruction:

- Abdominal pain.
- Distention (gases distention).
- Vomiting.
- Constipation.

- Intestinal obstruction can present as an acute problem of sudden onset like in the cases of intussusception, volvulus and infarction or chronic long standing problems like in the cases of **Hirschsprung** disease or tumors.

- Intussusception will be covered in detail in the next pages and it is usually seen in kids
- Hernia: it is protrusion of bowel segment and its mesentery through a defect in abdominal wall.
  - We have umbilical hernia, femoral hernia and inguinal hernia
- Adhesions: it is a complication of either previous inflammatory condition or after surgical procedures which will result in scarring and adhesion between two bowel lobes.
- Volvulus: it is like torsion of intestine in which we will have impaired venous drainage, edema, congestion and can be complicated later by infarction and ischemic damage to the bowel.




## Intussusception

- Most common cause of intestinal obstruction in children younger than 2 years.
- It happens when a small segment of the intestine constricted by a wave of peristalsis, telescopes into the immediately distal segment.
- Once trapped, invaginated segment is propelled by peristalsis, and pulls mesentery with it.
- Untreated progresses to infarction.

### Causes of intussusception:

- < 2 years: Idiopathic in most cases.
- Peyer patches hyperplasia (lymphoid hyperplasia) which is usually associated with rotavirus vaccine, viral infection.
  *Rotavirus is responsible for most cases of viral gastroenteritis in childhood.
- Meckel's diverticulum: it is a congenital disorder in the ileum.
- Old children & adults: Intraluminal mass or tumors.
  *So, whenever we see an intussusception in adult we should think of mass or tumor as the leading point of intussusception.

## Clinical features:

When we suspect intussusception especially in the children under the age 2?

You suspect it when you receive a child to the emergency room complaining of abdominal swelling and distention associated with vomiting and passing stools mixed with blood and mucus and is typically **called currant jelly stool**. If the patient is older, he can complain of pain but in the case of patients under the age of 2 the pain is usually expressed by continuous crying.

## Management:

- Contrast enemas (حقنة شرجية) in uncomplicated idiopathic cases or in early stage.
- Surgery if complicated or if masses are the leading point.

## Hirschsprung Disease:

- Congenital defect in colonic innervations.
- It is also called **Congenital aganglionic megacolon.**

**Congenital** because the disease is present after birth and **aganglionic** because the typical feature of this disease is absence of ganglion cells upon tissue microscopic examination. **Megacolon** due to dilated colon proximal to the area of lost ganglion cells. So, the name **Congenital aganglionic megacolon** is description of the disease process.

- More common in males.
- More severe in females.
- Risk increase in siblings.

## Typical presentation

- **Neonatal failure to pass meconium**

*Meconium is the first stool that is passed after delivery of the fetus. So, the failure in the passage of the meconium is an early feature that makes you suspect Hirschsprung Disease.

- Later, it is followed by chronic obstructive constipation.

## Pathogenesis

- The pathogenesis starts during embryogenesis in which there is a defect or a failure of the migration of neural crest cells from cecum to rectum and so the result is Lack of development of **Meissner submucosal plexus** and **Auerbach**

myenteric plexus. The result of this absence of these plexuses is failure of coordinated peristaltic contractions which will result constipation.

- Mutations in RET: in familial cases and 15% of sporadic

- Disease affects the rectum in almost of the cases. However, the length of the affected segment is different from one patient to another according to the severity of the disease.

- Other genes and environmental factors play role.

## Morphology

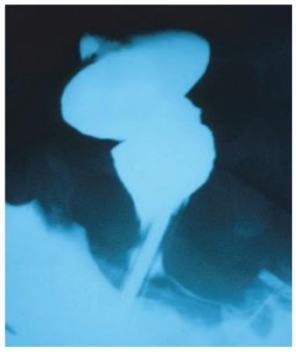
- **Rectum always involved.**
- Extent is variable.
- Most cases in **rectosigmoid**. however, in very severe cases may involve the entire colon.

