Lecture 4
Malabsorption

PATHOLOGY TEAM 435

{ ومن لم يذق مرّ التعلُّمِ ساعةً.. تجرع ذلَّ الجهل طوال حياتهِ }

Revised by
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Red: Important. Grey: Extra Notes Doctors Notes will be in text boxes

Objectives:

- **Define Malabsorption:** Abnormal digestion or small intestinal mucosa
- **Know the major malabsorption syndromes and its causes**
- **Know the many organ systems affected by the consequences of malabsorption:**
  - Alimentary tract.
  - Hematopoietic system.
  - Musculoskeletal system.
  - Endocrine system.
  - Skin.
  - Nervous system.
  - Anaemia, Osteomalacia and osteoporosis.
  - Bleeding failure to thrive.
- **Know the following aspects of celiac disease:**
  - Definition: Immune reaction to gliadin fraction of the wheat protein gluten
  - Pathogenesis:
    - Villous atrophy.
    - Crypt hyperplasia
    - Increased intraepithelial lymphocytosis
  - Clinical features
  - Pathology (gross and microscopic features)
  - Complications (T-cell lymphoma and GI tract carcinoma)
- **Know the cause and types of Lactose intolerance:**
  - Low or absent activity of the enzyme lactase.
  - Lactose not absorbed.
  - Lactose – colon.
  - In colon – fermentation.
  - Gases.

Upon completion of this lecture the students will:

- Understand that the malabsorption is caused by either abnormal digestion or small intestinal mucosa.
- Know that malabsorption can affect many organ systems (alimentary tract, hematopoietic system, musculoskeletal system, endocrine system, epidermis, nervous system).
- Concentrate on celiac disease and lactose intolerance as two examples of malabsoption syndrome.

Refrences: Doctors' slides, Robbins, Pathoma and First Aid 1

Physiology:

The main purpose of the GIT is to digest and absorb nutrients (fat, carbohydrate, and protein), micronutrients (vitamins and trace minerals), water, and electrolytes.

Malabsorption:

If there is malabsorption then there will be a defect in the function of the GIT

Malabsorption is characterized by defective absorption of fats, fat- and water-soluble vitamins, proteins, carbohydrates, electrolytes and minerals, and water.

Presents most commonly as chronic diarrhea.

Malabsorption Syndrome :

- Inability of the intestine to absorb nutrients adequately into the bloodstream.
- Impairment can be of single or multiple nutrients depending on the abnormality.

Mechanisms and Causes of Malabsorption Syndrome:

1. Inadequate digestion.
2. Deficient bile salt.
3. Inadequate small intestine.
4. Lymphatic obstruction.

Pathophysiology:

Inadequate digestion Or Small intestine abnormalities = Malabsorption

Small intestine abnormalities: the Surface area is affected so there will be no absorption.

Inadequate digestion:

Stomach:
Postgastrectomy.
Zollinger-Ellison syndrome.

Pancreas:
Deficiency of pancreatic lipase.
Chronic pancreatitis.
Cystic fibrosis.
Pancreatic resection.

Bile:
Obstructive jaundice.
Terminal ileal resection.

Small intestine abnormalities:

Mucosa:
Celiac disease.
Tropical sprue.
Whipple's disease, (caused by *Tropheryma whipplei*).
Giardiasis.

Inadequate small intestine:
Intestinal resection.
Crohn's disease.

Lymphatic obstructions:
Intestinal lymphangiectasia.
Malignant lymphoma.

Extra Explanation For Better Understanding

1) Inadequate digestion:

- **Cystic fibrosis :** It causes the production of abnormally thick mucus due to abnormality in the transport of chloride ions (Viscous fluid) "Which leads to the blockage of the pancreatic ducts, intestines, and bronchi".The most affected organs are : liver, pancreas,kidneys and lungs.
- **Zollinger-Ellison syndrome :** increases the acidity in the entire GIT which so the pancreatic enzymes won't work properly because they require an alkaline media.

2) Deficient bile salt:

- **Bacterial overgrowth :** over-metabolism of bile salts so they won't be absorbed normally.
- Only 5% of bile salts are excreted in stools, the rest are reabsorbed.
- In case of bacterial overgrowth there will be over-metabolism of bile salts so they won't be absorbed normally.
- **Terminal ileal resection :** in lymphoma patients.
- **Crohn's' disease :** an idiopathic inflammatory bowel disease in which the ileum is affected in 70% of cases.

