

Gastrointestinal problems in children with metabolic disorders

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Learning Objectives

- Review common GI problems in children with metabolic disorders
- Understand pathophysiology of some of the problems
- Understand symptoms of GER and GERD
- Recognize precipitating factors of GER and GERD
- Understand medical and surgical management of some of the GI problems

GI Problems of children with Metabolic disorders

- Gastro-esophageal reflux disease (GERD)
- Recurrent Vomiting
- Anorexia
- Nausea
- Chronic swallowing difficulties
- Chronic constipation
- Oral aversion
- Hyperactive gag reflex

Factors contributing to GI Problems in children with Metabolic disorders

- Hypotonia
- Developmental delay
- Dependence of G-tube
 - Oral aversion
 - Hyperactive gag reflex
- High osmotic loads of elemental formulas and dumping
- Medication side effects
- Bad taste and smell of metabolic formulas

Selected metabolic disorders

- Organic acid disorders
 - Propionic acidemia
 - Methylmalonic acidemia
 - Isovaleryl acidemia
- Amino acid disorders
 - Urea cycle defects
- Fatty acid oxidation disorders
 - MADD (Glutaric aciduria II)
- Mitochondrial disorders with GI manifestations
 - Pearson syndrome
 - MNGIE (Mitochondrial neurogastrointestinal encephalomyopathy)

Common presentation of Metabolic disorders

- Biochemical disturbances
 - Metabolic acidosis/alkalosis
 - Hypoglycemia
 - Hyperammonemia
- Poor growth (failure to thrive)
- Developmental delay/hypotonia
- Seizures

Common presentation of Metabolic disorders

- Liver function abnormalities
- Muscle and heart disease
- Intolerance to fasting
- Increased susceptibility to infection
- Bone marrow suppression leading to anemia

Anorexia, Nausea and Vomiting

Anorexia, Nausea and Vomiting

■ Anorexia

- loss of desire to eat, that is a true loss of appetite

■ Nausea

- the unpleasant sensation of the imminent need to vomit
- usually referred to the throat or epigastrium
- Sensation may or may not ultimately lead to the act of vomiting

Anorexia, Nausea and Vomiting

- Vomiting
 - Forceful oral expulsion of gastric contents associated with contraction of the abdominal and chest wall musculature

Why is anorexia, nausea and vomiting common in children with metabolic problems?

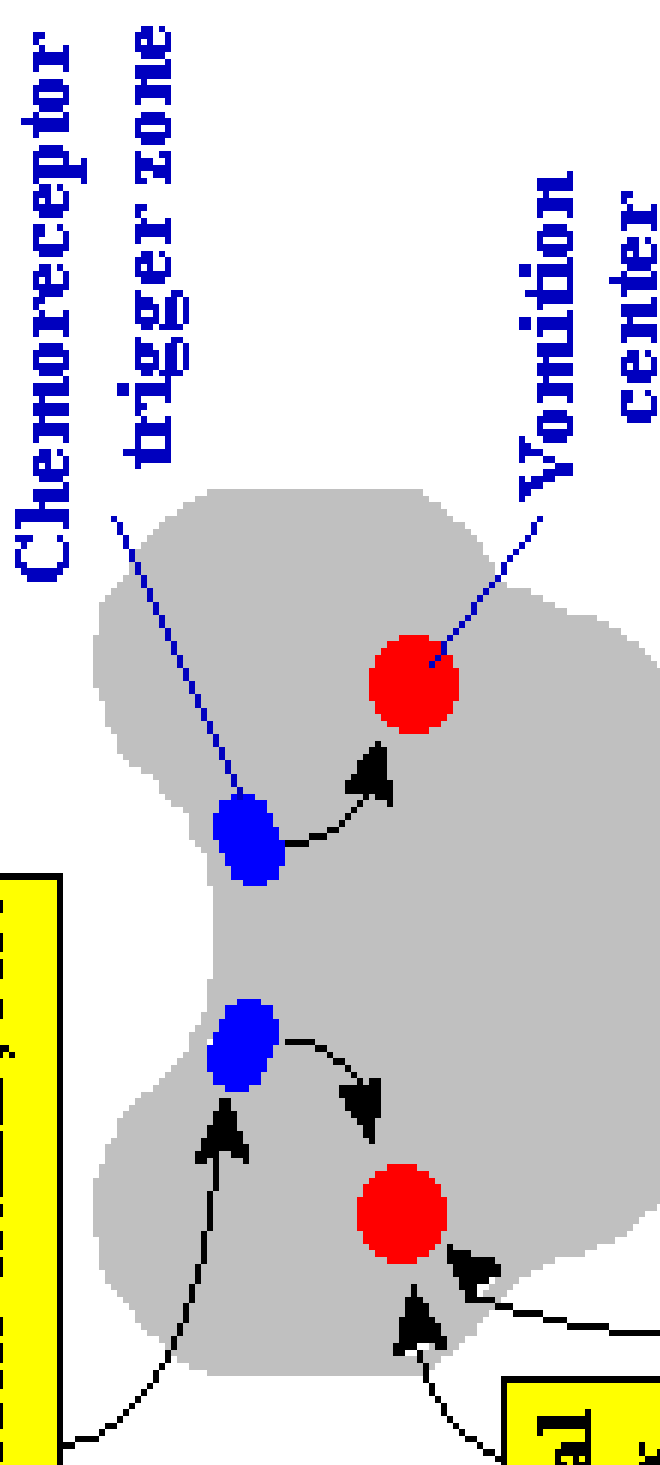
- High ammonia from
 - Organic acid disorders
 - FAOD
 - Urea cycle defects
- Metabolites from underlying disorder
- Gastric motility problems
- Fear of food
- Emotional issues



