Malabsorption Syndromes in Children

Oxana Turcu, PhD, assistant professor
Department of Pediatrics

**Malabsorption syndromes** include a number of different clinical manifestations, that result in chronic diarrhea, abdominal distention, and failure to thrive.

**Causes of malabsorption**
- congenital
- acquired

Affect one or more of the different steps in the intestinal hydrolysis and subsequent transport of nutrients.

The major site of absorption is the small intestine

**Pathophysiology**
- Carbohydrate, fat, or protein malabsorption is caused by a disorder in the intestinal processes of digestion, transport, or both of these nutrients across the intestinal mucosa into the systemic circulation.
- A congenital abnormality in the digestive or absorptive processes or, more commonly, a secondarily acquired disorder of such processes may result in malabsorption.

**Digestion and absorption**
- **Luminal phase:** dietary fats, proteins and carbohydrates – solubilized by digestive enzymes and bile
  - Deficiency in lipase and proteases leads to lipid and protein malabsorption
- **Mucosal phase:** brush-border hydrolase activity – more common primary or secondary lactase deficiency
- **Postabsorptive phase:** hydrolyzed nutrients are transported via lymphatic and portal circulation
  - Impairs of chylomicrons and lipoproteins may cause fat malabsorption or protein-losing enteropathy

**Absorption of carbohydrates**
- Of the carbohydrates most commonly present in the diet (starches, sucrose, lactose), only starches require preliminary luminal digestion by salivary and, more importantly, pancreatic amylases.
- Despite the slow development of pancreatic amylase, whose secretion reaches adult levels only at 1 year of life, cooked starch malabsorption is rare in infants because of the activity of the brush-border glucoamylase that develops early in life.
- The final hydrolysis of disaccharides and oligosaccharides occurs at the brush border of the enterocytes, where sucrase-isomaltase breaks down maltose, isomaltose (to glucose), and sucrose (to glucose and fructose)
- The entry of the final monosaccharides (glucose, galactose, fructose) into the enterocytes through the brush border occurs via carrier molecules

**Malabsorption of carbohydrate**
Disorders of these processes of carbohydrate absorption
- congenital (cystic fibrosis and Shwachman-Diamond syndrome, which cause amylase deficiency; the extremely rare congenital lactase deficiency; glucose-galactose malabsorption; sucrase-isomaltase deficiency; adult-type hypolactasia)
- acquired (lactose intolerance, typically secondary to a damage of the mucosa, such as a viral enteritis or conditions that cause mucosal atrophy, such as celiac disease).

**Absorption of proteins**
- Proteins are first digested in the stomach, where pepsinogen is activated to pepsins by a pH of less than 4, hydrolyze them in large molecular weight peptides.
- Upon entering the duodenum, the pancreatic proteases (activated by trypsin,) split large peptides into low molecular weight peptides (2-6 amino acid residues) for 70% and of free amino acids for 30%
• Free amino acids are taken up by enterocytes through specific Na-linked carrier systems

Disorders of protein digestion
• **Congenital disorders** of protein digestion (cystic fibrosis, Shwachman-Diamond syndrome, and enterokinase deficiency) cause inadequate intraluminal digestion.
  – No congenital defects have been described in any of the brush border-bound peptidases or in the peptide carrier.
• **Acquired disorders** of protein digestion and/or absorption are nonspecific (they also affect the absorption of carbohydrates and lipids)
  – Damage of absorptive intestinal surface, such as extensive viral enteritis, milk protein allergy enteropathy, and celiac disease.

Absorption of fats
• A lingual lipase is responsible for the first partial hydrolysis of triglycerides; this enzyme becomes active in persons with low gastric pH levels and is active even in premature infants.
• The largest part of triglyceride digestion is accomplished in the duodeno-jejunal lumen because of a complex of pancreatic enzymes – lipase-colipase complex.
  – Like amylase, these enzymes also develop slowly, and this low capacity of babies to absorb lipids, termed physiological steatorrhea of the newborn.
• Additionally, adequate concentrations of intraluminal conjugated bile salts are needed to form micelles, and the secretion of bile acids may also be partially inadequate in very young patients.

Epidemiology
Genetically determined syndromes
• Celiac disease is considered the most common inherited malabsorption syndrome because the documented prevalence is close to 1%.
• Cystic fibrosis is the second most common malabsorption syndrome.
• Other congenital disorders are rare, with the exception of adult-type hypolactasia, which has a prevalence that varies greatly among different ethnic groups.

