

***MITO 101 – Gastroenterology***

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## Gastroenterology

- 1) GERD
- 2) Cyclic Vomiting Syndrome (CVS)
- 3) Constipation
- 4) Motility

## GI Key points

- Gastrointestinal problems are a common feature of mitochondrial disease, but not all patients with mitochondrial disease develop gastrointestinal problems.
- The gastrointestinal problem is often seen early in the course and may be isolated for many years, when other symptoms may develop into a multi-system mitochondrial disorder.
- Gastrointestinal symptoms in mitochondrial disease often require medical and/or surgical management, but the severity can range from mild to severe.
- Gastrointestinal problems commonly encountered in mitochondrial disorders include: Gastroesophageal Reflux, Cyclic Vomiting Syndrome, Constipation, and Motility problems, but also include exocrine pancreatic insufficiency, hepatic insufficiency or failure, dysphagia, and diarrhea.
- In some mitochondrial disorders, such as Alpers syndrome, MNGIE, and Pearsons syndrome, GI symptoms are the cardinal features, but they have been documented in many other mitochondrial disorders, including various respiratory chain deficiencies and mtDNA point mutations
- The common underlying pathophysiologic mechanism causing this broad range of symptoms is neuromuscular dysfunction affecting peristalsis.

## GERD (gastro-esophageal reflux disease)

### GERD Key points:

- GER occurs when stomach contents back up into the esophagus due to opening of the LES (lower esophageal sphincter)
- GER is common in infants due to LES immaturity, but most children grow out of it by 1-2 years old
- GER may cause vomiting, coughing, hoarseness, painful swallowing, irritability, poor feeding, blood in the stools, poor growth, recurrent pneumonia, wheezing, breathing problems, hoarse/raspy voice, sore throat.
- Evaluation is necessary if symptoms persist or worsen
- Treatment depends on the symptoms and age and may include changes in eating habits/formula, medications, or surgery.

### GERD Red Flags:

- Persistent frequent vomiting: forceful, coordinated, retch/gag/vomit. (normal refluxers may gag and vomit a couple of times/day.)
- Bilious vomiting
- Abdominal distention
- Weight loss/failure to thrive

- Poor weight gain
- Respiratory symptoms

#### Diagnostic Testing for Complicated GER:

- Upper GI: Useful to detect anatomic abnormalities (pyloric stenosis, malrotation, hiatal hernia, annular pancreas and esophageal stricture) but not sensitive or specific for GER
- Milk Scan (young children) or Cookie Swallow (older children): advisable if respiratory symptoms are present; rules out aspiration, swallowing incoordination, and tracheo-esophageal fistula.
- Esophageal pH Monitoring:
  - Not used routinely.
  - Reliable and valid measurement of acid reflux.
  - Measures temporal relationship of reflux and patient symptoms.
  - Can assess response to therapy.
  - May be normal in some patients with respiratory complications.
- Endoscopy with biopsy:
  - Used to evaluate complicated/unresponsive GER.
  - Assesses degree of esophagitis, eosinophilic esophagitis or (rarely) Barrett's esophagus

#### GERD Treatment:

##### Initial Management of Uncomplicated GER

- Patient Education: eat more frequent smaller meals, avoid eating 2 to 3 hours before bed, raise the head of the bed 6 to 8 inches by putting blocks of wood under the bedposts; avoid carbonated drinks, chocolate, caffeine, and foods that are high in fat or contain a lot of acid (citrus fruits) or spices.
- consider changing formula or thickening formula in infants

##### Medical Management of GER

- H<sub>2</sub>-blockers (H<sub>2</sub>- receptor agonists): cimetidine (Tagamet), ranitidine (Zantac), famotidine (Pepcid), nizatidine (Axid)
- proton-pump inhibitors (PPIs): esomeprazole (Nexium), omeprazole (Prilosec), lansoprazole (Prevacid), rabeprazole (Aciphex), pantoprazole (Protonix)
- Prokinetic agents (alone or in combination with acid reducers): metoclopramide (Reglan), cisapride (Propulsid), erythromycin (DisperTab, Robimycin), bethanechol (Duvoid, Urecholine).

##### Surgical Management of GER

- Surgical Therapy: Nissen fundoplication
- Considered when other treatment options have failed and complications persist (hiatal hernia, ulcers, high risk of aspiration in a neurologically impaired child).
- Usually effective initially (60-90%).
- Up to 50% may still require medications

- Complications: may need to be repeated, gas, bloating, can't vomit, dumping syndrome, small bowel obstruction or perforation.