Pathophysiology

Anorexia, nausea and vomiting

Blood-borne toxins, etc.



Cerebral cortex

**Stomach and other viscera
Vagal and sympathetic afferents**

Pathophysiology

- Brain stem
 - Chemoreceptor trigger zone
 - Blood-borne toxins such as ammonia, etc
 - Vomiting center
 - Cerebral cortex
 - Stomach and other viscera
 - Vagal and sympathetic afferents

Proposed mechanism to explain how high ammonia cause anorexia

- Ammonia is a normal constituent of all body fluids (normal level is $< 35 \mu\text{mol/l}$)
- Excess ammonia excreted as urea by the liver through the urea cycle
- Metabolic disorders that result in build-up of ammonia will lead to problems such as (lethargy, coma, seizures, anorexia encephalopathy, etc.)

Proposed mechanism to explain how high ammonia cause anorexia

- Ammonia increases transport of aromatic amino acids (e.g. tryptophan) across the blood-brain barrier.
- This leads to increase in the level of serotonin
- Results in anorexia
- Preventing hyperammonemia may, in part, minimize anorexia

Vomiting and Gastroesophageal Dysmotility in Children with CNS Disorders

- Ravelli and Milla. 1998 J of Pediatr Gastroenterol Nutr 26:56-63
- 55 children with CNS disorders were studied
 - 50 had retching and/or vomiting (18 cases of fundoplication)
 - 24-hour pH probe and endoscopy
 - Gastric electrical activity by electro-gastrography (EGG)
 - Gastric half-emptying time (T_{1/2}) of a milk meal by electrical impedance tomography

Vomiting and gastroesophageal dysmotility

- 50 vomiting patients
 - 29 had GER
 - 31 had gastric dysrhythmias
 - 12 Tachyarrhythmia
 - 4 Bradyarrhythmia
 - 15 unstable electrical activity
 - 16 patients had GER and gastric dysrhythmia
 - 11/18 patients with fundoplication had gastric dysrhythmia
 - Gastric T1/2 was delayed in 12/13 with gastric dysrhythmia

Vomiting and gastroesophageal dysmotility

■ Conclusions

- Children with CNS disorders who vomit have **abnormal gastric motility** as often as **GER**
- Many patients continue to vomit after fundoplication possibly due to gastric dysrhythmia
- Foregut dysmotility may be related to abnormal modulation of the enteric nervous system by the CNS or to involvement of the enteric nervous system by the same process affecting the brain