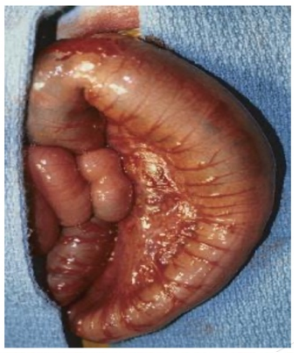
## Macroscopic

- Aganglionic rectosigmoid. region **normal or contracted on barium enema**.
- Proximal normal segment progressively dilated.

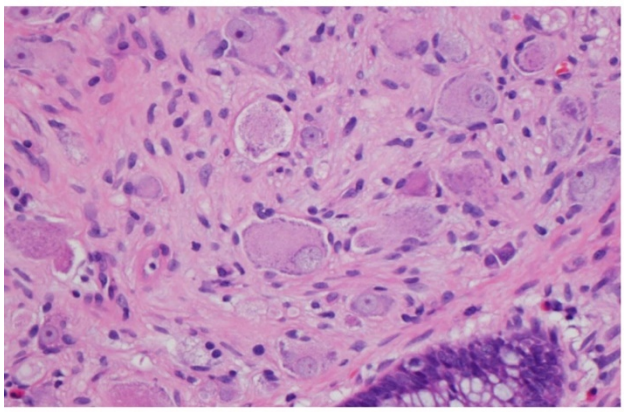
## Diagnosis: **BIOPSY, microscopic.**

Here you can see macroscopic appearance of Hirschsprung Disease. you can see the contracted rectum and progressively dilated proximal normal segment.
The adjacent picture illustrates barium enema with contracted rectum and a dilated proximal colon.





These are the normal ganglion cells.
The typical ganglion cells have an abundant eosinophilic cytoplasm and eccentrically (peripherally) located nucleus with prominent nucleolus.
The absence of these cells in the myenteric and submucosal plexus is needed to establish a diagnosis of Hirschsprung Disease.



**Complications:**

- Enterocolitis, fluid and electrolyte disturbances (dehydration), perforation and peritonitis.

**Treatment:**

Surgical resection of Aganglionic segment and anastomosis of normal segments.

## Vascular disorders of bowel

- **The vascular disorders of bowel are subdivided into:**
  - **Ischemic bowel disease: it is result from ischemia whether acute or chronic and usually seen in elderly patient.**
  - **Hemorrhoids: it is common in outpatient clinics.**

**Hemorrhoids:**

It is the dilated anal and perianal collateral vessels that connect the portal and caval venous systems. So, hemorrhoids are dilated veins in the submucosal location in the anal area or rectal area.

- **Predisposing factors:**
  - Constipation and straining
  - Venous stasis of pregnancy
  - Portal hypertension.

- Hemorrhoids is subdivided according to the location into:

- **Internal**: above the anal rectal line (in the rectal mucosa)
- **External**: below the anal rectal line.

**So, it is a thin walled, dilated, submucosal vessels beneath anal or rectal mucosa.**

**Symptoms:** Bleeding, pain, thrombosis and inflammation.

- The blood is fresh colored.

# Diarrheal Disease

⇨ Diarrhea is an increase in stool mass, frequency or fluidity.
⇨ Dysentery is painful, bloody, small volume diarrhea.

**Causes:**

1) Infectious Enterocolitis (discussed in microbiology)
2) Inflammatory bowel diseases (chronic~ discussed next lecture)
3) Malabsorptive diarrhea (discussed this lecture)
4) Ischemic colitis
5) Nutritional deficiency

## Malabsorptive Diarrhea

It is a chronic defect in the absorption of fats, fat- or water-soluble vitamins, proteins, carbohydrates, electrolytes, minerals and water. Its hallmark is **Steatorrhea** ~ which is greasy, fatty, bulky yellow to clay colored stool (and this is due to the malabsorbed nutrients in it)

**Causes of malabsorption:**

1) **Pancreatic insufficiency** ➔ due to lack of pancreatic enzymes
2) **Celiac disease**
3) **Crohn's disease** (Discussed next lecture)
4) Cystic fibrosis
5) Lactase (Disaccharide) Deficiency
6) Abetalipoproteinemia

*The causes above differ in their clinical presentation though they all cause diarrhea.
** **First 3** are the most common causes of chronic malabsorption in the west.