Acquired syndromes
• Among acquired conditions, cow's (and soy) milk protein allergic enteropathy is very common.
• The prevalence of milk protein allergy, of which enteropathy is one of the presenting clinical symptoms, is estimated to be around 3%.
• A transient and common form of malabsorption in infants results from acute-onset enteritis (mostly viral, specifically rotaviral), which causes transient lactose intolerance

GI tract symptoms
• Abdominal distention and watery diarrhea, with or without mild abdominal pain, associated with skin irritation in the perianal area due to acidic stools are characteristic of carbohydrate malabsorption syndromes.
• Periodic nausea, abdominal distention and pain, and diarrhea are common in patients with chronic *Giardia infections*.
• Vomiting, with moderate-to-severe abdominal pain and bloody stools, is characteristic of protein sensitivity syndromes or other causes of intestinal injury (eg, inflammatory bowel disease).
• Poor appetite is common in food sensitivity syndromes. The child becomes conditioned to refuse foods that cause inflammatory reactions of the intestine (this is typical in celiac disease).
• Malabsorption syndromes not associated with inflammatory reactions typically cause an increase in appetite (eg, cystic fibrosis)

Stool characteristics
• Patients with toddler's diarrhea often have loose stools with undigested food particles. This should not be taken to imply the presence of true malabsorption.
• Frequent loose watery stools may indicate carbohydrate intolerance.
• Pasty or loose foul-smelling stools indicate fat malabsorption, also termed steatorrhea (hepatic and pancreatic dysfunction, and protein sensitivity syndromes).
• Bloody stools are seen in patients with protein sensitivity syndromes.

Differential Diagnoses
• Congenital Microvillus Atrophy
• Constitutional Growth Delay
• Crohn Disease
• Cystic Fibrosis
• Gastroenteritis
• Giardiasis
• Celiac disease
• Irritable Bowel Syndrome
• Lactose Intolerance

Cystic fibrosis

Cystic fibrosis – a multisystem disease, autosomal recessive inheritance, most common lethal genetic disease in Causians
  – 30,000 affected individuals in US
  – 27,000 in Europe

Cause: mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) – chromosome 7
  – Over 1800 genotypes identified, most common F508del

Abnormality in CFTR blocks chloride transport, inadequate hydration results in thick secretion of exocrine glands and organ affection

Clinical manifestation
  • Chronic infection with CF pathogens (Ps.aeruginosa)
  • Bronchial disease
    – Cough/sputum production
    – Air obstruction – wheezing; evidence of obstruction on PFTs
    – Chest x-ray anomalies
    – Digital Clubbing
  • Sinus disease
    – Nasal Polyps
    – CT or x-ray findings of sinus disease
  • Pancreatic insufficiency
    – Pancreatic enzymes stay in ducts and are activated intraductally
      • Autolysis of pancreas
      • Inflammation, calcification, plugging of ducts, fibrosis
    – Malabsorption
      • Failure to thrive
      • Fat soluble vitamin deficiency
  • Intestinal abnormality
    – Meconium ileus (15% newborns with CF)
    – Distal intestinal obstruction syndrome (DIOS)
    – Rectal prolapse
  • Hypoproteic edema
    – Pancreatic endocrine dysfunction
    – Cystic fibrosis related diabetes (children older than 10 years)
  • Cystic fibrosis related liver disease
    • Focal inspissation of bile
      – Obstructs biliary ductules
    • Second leading cause of death in CF
    • Prevalence 9-37%
    • Spectrum of disease
      – increased liver enzymes
      – biliary cirrhosis
      – portal hypertension

Diagnosis

Sweat chloride
Technique first described by Gibson and Cooke in 1950s
- Chemical that stimulates sweating placed under electrode pad; saline under other electrode pad on arm
- Mild electric current is passed between electrodes
- Sweat collected

**Mutation analysis available**
- Varies from screening for most common mutations to sequencing entire CFTR gene

**Cystic fibrosis treatment**
- Airway Clearance
- Infection
- Nutrition
- Gastrointestinal
- Inflammation
- Infertility
- Social Issues

**Celiac disease**
Immune-mediated enteropathy caused by a permanent sensitivity to gluten in genetically susceptible individuals:
- DQ2 and/or DQ8 positive HLA haplotype is necessary but not sufficient

Occurs in symptomatic subjects with gastrointestinal and non-gastrointestinal symptoms, and in some asymptomatic individuals, including those affected by:
- Type 1 diabetes
- Down syndrome
- Selective IgA deficiency
- Williams syndrome
- Turner syndrome
- First degree relatives of individuals with celiac disease

**Clinical Manifestations**
- Gastrointestinal ("classical")
- Non-gastrointestinal ("atypical")
- Asymptomatic
- may be associated with other conditions including:
  - Autoimmune disorders
  - Some syndromes