Clinical features of 50 vomiting patients with CNS disorder

Symptom	Number	Percent
Retching and/or vomiting	50	100
Failure to thrive	31	62
Respiratory problems	23	46
Constipation	23	46
Non-ambulatory	23	46
Oropharyngeal incoordination	16	32
Spasticity	16	32
Scoliosis	10	20

Management of Nausea and Vomiting

- Recognize and correct complications of vomiting
 - Fluid and electrolyte replacement
 - Correct acid-base and metabolic disturbances
- Find underlying cause of vomiting
- Therapeutic strategies to suppress or eliminate symptoms
 - Mild symptoms – oral antiemetics
 - Severe symptoms – phenothiazines, butyrophenones, metoclopramide

Anti-emetic drugs

- Anti-cholinergics agents
 - Scopolamine – usually for motion sickness
 - Side-effects include dry mouth, drowsiness, vision disturbance
- Antihistamines
 - Benadryl
 - Dramamine
 - Phenergan
 - Side effects include sedation

Anti-emetic drugs

- Dopamine receptor antagonists
 - Phenothiazines
 - Compazine
 - Thorazine
 - Butyrophenones
 - Major tranquilizer
 - Haldol
 - Benzamide
 - Reglan (Metoclopramide)

Anti-emetic drugs

- Serotonin antagonists
 - Used in chemotherapy-induced nausea
 - 3 currently approved in the US
 - Ondansetron
 - Granisetron
 - Dolasetron
 - Favorable toxicity profile
 - Mild headache, constipation, dizziness

Anti-emetic drugs

- Neurokinin receptor antagonists
- Corticosteroids
- Cannabinoids
 - Limited clinical use
 - Modest antiemetic activity
 - Unfavorable side effects
 - Vertigo, xerostomia, hypotension, dysphoria
- Benzodiazepines

Anti-emetic drugs

- Most of these medications are for post-operative and chemotherapy-induced nausea and vomiting
- Has been used in cyclical vomiting
- Few control trials have compared various therapeutic strategies or available pharmacologic agents in the symptomatic therapy of nausea and vomiting

What does this mean for children with metabolic disorders?

- Treat underlying cause
- Side effects of some of these medications may mask symptoms of the disorder we are treating
- There is the need to have trials using some of these medications

Constipation in metabolic disorders

- Definition - A decrease in the frequency of bowel movements or the painful passage of bowel movement
- Very common in all ages – 3 % of pediatric clinic visits; 25% of pediatric gastroenterology visits
- Constipation seen in 46% of children with neurodevelopmental delay

Constipation

- Several factors lead to constipation
 - Hypotonia
 - Intestinal dysmotility
 - Decreased bulk in diet
- Retained stool fills the large intestine (the colon) and cause it to stretch
- An over-stretched colon cannot work properly and therefore more stool is retained

Treatment of Constipation

- Stool softeners – these are not habit-forming and may be taken for a long time without unusual side effects
- Some patients may require “clean-out” to help empty the colon of the large amount of stool
 - Laxatives by mouth, suppositories or enemas for short period of time
- Work with your gastroenterologist

Dumping syndrome

- Hertz in 1913 made the association between postprandial symptoms and gastroenterostomy
- Mix first used the term “dumping” in 1922 after observing radiographically the presence of rapid stomach emptying in patients with vasomotor and GI symptoms
- Symptom complex due large amounts of food passing quickly into the small intestine

Dumping syndrome

- Functions of the stomach
 - Reservoir
 - Initiate digestion
 - Release contents downstream into the duodenum in a controlled fashion
- Alterations in gastric anatomy after surgery or interference in its extrinsic innervation (vagotomy) may have profound effects on gastric emptying

Symptoms of dumping

- Early dumping
 - Occurs 30 to 60 minutes after eating
 - Accelerated gastric emptying of hyperosmolar contents into the small bowel
 - This leads to fluid shift from the blood vessels into the bowel lumen
 - Rapid bowel distention
- Late dumping
 - Occurs 1 to 3 hours after a meal
 - Initial hyperglycemia followed by hypoglycemia (hormone mediated)

Symptoms of dumping

- Early dumping systemic symptoms
 - Desire to lie down
 - Palpitation
 - Fatigue
 - Faintness
 - Syncope
 - Sweating
 - Headche
 - Flushing

Symptoms of dumping

- Early dumping abdominal symptoms
 - Epigastric fullness
 - Abdominal cramps
 - Borborygmi
 - Nausea
 - diarrhea

Symptoms of dumping

- Late dumping
 - Perspiration
 - Shakiness
 - Difficulty in concentration
 - Decreased consciousness
 - Hunger

When do we see dumping in children ?