3) Primary mucosal abnormalities:

- **Celiac disease (non-tropical sprue) :** the patients are allergic to gluten "protein". In this disease, the surface area needed for reabsorption of nutrients in the duodenum will be reduced which lead to malabsorption.
- Tropical sprue : affect people who visit tropical areas (على خط الاستواء) that usually have bacterial infections lead to loss of villi throughout the small intestine. It is a transient condition (can be easily treated with antibiotics).
- Notice that non-tropical sprue is not related to bacteria (In contrast to tropical sprue) and it mainly affects duodenum.
- Bothe of them (tropical & non-tropical sprue) will lead to villous-atrophy.

- **Whipple's disease (RARE) :** Bacterial infection (gram positive bacilli) affecting the small intestine, these bacilli are situated in the lamina propria. Lamina propria will be filled with foamy cells containing-bacilli which will cause to pressure on the lymphatics so there will be no proper absorption of fat. In addition, patients will have fever, arthralgia and other manifestations .
- **Amyloidosis :** Accumulation of amyloid protein which is difficult to be digested.
- **Radiation enteritis :** will lead to injury of blood vessels and atrophy of the mucosa.
- Abetalipoproteinemia : an inherited condition in which the patient have deficiency in beta lipoprotein which is needed for fat absorption.
- **Giardiasis** : infection caused by protozoa (duodenum).

4) Lymphatic obstruction :

- **Lymphangiectasia :** abnormality of blood vessels in which they are dilated and obstructed so they can't absorb fat normally.
- **Macroglobulinemia :** infiltration of lamina propria by abnormal lymphocytes.

Clinical Features:

General

- Abnormal stools:
  - Steatorrhea: increased fecal excretion of fat.
  - Stools become soft, yellow, malodorous[1], greasy and float on top of the water in the toilet.
- Failure to thrive[2] or poor growth in most but not all cases , weight loss despite increased oral intake of nutrients.
- Specific nutrient deficiencies, either singly or in combination.

Diagnosis:

There is no specific test for malabsorption

- The hallmark for diagnosis of malabsorption is the presence in fat in stool [Steatorrhea].
- Stool : yellow and greasy.

Investigation is guided by symptoms and signs:

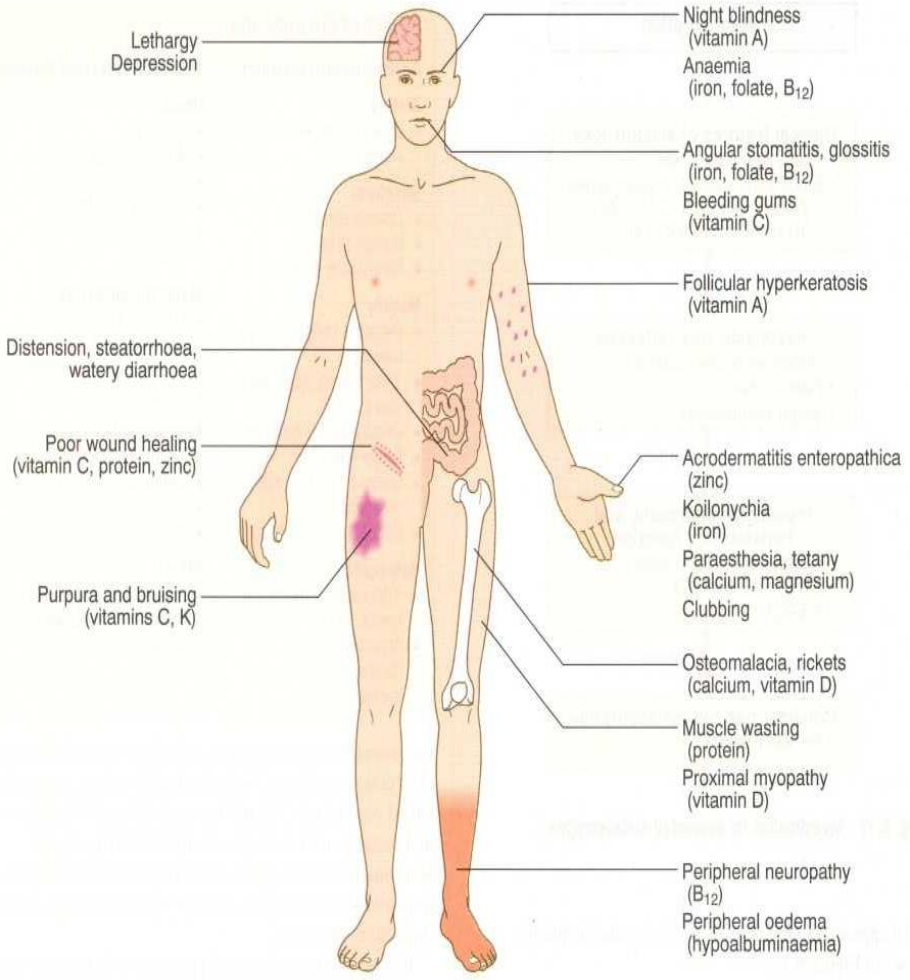
- Endoscopy: Biopsy of small bowel.
- Blood tests.
- Stool studies.
- Fecal fat study to diagnose steatorrhea.