### Cyclic Vomiting Syndrome (CVS)

#### CVS Key points:

- Cyclic vomiting syndrome (CVS) is a disorder characterized by stereotypical recurrent, discrete, self-limited episodes of vomiting. There must be a pattern or cycle identified.
- Severe nausea and vomiting can last for hours or days and alternate with longer periods of no symptoms.
- CVS occurs mostly in children (usually starts between 3-7 years old), but the disorder can also affect adults
- In adults, the episodes may be less frequent but last longer; triggers may be more easily identifiable in adults
- CVS has no known cause; it may be linked to migraine because many children with CVS either have a family history of migraine or develop migraines as they grow older; in addition, it may be secondary to metabolic disease or mitochondrial disorder.
- Triggers include: infection, emotional stress or excitement, certain foods, hot weather, physical exhaustion, menstruation, and motion sickness (triggers are similar to those of migraine headaches)
- Other symptoms can include: sensitivity to light, headache, fever, dizziness, diarrhea, and abdominal pain.
- Episodes usually last anywhere from 1 to 5 days, though they can last for up to 10 days.
- The Four Phases of CVS
  - Prodrome: signals that an episode of nausea and vomiting is about to begin, often with abdominal pain.
  - Episode: nausea and vomiting; inability to eat, drink, or take medicines without vomiting; paleness; drowsiness; exhaustion.
  - Recovery: the nausea and vomiting stop. Healthy color, appetite, and energy return.
  - Symptom-free interval: the period between episodes when no symptoms are present

#### Diagnostic Testing (preferentially during a crisis):

- electrolytes, AST/ALT, amylase/lipase, and glucose
- abdominal ultrasound to rule out transient hydronephrosis
- consider screening metabolic labs, including plasma amino acids, acylcarnitines, lactate, pyruvate, ammonia and urine organic acids
- typical lab findings of CVS include:

- mild-to-moderate degrees of an anion gap metabolic acidosis (calculated serum  $\text{Na}^+$  minus  $\text{Cl}^-$  minus  $\text{HCO}_3^-$  is often 15-20 mg/dl)
- lactic acidosis
- urinary ketosis (early in an episode and thus not a direct result of fasting)
- hypoglycemia

CVS Red flags (higher risk for neurometabolic disease):

1) Bilious vomiting, severe abdominal pain, hematemesis:

- rule out intermittent bowel obstruction, hepatitis and gallbladder disease, pancreatitis, uretero-pelvic junction obstruction

2) Attacks precipitated by intercurrent illness, fasting and/or high protein meal

- partial enzymatic defects of urea cycle enzyme deficiencies (marked by elevated plasma ammonia level of  $\geq 150 \mu\text{m/L}$  when symptomatic); amino and organic acidemias (marked clinically by altered mental status with possible history of developmental and growth delay, with a severe anion gap metabolic acidosis, substantial ketosis, and/or an unusual odor); fatty acid oxidation disorders (i.e. MCAD): serum amino acids, urine organic acids, plasma acylcarnitines, urine acylglycines
- mitochondrial disease; vomiting episodes associated with a severe anion gap metabolic acidosis ( $> 20 \text{ mg/dl}$ ), insulin-resistance, and/or multi-system failure (e.g. cardiomyopathy, seizures etc.), occasionally associated with a positive family history in maternal relatives

3) Abrupt resolution of symptoms after receiving dextrose-containing IV fluids.

Such a response may be indicative of an underlying disorder of metabolism

4) Abnormalities on neurologic exam including severe alteration of mental status, abnormal eye movements, papilledema, motor asymmetry and/or gait abnormality (ataxia).

- Progressive or focal neurological findings, new-onset ataxia, abnormal eye movements, papilledema, motor asymmetry, gait abnormality, developmental regression, or recent personality changes may indicate increased intracranial pressure (from a structural abnormality) or a metabolic disorder.
- "CVS+": global developmental delay, generalized seizures, hypotonia associated with CVS: earlier age of onset for vomiting episodes, increased prevalence for certain dysautonomia-related (migraine, chronic fatigue, regional pain syndromes) and constitutional (growth retardation and birth defects) disorders; indication for further evaluation with serum amino acids and urine organic acids (early in an episode)

CVS Treatment:

- Episode: Severe nausea and vomiting may require hospitalization and intravenous fluids to prevent dehydration; ondansetron (Zofran); sleep (aided by lorazepam or diphenhydramine): MAY NEED TO PROVIDE A LETTER TO THE ER TO ENSURE PATIENT RECEIVES PROMPT AND THOROUGH TREATMENT

- Prodrome: ibuprofen, ranitidine (Zantac), omeprazole (Prilosec)
- Recovery: rehydration and refeeding
- Prevention of episodes, especially if frequent or severe, can be achieved with migraine prophylaxis medications: propranolol, cyproheptadine, and amitriptyline are most commonly prescribed; carnitine and coenzyme Q10 have been used; lifestyle issues such as regular sleep, meals, hydration, exercise and stress-management; frequent snacking of high carbohydrate foods and the avoidance of stress (fasting, dehydration, over-exertion, environmental temperature extremes, etc.): keeping an episode diary to note potential triggers
- Treatment/prevention of complications including: dehydration, electrolyte imbalance, esophagitis, hematemesis, Mallory-Weiss tear, tooth decay.