- After fundoplication
- Generalized autonomic dysfunction
- Malplacement of feeding gastrostomy tube
- After surgery for peptic ulcer

Dumping in FAOD

- “Dumping” has been used to describe hyperglycemic episodes seen in patients with fatty acid oxidation defects during intercurrent illnesses
- Hyperglycemia may be due to stress of hypoglycemia
 - Probably mediated through Epinephrine and Cortisol release
- Should we call this phenomenon “dumping” or not?

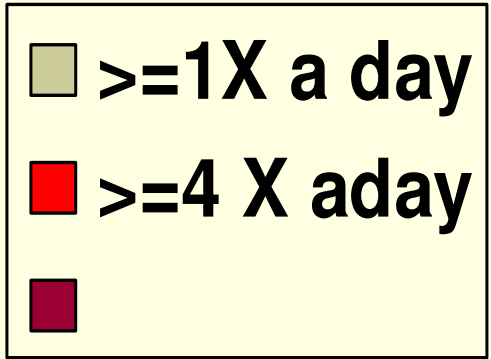
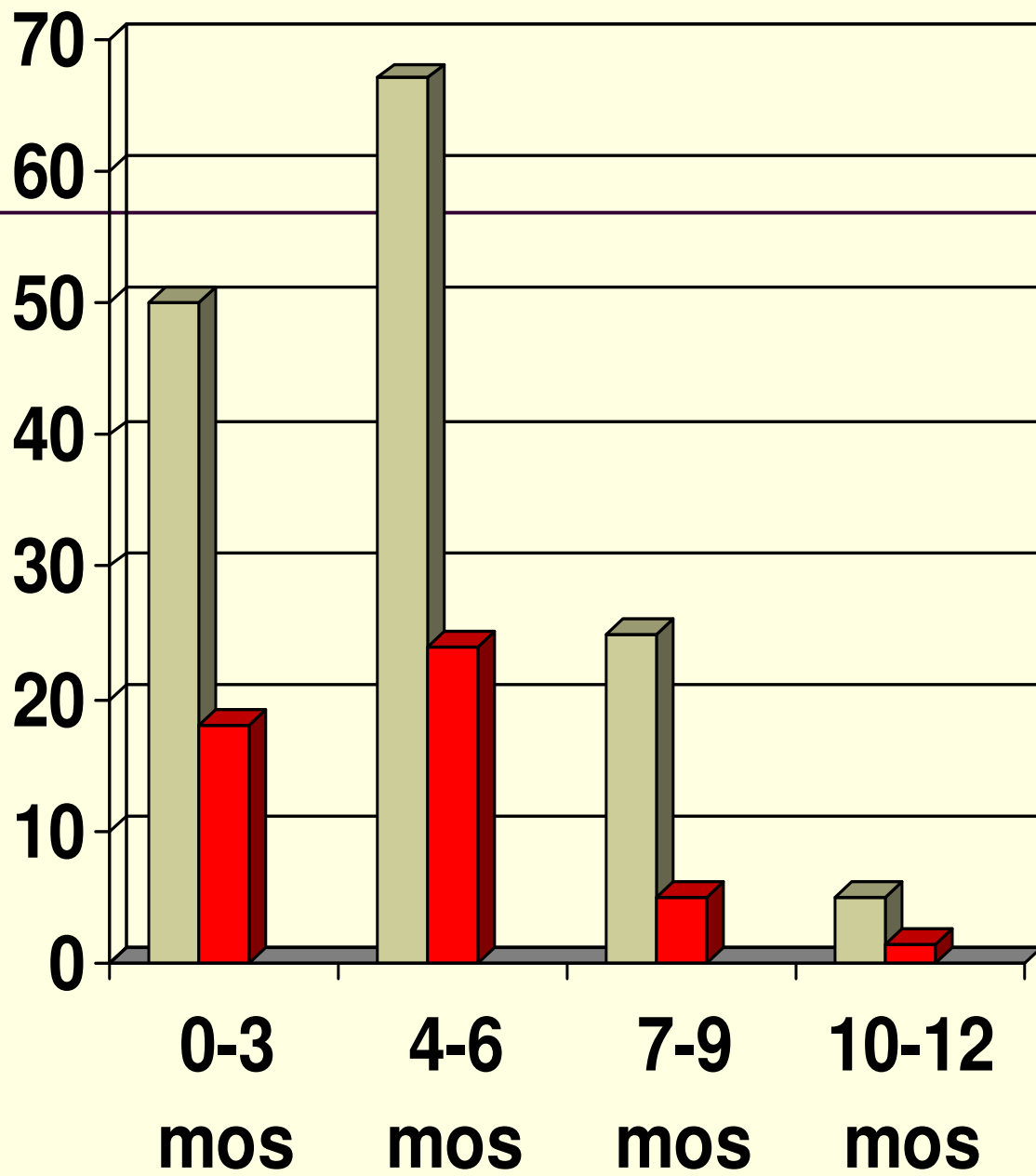
Gastroesophageal reflux