**Diagnosis**

**Antigliadin Antibodies**
Antibodies (IgG and IgA) to the gluten protein in wheat, rye and barley
Advantages
- relatively cheap & easy to perform
Disadvantages
- poor sensitivity and specificity

**Endomysial Antibody – EMA**
IgA based antibody against reticulin connective tissue around smooth muscle fibers
Advantages
- high sensitivity and specificity
Disadvantages
- false negative in young children
- operator dependent
- expensive & time consuming
- false negative in IgA deficiency

**Tissue Transglutaminase – TTG**
- IgA based antibody against tissue transglutaminase (Celiac Disease autoantigen)
• Advantages
  – high sensitivity and specificity (human TTG)
  – non operator dependent (ELISA/RIA)
  – relatively cheap
• Disadvantages
  – false negative in young children
  – false negative in IgA deficiency
  – possibly less specific than EMA

Treatment
 • Only treatment for celiac disease is a gluten-free diet (GFD)
  – Strict, lifelong diet
  – Avoid:
    • Wheat
    • Rye
    • Barley

Lactose intolerance
 • Lactose intolerance is most common of all the syndromes of carbohydrate malabsorption
 • Types of Lactose intolerance
  – Congenital – very rare
  – Primary – develops after 2 years of age
  – Secondary – usually resolves in 1-2 weeks
  – Developmental lactase deficiency

Lactose intolerance is a clinical syndrome of 1 or more of the following: abdominal pain, diarrhea, nausea, flatulence, and/or bloating after the ingestion of lactose or lactose-containing food substances.
  – The amount of lactose that will cause symptoms varies from individual to individual, depending on the amount of lactose consumed, the degree of lactase deficiency, and the form of food substance in which the lactose is ingested.

Lactose malabsorption is the physiologic problem that manifests as lactose intolerance and is attributable to an imbalance between the amount of ingested lactose and the capacity for lactase to hydrolyze the disaccharide.

Primary lactase deficiency is caused by relative or absolute absence of lactase that develops in childhood at various ages and is the most common cause of lactose malabsorption and lactose intolerance. Primary lactase deficiency is also referred to as adult-type hypolactasia, lactase nonpersistence, hereditary lactase deficiency.

Secondary lactase deficiency results from small bowel injury, such as acute gastroenteritis, persistent diarrhea, small bowel overgrowth, or other causes of injury to the small intestinal mucosa, and can present at any age but is more common in infancy

Congenital lactase deficiency is extremely rare; infants with congenital lactase deficiency would not be expected to survive before the 20th century, when no readily accessible and nutritionally adequate lactose-free human milk substitute was available.

Developmental lactase deficiency is relative lactase deficiency in preterm infants of less than 34 weeks’ gestation.

Clinical presentation
 • Symptoms of lactose intolerance, are independent of the cause of lactose malabsorption and are directly related to the quantity of ingested lactose
  – abdominal distention, flatulence
  – abdominal cramping
  – diarrhea
 • These symptoms are not necessarily correlated with the degree of intestinal lactase deficiency.
 • Malabsorbed lactose generates an osmotic load that draws fluid and electrolytes into the intestinal lumen, leading to loose stool.
  – The onset of diarrhea and other symptoms is related to the amount of lactose that is not absorbed.
**Diagnosis of lactose intolerance**
A good clinical history often reveals a relationship between lactose ingestion and symptoms.
When lactose intolerance is suspected, a lactose-free diet can be tried
- During a diagnostic lactose-free diet, it is important that all sources of lactose be eliminated, requiring the reading of food labels to identify “hidden” sources of lactose.
- Generally, a 2-week trial of a strict lactose-free diet with resolution of symptoms and subsequent reintroduction of dairy foods with recurrence of symptoms can be diagnostic.

In more-subtle cases, the hydrogen breath test is the least invasive and most helpful test to diagnose lactose malabsorption.

**Treatment of lactase deficiency**
Lactose-free and lactose-reduced milks (and lactose-free whole milk for children younger than 2 years):
Lacto-free, NAN lactose-free.
In older children elimination of milk and other dairy products is not usually necessary given newer approaches to lactose intolerance, including the use of partially digested products (such as yogurts, cheeses, products containing *Lactobacillus acidophilus*).
Evidence that avoidance of dairy products may lead to inadequate calcium intake and consequent suboptimal bone mineralization makes these important as alternatives to milk.
Mineral (calcium, iron, zinc) and vitamin (A,B,E,D) supplementation
Dairy products remain principle sources of protein and other nutrients that are essential for growth in children.
Lactase enzymes medication may used.