The mechanism of malabsorptive diarrhea is usually a defect in one or more of the following…

A) Intraluminal digestion → Malabsorption of macromolecules (fat, carbs & proteins) due to main enzymes deficiency e.g. Pancreatic enzymes
B) Terminal digestion → Malabsorption of end products due to deficiency in disaccharidases/ peptidases at the intestinal brush border e.g. Lactase enzyme

C) Transepithelial transport → defect in the transport across the epithelial cells (nutrients can't reach vascular side)
D) Lymphatic transport → absorbed lipid is transported by lymphatics to reach circulation

**Manifestations (Clinical symptoms)** differ according to the malabsorbed substance but some **general symptoms** are:

- **Weight loss**
- **Anorexia:** loss of appetite
- **flatus:** gaseous abdominal distention, which is due to unabsorbed disaccharides which get fermented by intestinal flora producing gas.
- **Borborygmi:** rumbling noise due to intestinal gas movement.
- **muscle wasting:** main intestinal muscles look atrophied.

**More specific symptoms are:**

1) **Anemia and mucositis** {inflammation of mucous membranes at the angle of the mouth} ➔(iron, pyridoxine (Vitamin B6), folate, or vitamin B12 deficiency)
2) **Bleeding** ➔(vitamin K deficiency) ~ fat-soluble vitamin needed for thrombotic cascade
3) **Osteopenia and tetany** {may develop to osteoporosis in young} ➔(calcium, magnesium, or vitamin D deficiency)
4) **Neuropathy** {peripheral numbness + burning sensation in hands and feet + muscle weakness} ➔(vitamin A or B12 deficiency)
5) **Skin and endocrine disorders** ➔(Iodine results in thyroid hormone deficiency)

Next we discuss some of the causes of malabsorptive diarrhea mentioned earlier.

## Cystic Fibrosis

⇨ It is a **multiorgan system disease** with genetic basis, ~**mutations** in cystic fibrosis transmembrane conductance regulator (CFTR)
⇨ Defects in **ion transport across intestinal and pancreatic epithelium**, which causes the pancreatic **secretions** to be **thick and viscous** (less ions > less water > more viscous secretions)

⇨ **Mucus** secretions plugs pancreatic ducts causing **pancreatic insufficiency** in 80% of patients
⇨ This leads to a defect in in the **intraluminal digestion** (main enzymes, as we mentioned earlier)