Definitions

- GER - passage of gastric contents into the esophagus
- GERD – symptoms or complications that may occur when gastric contents reflux into the esophagus or oropharynx
- Regurgitation – passage of refluxed gastric content into the oropharynx

Gastro-esophageal reflux

- 40% of healthy infants spit up >1X /day
- Onset is first few weeks of life
- Peaks at 4 months and resolves by 8 to 12 months
- 1 in 300 infants have significant and associated complications



Gastro-esophageal reflux

- Non-pathogenic reflux
 - No weight loss
 - No irritability or behavior problems to suggest esophagitis
 - No respiratory disease or apnea

Gastroesophageal reflux disease (GERD)

- Symptom complex due to reflux of gastric contents through the lower esophageal sphincter into the esophagus
- May cause inflammation and scarring if acid is not cleared quickly

Gastroesophageal reflux disease (GERD)

- Etiology
 - Incompetent lower esophageal sphincter
 - Abdominal position of sphincter
 - Angle of insertion of esophagus into the stomach
 - Low sphincter pressure
 - Higher pressure in stomach than in esophagus
 - Placement of gastrostomy tube encourages reflux
 - Large hiatus hernia in a neurologically impaired children

Risk factors for Gastroesophageal reflux disease

- Neurological disorder
 - Cerebral palsy
- Congenital malformations
 - Esophageal atresia
 - TE fistula
- Severe chronic pulmonary disorders
 - Cystic fibrosis
 - Reactive airway disease

Gastroesophageal reflux disease (GERD)

- Signs and symptoms
 - Usually due to esophagitis
 - Chest pain
 - Irritability
 - Refusing feeds
 - Hyperactive gag reflex
 - Swallowing difficulties
 - Anemia, blood in vomit

Gastroesophageal reflux disease (GERD)

■ Signs and symptoms

■ Aspiration

- Pneumonia
- Wheezing or coughing
- Apnea, cyanotic episodes (turning blue)
- Miscellaneous: stridor, hoarseness, hiccups

■ Failure to thrive

- Vomiting
- Weight loss

Gastroesophageal reflux disease (GERD)

- Neurobehavioral symptoms
 - Infant spells (including seizure-like events)
 - Sandifer syndrome
 - Abnormal behavior
 - posturing with tilting of head to one side
 - Bizarre contortions of trunk

Gastroesophageal reflux disease (GERD)

- Clinical evaluation
 - Referral to Gastroenterologist
 - Upper GI studies
 - pH probe
 - Endoscopy and esophageal biopsy