## Constipation

### Constipation Key points:

- Common causes include: lack of fiber in the diet, lack of physical activity, medications (narcotics, antacids that contain aluminum and calcium, blood pressure medications/calcium channel blockers, antiparkinson drugs, antispasmodics, antidepressants, iron supplements, diuretics, anticonvulsants), milk, irritable bowel syndrome, changes in life or routine such as pregnancy, aging, and travel, abuse of laxatives, ignoring the urge to have a bowel movement, dehydration.
- specific diseases or conditions, such as neurological disorders: stroke, Parkinson's disease; chronic idiopathic intestinal pseudo-obstruction, diabetes, hypothyroidism; dysmotility.
- Symptoms of constipation include: no bowel movement for several days (fewer than 3 times per week) or daily bowel movements that are hard and dry and difficult to pass, usually associated with cramping abdominal pain, straining, bloating, feeling of fullness, nausea and/or vomiting; weight loss, liquid or solid, clay-like stool in the underwear—a sign that stool is backed up in the rectum

### Constipation Red Flags:

- episodes of constipation last longer than 3 weeks
- the patient is unable to participate in normal activities
- small, painful tears appear in the skin around the anus
- a small amount of the intestinal lining is pushed out of the anus (hemorrhoids)
- normal pushing is not enough to expel stool

- liquid or soft stool leaks out of the anus

#### Treatment:

- Increasing fiber, liquids, and exercise; regular toileting
- Medications: bulk-forming (Metamucil, Citrucel) , stimulants (Correctol, Dulcolax, Senokot), osmotics (Sorbitol, Miralax), stool softeners (Colace) lubricants (Fleet), saline laxatives ( Milk of Magnesia), or chloride channel activators (Amitiza)
- Removal of causative medication if possible
- Weaning of laxatives
- Surgery if necessary

#### Motility/Dysmotility (abnormal motility):

##### Motility Key points:

- A collection of digestive disorders: range from 'mild' (functional) disorders to severe disorders (failure or paralysis of gut requiring parenteral feedings)
- result from varying degrees of neuromuscular dysfunction of the digestive tract; named for area of dysfunction: esophagus (achalasia), stomach (gastroparesis or delayed gastric emptying), intestinal (CIPO: Chronic Intestinal Pseudo-obstruction)
- may be due to a GI neuropathy (nerves to the GI tract are part of the autonomic nervous system and therefore; GI symptoms may be part of a systemic dysautonomia: flushing, fluctuations in temperature, heart rate and blood pressure,
- or GI myopathy
- may be secondary (to another disease or medication)
- may occur following infection, especially GI virus
- may cause bacterial infections, malnutrition, bladder problems.

##### Motility Evaluation:

- manometry studies can determine area of GI tract that has dysmotility and whether problem is neuropathy or myopathy

##### Motility Treatments:

- nutritional support (intravenous nutrition/TPN or tube feeding) to prevent malnutrition
- antibiotics to treat bacterial infections or bacterial overgrowth
- Retching/vomiting: slowing down feeds or decreasing volume for bolus feeds or switching to continuous feeding
- Venting if tube fed
- Promotility drugs (erythromycin, Reglan, Domperidone, octreotide)

- Surgery: decompression , resection, transplantation

## References:

### All GI topics:

#### National Digestive Diseases Information Clearinghouse

2 Information Way  
Bethesda, MD 20892-3570  
Phone: 1-800-891-5389  
Fax: 703-738-4929  
Email: [nddic@info.niddk.nih.gov](mailto:nddic@info.niddk.nih.gov)  
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### Cyclic Vomiting:

Cyclic Vomiting Syndrome Association USA/Canada [www.cvsaonline.edu](http://www.cvsaonline.edu)

The North American Society for Pediatric Gastroenterology, Hepatology and Nutrition Guideline for the Diagnosis and Management of Cyclic Vomiting Syndrome

Task Force:

B U.K. Li, Frank Lefevre, Gisela G. Chelimsky, Richard G. Boles, Suzanne P. Nelson, Donald W. Lewis, Steve L.Linder, Robert M. Issenman, Colin D. Rudolph

Boles RG, Adams K, Ito M, Li BU. Maternal inheritance in cyclic vomiting syndrome with neuromuscular disease. *Am J Med Genet A* 2003;120(4):474-82.

Boles RG, Adams K, Li BU. Maternal inheritance in cyclic vomiting syndrome. *Am J Med Genet A* 2005;133(1):71-7.

CVS Clinic  
Cleveland Clinic  
9500 Euclid Ave  
Cleveland, OH  
<http://cms.clevelandclinic.org/neuroscience/body.cfm?id=961>

### Reflux:

North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN)  
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NASPGHAN's Children's Digestive Health and Nutrition Foundation (CDHNF)  
Internet: [www.CDHNF.org](http://www.CDHNF.org)  
[www.KidsAcidReflux.org](http://www.KidsAcidReflux.org)  
[www.TeensAcidReflux.org](http://www.TeensAcidReflux.org)

## Motility:

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