Depending on the deficient nutrient:

- Protein → Swelling or edema , Muscles wasting.
- B12, folic acid and iron deficiency → Anemia (fatigue and weakness).
- Vitamin D, calcium → Muscle cramp, Osteomalacia and osteoporosis.

see picture ☺ ↓

Vitamin K is needed for the synthesis of factor (2, 3,5,7&9).



[1] Smells bad
[2] Grow

Celiac Disease:

- An immune reaction to **gliadin** (pathogenic component) fraction of the wheat protein gluten in genetically predisposed persons. More in European whites.
- Usually diagnosed in childhood – mid adult.
- Patients have raised antibodies to gluten autoantibodies.
- Highly specific association with class II HLA DQ2 (95% of cases) and, to a lesser extent, DQ8 (5% of cases).

- Autoimmune-mediated intolerance of **gliadin** (gluten protein found in wheat) malabsorption and steatorrhea.
- Associated with: **HLA-DQ2, HLA-DQ8**, northern European descent, dermatitis herpetiformis, bone density.
- Findings: **anti-endomysial, anti-tissue transglutaminase, and anti-gliadin antibodies**; blunting of villi; and lymphocytes in lamina propria .
- Moderately risk of malignancy (e.g., T-cell lymphoma).

Pathology:

- Once absorbed ,**gliadin** is deamidated by **tissue transglutaminase (tTG).**
- Deamidated gliadin is presented → **Antigen presenting cells** → **MHC class** 2
- CD4 T cells produce cytokines that release matrix proteases causing cell death and degradation in the epithelial cells, resulting in the loss of the villous surface in the small intestine.
- This results in impaired mucosal function and inability for absorption.

Typical Presentation:

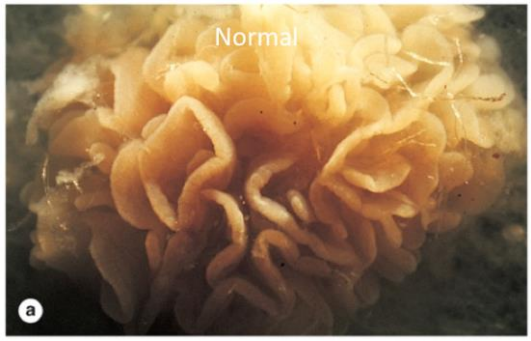
- GI symptoms that characteristically appear at age 9-24 months.
- Symptoms begin at various times after the introduction of foods that contain gluten e.g**(Wheat, barley, flour).**

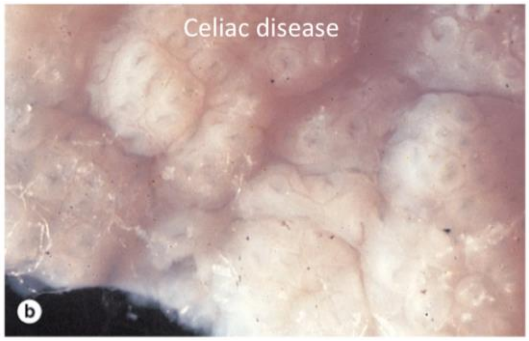
A relationship between the age of onset and the type of presentation:

Infants and toddlers	**GI symptoms and failure to thrive**
Childhood	**Minor GI symptoms, inadequate rate of weight gain.**
Young adults	**Anemia is the most common form of presentation.**
Adults and elderly	**GI symptoms are more prevalent.**

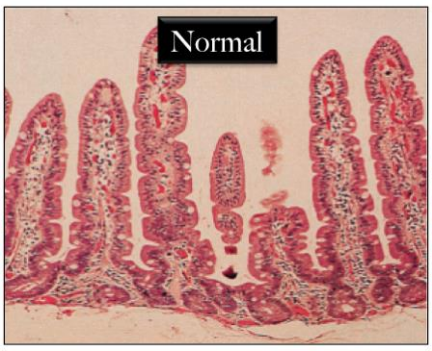
Investigations:

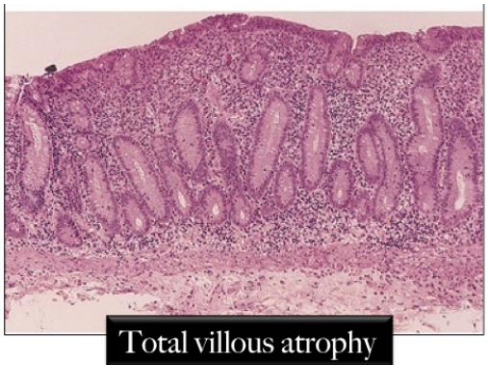
1. Endoscopy:





2. Histology:





- Mucosa is flattened with marked villous atrophy.
- Increased intraepithelial lymphocytosis
- Crypt elongation or hyperplasia

Diagnosis: **(very important)**

- Clinical documentations of malabsorption.
- Stool has ↑ Fat.
- Serology is +ve for IgA to tissue transglutaminase (anti-TTG-IgA) or IgG to deamidated gliadin or anti-endomysial antibodies (not specific).
- Small intestine biopsy demonstrate villous atrophy.
- Improvement of symptom and mucosal histology on gluten free diet. (Wheat, barley, flour Other grains, such as rice and corn flour, do not have such an effect).

Complications:

- Osteopenia , osteoporosis.
- Infertility in women.
- Short stature, delayed puberty, anemia.
- Malignancies [intestinal T-cell lymphoma].
- 10 to 15% risk of developing GI lymphoma.

Gliadin : 33 amino acid chains which cannot be digested in the intestine. (Normally they pass into stool)

- Class II HLA DQ2 and DQ8: more susceptible to develop celiac disease.
- Gluten is broken down into amino acids.

Glidin resist degradation by enzymes and remain as it is (2 effects):