Upper GI radiography

- Advantage

- Useful for detecting anatomic abnormalities.
 - Pyloric stenosis, malrotation, esophageal stricture, hiatal hernia, etc

- Limitation

- Cannot discriminate between physiologic and non-physiologic GER episodes

Esophageal pH monitoring

■ Advantages

- Detects episodes of reflux
- Determines temporal association between acid GER and symptoms
- Determines effectiveness of esophageal clearance mechanisms
- Assesses adequacy of H₂RA or PPI dosage in unresponsive patients

Esophageal pH monitoring

■ Limitations

- Does not detect non-acid reflux
- Does not detect GER complications associated with “normal” range of GER
- Not useful in detecting association between GER and apnea unless combined with other testing techniques

Endoscopy and esophageal biopsy

■ Advantages

- Enables visualization and biopsy of esophageal lining
- Determines presence of esophagitis, Barrett's esophagus and other complications
- Discriminates between reflux and non-reflux esophagitis

Endoscopy and esophageal biopsy

- Limitations

- Need for sedation or anesthesia
- Correlation between appearance on endoscopy and histopathology findings is poor
- Not useful for extraesophageal GERD

Treatment of Gastroesophageal reflux disease (GERD)

■ Goals

- Control symptoms
 - Alleviate pain or symptoms
 - Diminish frequency of reflux
- Promote healing and growth
- Improve health-related quality of life
- Avoid complications
- Prevent recurrence
- Avoid adverse effects of treatment

Treatment of Gastroesophageal reflux disease (GERD)

- Lifestyle changes
- Pharmacotherapy (drug therapy)
- Surgical therapy
- Combination of above

Lifestyle changes

- Thicken feedings (1 Tbsp rice cereal to 1 oz formula)
- Small, frequent feeding
- Avoid foods and medications that lower the LES tone or increase gastric acidity
 - Fatty foods, citrus, tomato, carbonated drinks, acidic beverages, tobacco smoke
- Place infant in a head-elevated prone position if at all necessary (remember SIDS and lying in prone position)
- Loose fitting clothes
- Avoid obesity

Drug treatment of GERD

- Antacids
- Histamine-2 receptor antagonists
 - Cimetidine, Ranitidine, Famotidine
- Proton pump inhibitors
 - Nexium, Prevacid, Protonix, Prilosec
- Prokinetic agents
 - Reglan

Drug treatment of GERD

- Prokinetic drugs
 - Increases LES tone and helps increase stomach emptying
 - Example:
 - Reglan (causes abdominal cramps, diarrhea, CNS depression, extrapyramidal signs)
 - Propulsid – withdrawn from the market because of heart rhythm problems and deaths.
 - Not effective in treatment of GERD

Drug treatment of Gastroesophageal reflux disease (GERD)

- Antacids
 - Used to neutralize stomach acids
 - Provides symptomatic relief
 - Does not promote healing of esophagitis
 - Examples: Maalox, Mylanta, Carafate

Drug Treatment of GERD

- H2 receptor antagonists
 - Partial suppression of stomach acid secretion
 - Examples: Cimetidine, Famotidine, Ranitidine

- Proton Pump inhibitors
 - Inhibits acid secretion
 - Examples: Nexium, Prevacid, Protonix, Prilosec

Surgical treatment of GERD

- Nissen fundoplication
 - Wrap upper part of stomach around the lower esophagus (like hotdog in a bun)
 - Complete versus loose wrap ± gastrostomy ± pyloroplasty
- Gastrojejunostomy feedings (also usually requires pharmacotherapy)

Treatment of GERD in neurologically impaired children

- These patients are often resistant to standard medical therapy
- Surgical options
 - Nissen fundoplication
 - Gastrostomy or gastro-jejunostomy
- Surgery associated with high risk of complications and revisions

Summary

- Gastrointestinal problems are common in children with metabolic problems
- They could be a major source of morbidity
- Early recognition of problems are very important in management in hopes of minimizing complications and ensure growth
- Multi-disciplinary team approach
 - Metabolic specialists
 - Gastroenterologists
 - Metabolic nutritionists
 - Speech, Occupational and physical therapists
 - Behavioral therapists

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