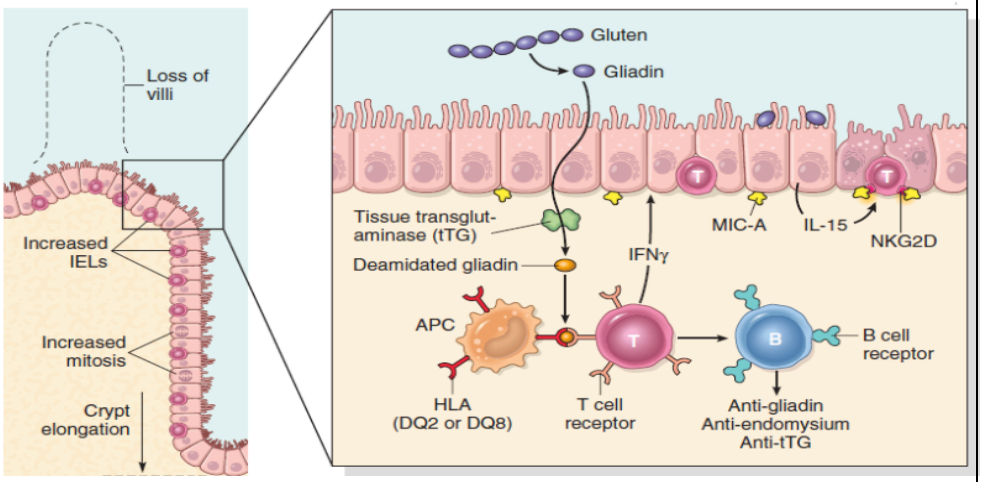
## Celiac Disease

⇨ It is an **immune mediated** reaction to **gluten** (found in Wheat, rye or barley) affecting the small intestine ~ enteropathy
⇨ Patients carry the **HLA-DQ2 or HLA-DQ8 alleles** on the surface of their antigen presenting cells **APCs** ~ genetic predisposition
⇨ Its associated with other immune diseases like type 1 diabetes, thyroiditis and Sjogren syndrome
⇨ **Treatment** by following a **gluten-free diet** which reverses symptoms

### Pathogenesis

➔ When gluten reaches the small intestine, it gets digested by its enzymes to a shorter peptide ~Gliadin~ which is resistance to digestion and needs deamidation
➔ Gliadin enters the lamina propria and gets deamidated by tissue transglutaminase
➔ Deamidated gliadin reacts with HLA-DQ2 or HLA-DQ8 on APCs surface and this activates CD4+ T helper cells in the lamina propria causing tissue damage by multiple **ways:**

1) It releases cytokines which damage the epithelial cells
2) It attracts intraepithelial lymphocytes which are CD8+ Cytotoxic T Cells embedded in the epithelium



3) It activates B cells to produce the following antibodies
   - Anti-tissue transglutaminase antibodies
   - Anti-gliadin antibodies
   - Anti-endomysial antibodies

   *Serologically, Abs are useful in diagnosis and in monitoring response of the gluten free diet

   *It's unknown if the Abs are the disease's cause or if they are produced in response to gliadin

➔ All together cause **tissue damage** by the loss of villus architecture and loss of epithelial cells lining the mucosa therefore decreasing the surface area exposed for absorption leading to malabsorption

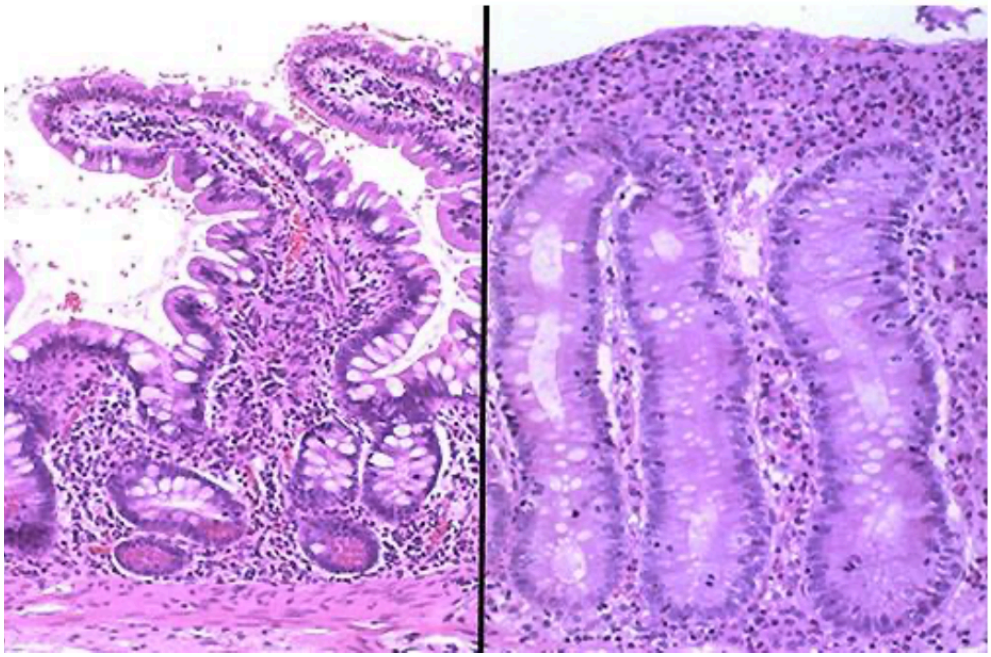
*Loss of villi could be **total** (flattening), **subtotal** or just **shortening** of villi