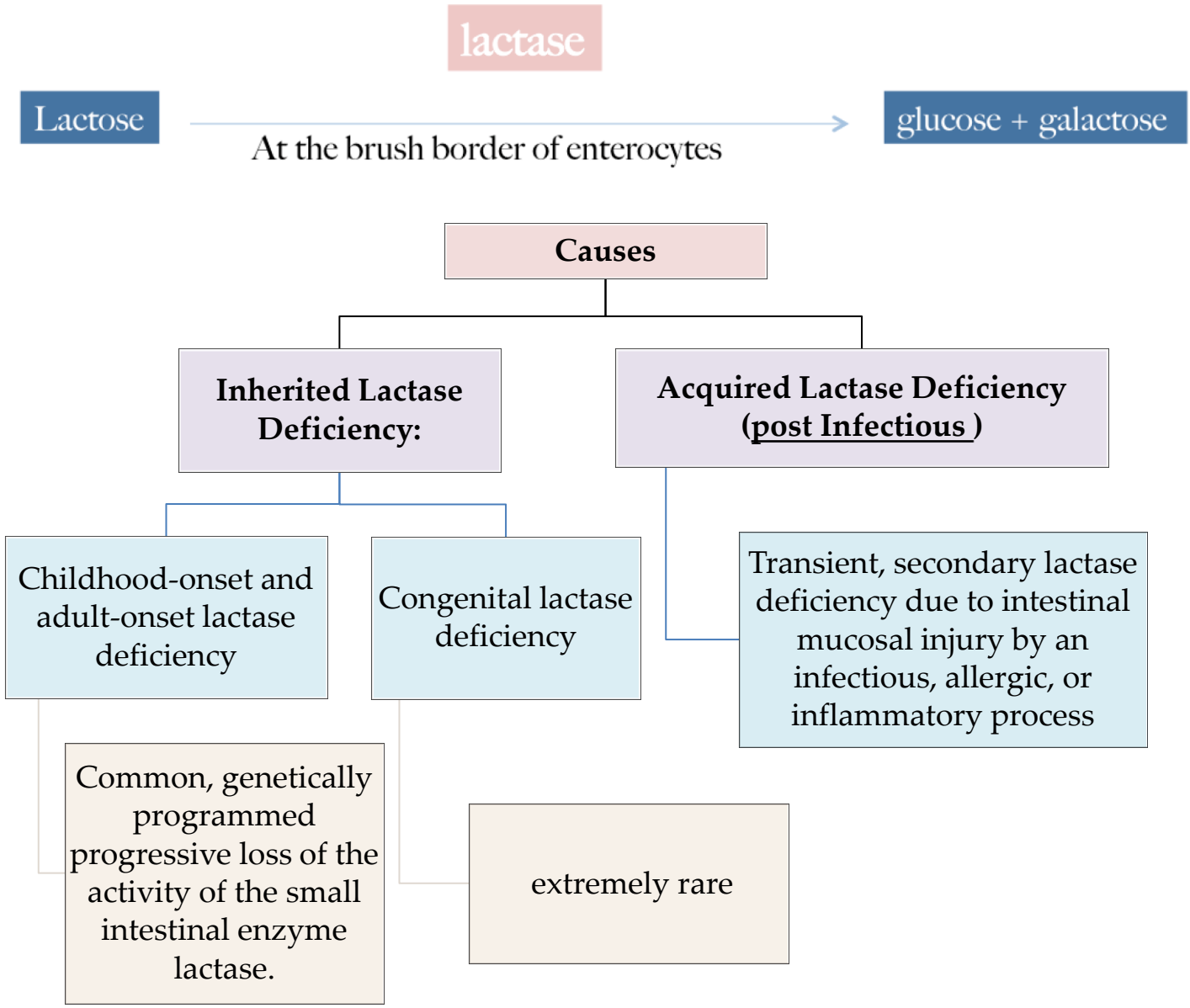
1. It could directly affect the epithelium → induction of influx of T-lymphocytes by the production of IL-15.
2. Glidin will be absorbed in lamina propria. There is an enzyme called Tissue transglutaminase that transform glidin into smaller protein that becomes attached to the surface of macrophages → activation of lymph nodes → activation of T-helper cells → Interferon gamma production → stimulation of B-cells to become plasma cells → there will be antibodies against glidin.

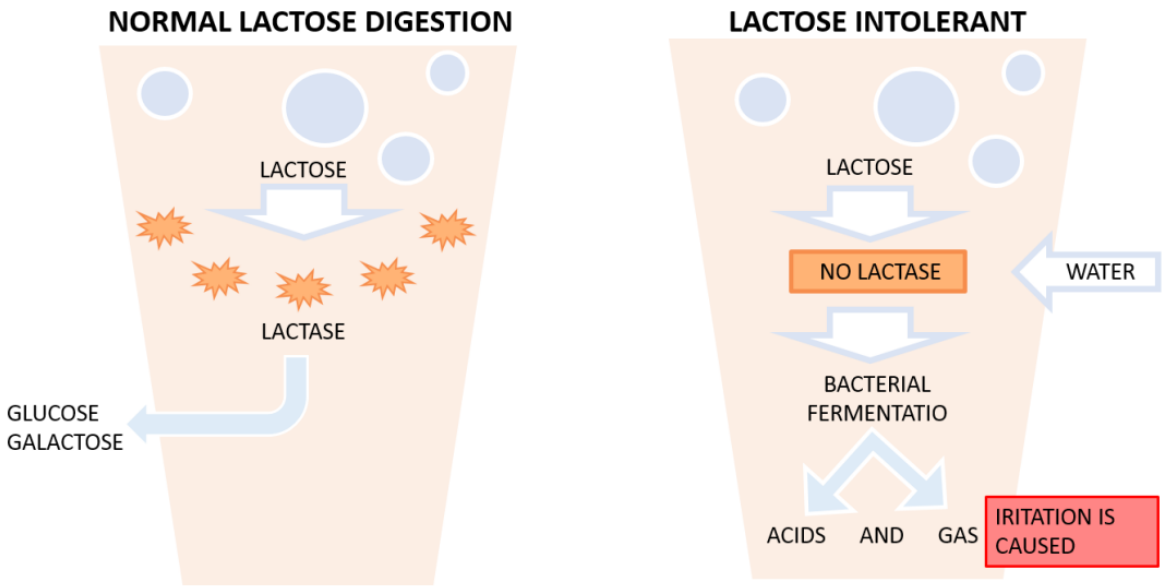
3 morphological features of celiac disease :

