Cyclic vomiting syndrome

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Introduction:

- An idiopathic disorder with recurrent discrete episodes of vomiting.
- CVS is no longer considered to be rare in children or adults.
- The prevalence : 1.9 to 2.3 percent, with an incidence of 3.2 per 100,000 population.
- The average age: 9.6 years at the time of diagnosis
- The average age at the onset of symptoms : 5.3 years.
- More common in girls than boys (55:45).

- Highly associated with a history of migraines, either in the patient (especially in children) or a maternal family member (72 to 82 percent) .

PATHOGENESIS

- Multifactorial, with several potential pathways.
- An association between CVS and **migraine headaches** in children and adults.
- ✓ Similar temporal patterns and triggers to chronic migraine, epilepsy, panic disorder.
- **Autonomic abnormalities** (elevated sympathetic tone and impaired parasympathetic regulation),
- **Hypothalamic-pituitary-adrenal activation** (Sato variant),
- **Mitochondrial dysfunction**,
- **Cannabis use**,
- **Menses** (estrogen sensitivity),
- **Food allergy**.

CLINICAL MANIFESTATIONS

- **The essential features:**
- ✓ Recurring episodes of vomiting,
- ✓ A stereotypical pattern regarding time of onset and duration,
- ✓ Accompanying symptoms and signs (eg, pallor, lethargy),
- ✓ The absence of vomiting between episodes .
- **Other common features:**
- ✓ A history of migraine headaches (patient or family member);
- ✓ The self-limited nature of the attacks;
- ✓ Associated symptoms of nausea, abdominal pain, headache, motion sickness, and photophobia;
- ✓ Associated signs of profound lethargy and pallor , excess salivation, diarrhea, dehydration, and social withdrawal.

Children and adolescents:

- The specific pattern of vomiting episodes is variable .
- Remain stereotypical for an individual patient .
- Begin in the early morning hours (2:00 to 7:00 AM) .
- A prodromal period : pallor, anorexia, nausea, abdominal pain, and/or lethargy .
- Usually last an average of 24 to 48 hours (up to 7 to 10 days) .
- Regular intervals in one-half of children: every two to four weeks
- Unpredictable intervals in the remainder
- Approximately 3/4 of parents can identify triggers (psychological or infectious)
- Multiple comorbid conditions that affect the patient even between vomiting episodes .

- **Anxiety :** the most prevalent comorbidity ,
  - ✓ 47 percent of (59 percent of school-aged) children with CVS .
  - ✓ The lower health-related quality of life correlated with trait anxiety and coping abilities rather than with medical severity.
- **Postural orthostatic tachycardia syndrome (POTS):** adolescents
  - ✓ Altered autonomic tone at baseline with elevated sympathetic tone and low to normal parasympathetic tone .
- **Coalescent CVS:** chronic daily nausea between vomiting episodes later in the course of disease.
  - ✓ The nausea typically peaks in the morning,
  - ✓ most common in adolescent girls .
  - ✓ Some: the episodic vomiting and the persisting nausea (diagnosed as functional nausea).

NATURAL HISTORY

- Many children outgrow CVS by their preteen or early teenage years.
- Up to 75 percent of children: migraine headaches by age 18 .
- Some of them will first pass through a phase of abdominal migraines .
- Abdominal migraines: the core symptom is abdominal pain, with little or no vomiting.
- Both syndromes may have headache as a feature and respond to antimigraine therapy .

DIAGNOSIS

- Based on the clinical history and exclusion of alternative diagnoses .
- Two sets of criteria based upon a consensus of experts:
- **Pediatric criteria** – by the NASPGHAN :

✓ At least five attacks in any interval or a minimum of three attacks during a six-month period;

✓ Episodic attacks of intense nausea and vomiting lasting one hour to 10 days and occurring at least one week apart;

✓ Stereotypical pattern and symptoms in the individual patient;

✓ Vomiting: at least four times per hour for at least one hour;

✓ Return to baseline health between episodes;

✓ Not attributed to another disorder.