**Morphology:**

→ Endoscopist takes multiple biopsies (to increase diagnostic yield) from second portion of the duodenum or proximal jejunum (avoiding the proximal duodenum because of the gastric juice effect on it)

→ **Microscopically**, we look for the following **triad**:

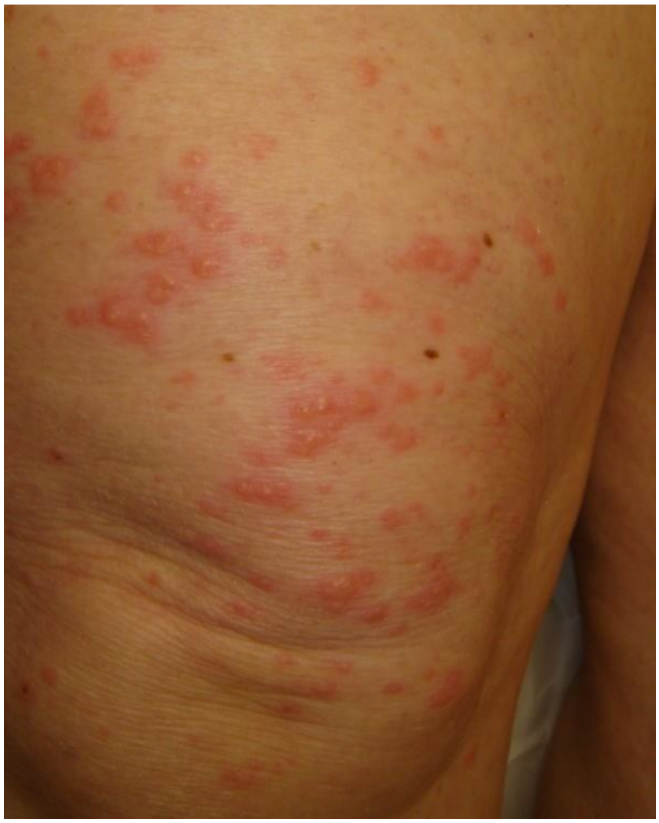
1) **Intraepithelial lymphocytosis (CD8+ T cells) ~IEL~** which is the earliest manifestation of celiac disease even in the absence of the other two
2) **Crypt hyperplasia** which are elongated pits/grooves as a result of increased damage and turnover of intestinal epithelium



**3) Villous atrophy**

→ In the lamina propria we see lymphocytes, plasma cells, eosinophils
→ IEL & villous atrophy are **not pathognomonic** as they're seen in viral enteritis
→ Diagnosis is a correlation between clinical, histologic and serologic aspects

## Clinical features in children:



➔Symptoms start showing 6-24 months after birth due to introduction of gluten to diet (cereals)
➔Symptoms are divided to classical and non-classical

**Classical**: Irritability, abdominal distention, anorexia, diarrhea, failure to thrive (due to decreased anabolic reaction), weight loss, or muscle wasting

**Non-classical**: abdominal pain, nausea, vomiting, bloating, or constipation

➔10% of patients develop highly itchy, blistering skin lesions which look like herpetic vesicles in what is called **dermatitis herpetiformis**

## Clinical features in adults:

➔Usually aged (30-60 years)
➔ **Anemia: iron deficiency** (common because iron is mainly absorbed in the duodenum and jejunum which get affected by celiac disease)
➔ **B12 and folate deficiency** (less common because they're mainly absorbed in ileum)

**Classical symptoms**: diarrhea, bloating (gaseous abdominal distention), fatigue (due to iron deficiency), weight loss and muscle wasting

➔Some celiac disease cases are missed during diagnosis but will develop to the full disease if not treated, they're divided into:

→**Silent celiac**: Positive Serology + Positive histological diagnosis but no clinical symptoms
→**Latent celiac:** Positive Serology but normal histological appearance and asymptomatic

➔As we stated earlier, gluten-free diet is the treatment as it reverses symptoms but if the patient develops **resistance to the diet** and starts showing **refractory symptoms**, we suspect **enteropathy associated T cell lymphoma** or **Small intestinal adenocarcinoma** (next lecture)

**Diagnosis:**
→It's a combination of clinical history, physical examination, laboratory investigation, imaging and histopathology. Tests are divided to **non-invasive** and **invasive**; we start with the non-invasive.