1. Atrophy of the villi.
2. Increased intraepithelial Lymphocytes.
3. Elongation of the crypts.

Lactose Intolerance:

Low or absent activity of the enzyme lactase (lactose not absorbed).





Clinical Features :

- Bloating.
- Abdominal discomfort.
- Flatulence.

Starts 1 hour to a few hours after ingestion of milk products

Diagnosis:

Empirical treatment with a lactose-free diet, which results in the resolution of symptoms.

➢ **Hydrogen breath test:**

- An oral dose of lactose is administered
- The sole source of H_2 is bacterial fermentation.
- Unabsorbed lactose makes its way to colonic bacteria, resulting in excess breath H_2.
- Increased exhaled H_2 after lactose ingestion suggests lactose malabsorption.

A 3-week trial of a diet that is free of milk and milk products is a satisfactory trial to diagnose lactose intolerance.

- Lactase enzyme is found on the brush border of enterocytes.
- In lactose intolerance there is absence activity of lactase enzyme, it could be inherited or acquired
- **Xylose Absorption Test :** Xylose is not digested by pancreatic enzymes. It is absorbed through the small intestine or excreted in the urine. If there is abnormality in the small intestine, the Xylose will not be absorbed.

Tropical sprue:

- A chronic and progressive malabsorption syndrome without a definable cause; seen in patients who live or have lived in the **tropics**, and in **absence of other intestinal disease or parasites**.
- The disease occurs mainly in the West Indies and Asia.
- Etiology: unclear; however, the condition is thought to be infective, probably **toxigenic Escherichia coli.**
- Clinical features and histological appearances resemble those of coeliac disease. However, a gluten-free diet has little beneficial effect.

Bacterial overgrowth syndrome:

In this syndrome, there is malabsorption secondary to excessive bacteria in the small intestine, usually the jejunum.

Causes:

- Excessive entry of Bacteria.
- Stagnant region.
- Disturbed motility.
- Defective immune-mechanisms.

Malabsorbtion as a result of:

- Deconjugation of bile salts by the bacteria, hence steatorrhea.
- Damage to the small intestinal mucosa, probably by bacterial products.
- Binding of vitamin B12 by bacteria, hence vitamin B12 deficiency.

Diarrhoea is both secretory (due to bacterial products affecting mucosa) and osmotic (due to unabsorbed products and deficiency of disaccharidases because of mucosal damage).

Cause	Example
Excessive entry of bacteria	Achlorydria Infected bile ducts Gastrocolic fistula Gastric surgery Resection of ileocaecal valve
Defective immune mechanisms	Hypogammaglobulinaemia Malnutrition Old age
Stagnant region	Blind loops Enterocolic fistulae Jejunal diverticula Strictures or other obstruction Continent ileostomy
Disturbed motility	Systemic sclerosis Intestinal pseudo-obstruction Diabetic autonomic neuropathy

Clinical features:

Weight loss, diarrhoea and anaemia (due to vitamin B12 deficiency).

Management:

Antibiotic therapy and surgical resection for a localized abnormality, e.g. stricture, fistula.

Summary of Lactose Intolerance:

- Deficiency/absence of the enzyme lactase in the brush border of the intestinal mucosa → maldigestion and malabsorption of lactose
- Unabsorbed lactose draws water in the intestinal lumen
- In the colon, lactose is metabolized by bacteria to organic acid, CO2 and H2; acid is an irritant and exerts an osmotic effect
- Causes diarrhea, gaseousness, bloating and abdominal cramps

Check Your Understanding

MCQs:

1/A 4-year-old girl is brought to the physician because her parents noticed that she has been having pale, fatty, foul-smelling stools. The patient has short stature. Her symptoms respond dramatically to a gluten-free diet. Which of the following is the most likely diagnosis?