- **Pediatric Rome IV criteria:**
  - ✓ A minimum of two episodes and
  - ✓ Eliminating the quantitative severity of vomiting of as least four times per hour at the peak.
  - ✓ A higher sensitivity but possibly lower specificity than the NASPGHAN criteria.

- **Exclusion of other causes of vomiting** – CVS should be considered among other diagnoses in patients presenting with nausea and vomiting.

- **Alarm symptoms and signs** – Alarm symptoms and signs alerting the clinician to a diagnosis other than CVS include the following;

- **Gastrointestinal:** Gastrointestinal bleeding
  Unilateral abdominal pain
  Bilious vomiting
  Weight loss
- **Metabolic:** In toddlers, episodes triggered by fasting, illness, or high-protein meal, or by marked anion gap acidosis, hypoglycemia, or hyperammonemia.

- **Neurologic:** Severe headaches (continuous or worsening)
  Altered mental status
  Gait disturbances or other new neurologic signs
- **Other:** Severe clinical course (failure to respond to treatment, progressive worsening, prolonged episodes requiring hospitalization)

A change in the vomiting pattern or symptoms

Alarm signs absent

- The typical symptoms with no warning symptoms: only a limited screening evaluation to exclude other disorders.
- ✓ **Imaging –** An upper gastrointestinal series: to exclude intestinal malrotation or nonfixation with possible intermittent volvulus .
- ✓ **Laboratory testing –** During at least one episode
  - Electrolytes, glucose, BUN, creatinine, and urinalysis.
  - Monitor for hypovolemia and electrolyte disturbances (result from protracted vomiting), and chronic kidney disease or Addison disease.
  - Mild metabolic acidosis, hypoglycemia, and ketosis are consistent with CVS.
  - Severe acidosis or hypoglycemia: further evaluation for an inborn error of metabolism, especially in infants and toddlers.

- ✓ Trial of prophylactic therapy – For patients whose symptoms warrant a trial of prophylactic therapy, the diagnosis of CVS is further supported if the CVS improves.
- ○ Do not respond to prophylactic therapy : further evaluation

- ☸ No alarm signs and typical symptoms: a provisional diagnosis of CVS can be made on the basis of the clinical history and basic testing outlined above.
- ☸ An extensive evaluation is not recommended because of low yield and high costs .
- ☸ A more cost-effective diagnostic strategy in children :
- ✓ An upper gastrointestinal series to rule out malrotation and the possibility of subsequent volvulus,
- ✓ Followed by a two-month trial of antimigraine therapy, with further studies reserved for those with continued symptoms .

Alarm signs present

- **Acute-onset unilateral or flank pain:** an abdominal ultrasound to exclude acute hydronephrosis .
- **Metabolic warning signs:** measure serum concentrations of lactate, pyruvate, ammonia and serum amino acids, and urine organic acids.
  - performed during the early part of the episode, prior to administration of intravenous fluids.
- **Neurologic signs:** MRI of the brain and/or evaluation for epilepsy.
- **Upper gastrointestinal bleeding :** an endoscopic evaluation in severe or persistent GIB.
- **Upper GI symptoms** that persist between episodes : Perform an upper endoscopy between episodes.

MANAGEMENT

- **Lifestyle interventions:** to reduce the risk of inducing an attack and improve self-efficacy and quality of life.
- **Supportive care:** provided during any severe bout of cyclic vomiting.
- **Abortive medication:** during the prodrome to prevent or attenuate the attack.
  - Sufficient for patients with relatively mild or infrequent symptoms and, if possible, should be initiated at home.
- **Prophylactic medication:** given daily to prevent further episodes.
  - For patients with frequent prolonged or severe symptoms.

  - Referral to a pediatric cnsultant, pediatric gastroenterologist, neurologist, or metabolic specialist:
    - ✓ frequent or severe disabling episodes
    - ✓ mild episodes that persist despite lifestyle changes, supportive care, and a therapeutic trial.