**Non-invasive**:

| **Most sensitive but less specific** | **Most specific but less sensitive** |
|---|---|
| Anti-tissue transglutaminase antibody, IgA<br>Anti-deamidated gliadin antibodies, IgA & IgG | Anti-endomysial antibody. |

**Invasive**:
Small bowel biopsy ~ microscopically look for the triad

## Lactase (Disaccharidase) Deficiency

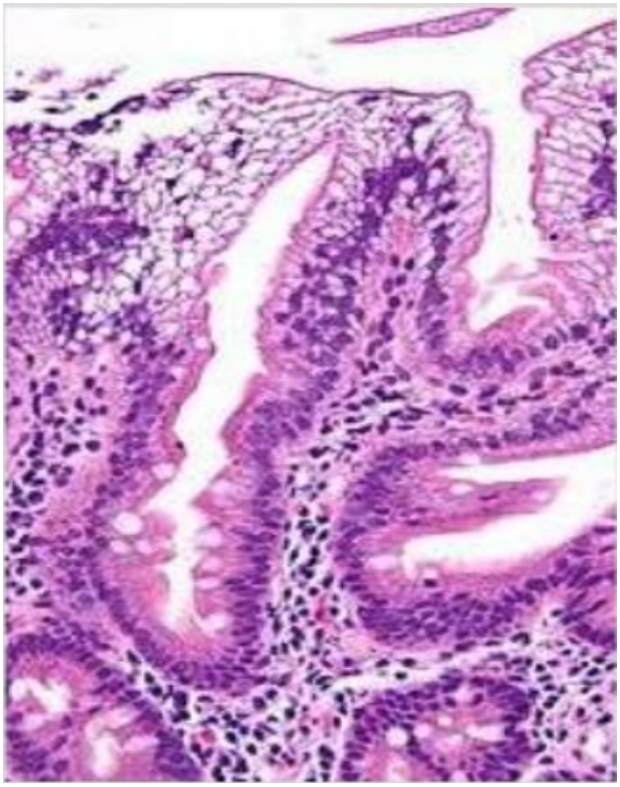
➔Lactase is found on the apical brush border membrane; it hydrolyses lactose to glucose and galactose. If deficient, lactose accumulates in the gut lumen absorbing water and causing osmotic diarrhea

➔Biopsies are normal because the problem is on a biochemical level (enzymes)
➔When patient stops ingestion of milk and diary products symptoms will abate
➔**Two types:**

1) **Congenital**: Due to autosomal recessive (AR) genetic mutation therefore rare
   Presents as explosive diarrhea + watery, frothy stools + abdominal distention, after milk ingestion (lactose)
2) **Acquired**: Following viral or bacterial enteritis → which damage the apical brush border →loss of lactase

Or due to downregulation of the lactase gene after childhood as the need for milk decreases

## Abetalipoproteinemia



➔ Absence of ß-lipoproteins in the blood

➔ It's an autosomal recessive rare disease characterized by the inability to secrete triglyceride-rich lipoproteins due to a transepithelial transport defect of triglycerides, monoglycerides and fatty acids in which they enter the epithelial cells but don't reach the blood (accumulate)

➔So, there is a lack of absorption of fat and fat-soluble vitamins + decreased synthesis of lipoproteins which are an important part of the plasma membrane

➔Infants present with failure to thrive, diarrhea and steatorrhea

➔Microscopic appearance: clear cytoplasm due to fat globules and lipid accumulation in enterocytes (epithelial cells of small intestine)

**Best of luck**
**Stay safe**

🔥