a. Celiac disease
b. Cystic fibrosis of the
c. Ménétrier disease
d. Tropical sprue

2/ A 30-year-old woman presents with 2 days of abdominal cramping and diarrhea. Her temperature is 38°C (101°F), Stool culture shows a toxigenic Escherichia coli infection. Which of the following best explains the pathogenicity of this organism in this patient?

a. Destruction of Peyer's patches
b. Invasion of the mucosa of the colon
c. Invasion of the mucosa of the ileum
d. Stimulation of acute inflammation in the superficial bowel mucosa
e. Stimulation of fluid transport into the lumen of the intestine

3/A 16-year-old girl complains of chronic abdominal distention, flatulence, and diarrhea after drinking milk. Elimination of milk and other dairy products from the patient's diet relieves these symptoms. This example of malabsorption is caused by a functional deficiency of which of the following enzymes associated with the intestinal brush border membrane?

a. Disaccharidase (lactase).
b. Glycogenphosphorylase.
c. Hyaluronidase.
d. Mannosidase.
e. Sphingomyelinase.

1: A 2: E 3: A

SAQs:

Scenario 1 :

A 44-year-old white male presented with a seven-month history of diarrhea. The frequency of his bowel movements had increased to 5-7 per day, and his stools were yellow and floated at the top of the water in the toilet. He had occasional abdominal cramping, but no tenesmus, melena, or bleeding. His appetite was good, but he had experienced gradual weight loss. His bowel movement frequency would decrease upon fasting and would increase with food intake. Stool tests revealed increased stool output with fat excretion of 17 g/d (nl <5 g/d).

Microscopic examination for ova and parasites and cultures for bacterial pathogens and acid-fast bacilli were negative. Blood testing showed mild anemia , hypoproteinemia (4.9 mg/dL), and hypoalbuminemia (3.4 mg/dL).

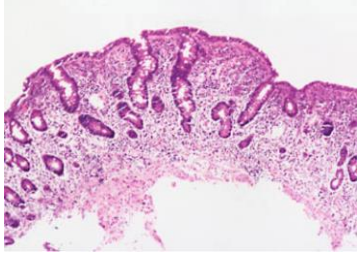
Duodenal biopsy:

1. Exposure to what dietary antigen is thought to be the cause of these changes?
2. What food components contain this antigen?
3. Would these histologic changes resolve with dietary modification?

Scenario 2:

A 6-year-old boy has been brought to outpatients by his mother because he has abdominal pain after some meals. This has been getting increasingly frequent and it sounds, from his description, somewhat colicky (a form of pain which starts and stops abruptly.) in nature. You discover that he has always had very smelly, loose, pale bulky stools, which his parents have put down to the fact that he likes milk. On examination, he is pale, underweight, and of short stature.

1. What are the important differential diagnosis on presentation?
2. Blood tests reveals a mild macrocytic anemia . There is a low level of vitamin B12, and folate is at the lower end of normal. Autoantibody screens reveal a positive reaction to anti-gliadin antibodies. Do these tests help to narrow down the diagnosis?
3. What is your final diagnosis after seeing the duodenal biopsy?
4. What treatment options are available?



Answers of 1st Scenario:

1. Exposure to gluten (specifically, the gliadin constituent of this protein)
2. Wheat, barley, flour, and possibly oats contain gluten.
3. Yes.

Answers of 2nd Scenario:

1. Celiac disease is the most likely diagnosis. Parasitic infection (e.g. giardiasis) and pancreatic insufficiency (e.g. due to chronic pancreatitis or cystic fibrosis) may give rise to a similar presentation, but these are not supported by the results of the investigations.
2. Yes,These results are very suggestive of celiac disease due to the low levels of vitamin B and the hypersensitivity reaction to α-gliadin, a component of gluten. The finding of villous atrophy would support the diagnosis, and this is achieved by endoscopic biopsy of the first part of the duodenum.
3. The final diagnosis is celiac disease, provided the patient's symptoms respond to a gluten-free diet and the histological changes relapse on re-challenge. Such criteria are necessary before confining a patient to a lifelong gluten-free diet.
4. Treatment is by adhering to a strict gluten-free diet.

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قال ﷺ: {من سلك طريقًا يلتمس فيه علمًا سهَّل الله له بهِ طريقًا إلى الجنة}

دعواتنا لكم بالتوفيق