Lifestyle interventions:

- Adequate fluid intake, avoidance of fasting, using long-acting caloric snacks, good sleep hygiene, and regular exercise.
- Recognized precipitating factors should be avoided whenever feasible.
- physical exhaustion from lack of sleep, stressors such as bullying at school, motion (car rides, amusement park rides), fasting, and certain foods (eg, chocolate, cheese, cow's milk).
- Management should address comorbid conditions as well.
- ✓ First among them is anxiety, panic attacks, or depression
- Referral to a medical psychologist for cognitive behavioral therapy
- In more severe cases, the addition of anxiolytic agents (citalopram, sertraline) may be necessary.

Supportive care and antiemetics :

- During an episode of vomiting to alleviate symptoms and complications.
- alleviating symptoms including vomiting, nausea, abdominal pain, and headache and replenishing fluid, energy, and electrolytes.
- The following strategies are often used:
- **Intravenous hydration** –decrease the frequency of vomiting and duration of episodes in one-half of patients.
  - First, hypovolemia should be corrected (one or more fluid boluses),
  - Subsequently or simultaneously (piggy-backed), additional intravenous hydration (half-normal saline with 10% dextrose) .
  - Dextrose: attenuate the catabolic state and ketosis induced by the acute CVS episode, which can prolong vomiting.

- Significant electrolyte derangements (hypokalemia, hypochloremia, and hyponatremia): adjustments to intravenous fluids.
- Persistent moderate to severe anion gap acidosis or hypoglycemia: further evaluation for a metabolic disorder.

- **Environment** – Some patients benefit from staying in a quiet, dark room with limited vital sign checks to reduce sensory stimulation, which can exacerbate episodes.
- **Feeding** – Provision of calories during the emetic phase is thought to help children with mitochondrial variants of CVS and suspected disorders of carbohydrate or fat metabolism.
- However, most children can only tolerate delivery by parenteral or jejunal routes.
- After ceasing vomiting: initiation of frequent small feedings with low-fat foods for nutritional recovery.

- **Antiemetics**
- **Ondansetron –**recommended for use in emergency and inpatient settings to reduce the frequency of emesis and fluid requirements .
  - Parenteral ondansetron, even if administered early, may attenuate the vomiting but usually does not abort the episode .
  - Dosing for ondansetron is:
  - Children – 0.3 mg/kg/dose, up to a maximum of 8 mg.
  - May give an additional dose every four to six hours, with a maximum total dose of 32 mg/24 hours.
  - Use with caution in patients with risk factors for QTc prolangation: other medications that also prolong the QT interval (TCA and phenothiazine antiemetics) or family history of sudden death.
- **Fosaprepitant** – an alternative to intravenous ondansetron as it appears to be more effective with fewer side effects.

- **Sedating agents** – Because vomiting is not completely controlled by a 5-HT_3 antagonist therapy alone.
  - Both antiemetic and sedating effects: diphenhydramine or lorazepam
  - Clinical observations: induction of deep sleep may alleviate both nausea and vomiting in some cases or stop episodes already in progress.

  - Occasionally, administration of benzodiazepines or use of closely monitored general anesthesia will terminate an episode.
  - The efficacy is also supported by experience with these drugs in other settings (eg, chemotherapy-induced nausea and vomiting, postoperative nausea and vomiting, cannabinoid hyperemesis) .

  - In pediatric practice: begin with diphenhydramine and if sedation is inadequate switch to lorazepam.

- **Antihypertensives** – A small subset of patients (the Sato variant) may present with more severe and persistent hypertension .
  - If pharmacologic therapy is needed for such patients, short-acting antihypertensives can be used as needed during the episode.
  - Prolonged use of antihypertensives is not necessary.

- ●**Other medications** – Management of abdominal and headache pain usually begins with the NSAIDs drug intravenous ketorolac.
  - It reduces elevated prostaglandin E2.
  - Oral or intravenous acetaminophen : less effective than ketorolac.
  - If possible, narcotics should be avoided as they can worsen vomiting and induce dependence over time.
  - A variety of other antiemetic medications: high dose dexamethasone, metoclopramide, and naloxan .
  - Usually unsuccessful .

Abortive medications

- **For prodrome**
- Promptly after the patient presents to the emergency department.
- Patients with delayed intervention: more likely to require hospital admission .
- Abortive therapy alone: in relatively mild or infrequent episodes.
- Frequent or severe symptoms: in conjunction with ongoing prophylactic therapy.
- The primary choice: sumatriptan and aprepitant (a neurokinin 1 antagonist)

- **Sumatriptan** –moderately effective if given early in the prodromal phase and some effect if given within one hour after onset of vomiting.
- More effective when the episodes are shorter in duration (<1 day)
- First do a trial by the intranasal route.
- If symptoms persist: repeated dose in two hours.
- If intranasal administration fails: a trial of a subcutaneous sumatriptan injection during the next episode of vomiting, repeated dose in one hours
- Contraindication: coronary or peripheral vascular disease and complex (eg, basilar) migraines.

- **Aprepitant** – As an alternative, oral neurokinin 1 antagonist.
- Particularly appropriate for patients with no family history of migraine or who failed to respond to triptans.

Prophylactic medications :

- More than monthly or last more than one to two days in a child or adolescent,
- Severe enough to require hospitalization
- Cause substantial school absenteeism or work disability.
- Abortive therapy in addition to prophylactic therapy for patients who continue to have breakthrough vomiting episodes.
- **Prophylactic agents :**
- Antimigraine agents: cyproheptadine, pizotifen, propranolol, amitriptyline, nortriptyline, mirtazapine .
- Antiemetics: ondansetrone, aprepitant
- Anticonvulsants: topiramate, phenobarbital .
- Adjunctive treatment: mitochondrial supplements.

- Selection among them: side effects and toxicities, differences in clinician experience.
- **First-line :**
- •Children <5 years – Cyproheptadine or pizotifen .
- •Children ≥5 years – Amitriptyline .
- The use of cyproheptadine is supported by several case series (response rates 41 to 83 percent).
- Also supported by its use for migraine headaches .
- In younger children: cyproheptadine is prefered based upon expert experience and respective side effect profiles.
- Cyproheptadine: well tolerated by young children;
- side effects: excessive weight gain and sedation.
- Alternative agent: in children who are already overweight.
- Tachyphylaxis: intermittent dosing (skipping on weekends or skipping one week per month.

- Amitriptyline: the single most effective agent ; response rates (70 to 90 percent).
- More effective for those with a personal or family history .

- Nortriptyline: a less sedating alternative to amitriptyline.

- Optimal tolerance of amitriptyline requires gradual titration, monitoring (ECG), and, in some cases, obtaining therapeutic blood levels, especially in children on higher doses.
- Anticholinergic (dry mouth, constipation) and sedative side effects (morning tiredness).
- ECG monitoring before starting and again 10 days after reaching the peak dose.
- It typically takes up to one to two months for the effects of amitriptyline .

- **Second-line** – If the first-line agents are not effective after optimal titration, the next step is a trial of either aprepitant or propranolol.
- Aprepitant : a newer antiemetic agent with good efficacy.
- Propranolol, response rates (46 to 83 percent) .
- Other agents:
  - ✓ Anticonvulsants phenobarbital or topiramate,
  - ✓ Antidepressant mirtazapine .
- Reversible cognitive side effects associated with the use of anticonvulsants.

Adjunctive therapy：

- Coenzyme Q10 and/or L-carnitine supplements and riboflavin for at least four months.
- In some milder cases of CVS, these supplements may be effective as sole therapy rather than as adjuncts to other medications.
- Some children with limited physical stamina or chronic fatigue experience marked improvement on mitochondrial supplements.

Stopping treatment :

- In children, CVS tends to persist for three to five years.
- Improvement around age 10 years and resolves by 18 years (75 percent).
- Although the vomiting symptoms are often replaced by migraine headaches .

- weaning off of prophylactic medication:
- ✓ adolescents who have had no episodes for one to two years
- ✓ done well with few episodes for three years.
- during the summer holidays when school is in recess.


Thank you