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Case Report

Cyclic Vomiting Syndrome in an Adolescent Girl. A Case Report and Review of the Literature

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Abstract

Purpose: The presentation of the cyclic vomiting syndrome in an adolescent girl and a brief review of the literature.

Topic: The cyclic vomiting syndrome is an idiopathic disorder characterized by recurrent, stereotypical, self-limiting episodes of vomiting with symptom-free intermediate periods.

Case Report: A 15 years old girl presented to the Pediatric ER with reported multiple episodes of vomiting (> 25) within hours, intense nausea and abdominal pain. She had a history of 4 more similar episodes during the past 10 months. All episodes were associated with menstruation an exhibited stereotypical symptomatology. She reported symptom free periods between the episodes. The patient was hospitalized in the pediatric department for 8 days. Gastroenterological, neurological assessment and CT/MRI, gynecological and psychiatric assessment as well as control for metabolic diseases took place and organic disorders were excluded. By the end of the menstrual period the adolescent's condition was gradually restored. She received symptomatic treatment.

Achievements: Based on the latest guidelines of NASPGHAN the patient was diagnosed with cyclic vomiting syndrome. In the precursor stage NSAIDs and ondansetron were administered. But the patient relapsed and therefore prophylactic treatment with antidepressants begun. Decline of the intensity of symptoms and reduction in frequency of the episodes were observed.

Keywords: *Cycling Vomiting Syndrome; Adolescence; Menstruation; Antidepressants*

Introduction

The cyclic vomiting syndrome (CVS) is an idiopathic disorder characterized by recurrent, stereotypical, self-limiting episodes of vomiting with symptom-free intermediate periods [1]. It was first described by Lombard Henri Clermont in 1861, while the first description of the syndrome in children occurred in 1882 by Samuel Jones Gee [2,3].

According to Gee, CVS was characterized by three or more recurrent episodes of vomiting with various intermediate symptom-free periods and stereotypy as far as the onset, the symptoms and the duration of the episodes is concerned [3]. Many years later, the exclusion of possible organic causes to induce vomiting was added to the CVS diagnostic criteria. The last NASPGHAN diagnostic criteria for CVS are shown on table 1 [4].

At least 5 attacks in any interval, or a minimum of 3 attacks during a 6-mo period
Episodic attacks of intense nausea and vomiting lasting 1h-10 days and occurring at least 1 wk apart
Stereotypical pattern and symptoms in the individual patient
Vomiting during attacks occurs at least 4 times/h for at least 1h
Return to baseline health between episodes
Not attributed to another disorder
* All of the criteria must be met to meet this consensus definition of CVS.

Table 1: *2008 NASPGHAN diagnostic criteria for CVS [4].*

The true incidence and prevalence of the syndrome are not known. The incidence in 1, 8 - 15 year-old Irish children in 2008 was 3,15/100.000 [5]. The prevalence in 5 - 15 year-old Scottish children in 1995 was 1,57% and the boys:girls ratio was 1:1 [6]. Studies from Italy and Malaysia, on the other hand, showed that the syndrome was more often seen in girls (boys:girls = 43:57) [7,8]. As far as the general population in the USA is concerned, the prevalence in 2000 was 0,004% and the men:women ratio in 2002 was 24:17 [9,10].

The mean age of onset in children is 4 - 5 years old. What is more, the duration of each episode varies from 1 hour to 5 days (mean: 1 day) and the median number of episodes per year is 8 [5,6].

Complications at the acute phase are the dehydration, electrolyte disorders, inappropriate antidiuretic hormone secretion, metabolic acidosis and hematemesis. Long-term complications are the chronic esophagitis and the weight loss. Children with CVS are at increased risk for anxiety disorders [11,12].

The prognosis of CVS is generally good. It lasts 2,5 - 5,5 years and in the long run it can lead to chronic abdominal pain and later on in chronic migraine [12,13].

Purpose of the Study

The purpose of our study is the presentation of CVS in an adolescent girl while conducting a brief review of the literature.

Case Report

A 15 years old girl presented to the Pediatric ER with reported multiple episodes of vomiting (> 25) within hours, intense nausea and abdominal pain. It was in the first 24 hours of menstrual period.

She had a history of 4 more similar episodes during the past 10 months, with an average frequency of one episode every two months. All episodes were associated with menstruation an exhibited stereotypical symptomatology. Furthermore, she presented elevated prolactin levels and her symptoms did not improve with symptomatic treatment. She reported symptom free periods between the episodes.

The clinical presentation of CVS has four phases as seen in figure 1. The stereotypical model begins with prodromal symptoms of nausea and pallor (duration: 1.5 hour). Vomiting climaxes in the first hour followed by gradual decline every 4 - 8 hours. Usually it stops at the end of the first day. The episodes usually start at 2:00 - 4:00 am or upon awakening 6:00 - 8:00 am. The recovery phase, from the end of vomiting to restoration of food and fluid intake, takes proximately 5 hours. Only half of the patients have a fixed frequency of the episodes [9].

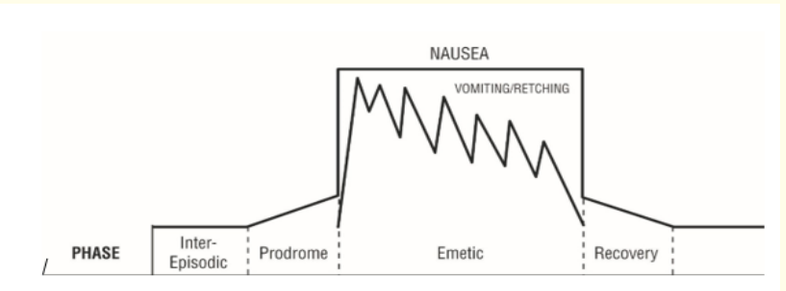

Figure 1: *CVS phases.*

Signs and symptoms that can be seen during phases II and III are fever and diarrhea, vomit tendency and nausea, acute abdominal pain, lethargy, pallor and intense salivation. From the neural system phonophobia, photophobia, headache and vertigo can be noted [9,10,14,15].

The differential diagnosis includes diseases from the gastrointestinal system, the urinary tract, endocrine disorders, psychiatric disorders, metabolic disorders and neurologic diseases (Table 2).

Gastrointestinal system	Abnormal fixation and twisting of the intestine with intermittent twist Pancreatitis Gallstone disease Infection with *H. pylori* Gastritis Idiopathic inflammatory bowel disease (IBD) Gastroesophageal reflux disease Hirschsprung disease Chronic appendicitis
Metabolic disorders	Disorders of fatty acid Oxidation disorders of urea cycle Mitochondrial encephalomyopathy Acute intermittent porphyria
Neurologic diseases	Migraine and abdominal migraine Brain tumors (cerebellar medulloblastoma, glioma stem) Panagiotopoulos syndrome Chiari malformation Riley-Day syndrome
Urinary tract	Acute hydronephrosis Nephrolithiasis
Endocrine disorders	Addison's disease Diabetic ketoacidosis Pheochromocytoma
Psychiatric disorders	Anorexia Bulimia Depression Munchausen by proxy

Table 2: *Differential diagnosis of CVS.*

The patient was hospitalized in the paediatric department for 8 days for investigation. Gastroenterological, neurological assessment and CT/ MRI, gynecological and psychiatric assessment as well as control of metabolic diseases took place and organic disorders were excluded (Table 3).

Evaluation tests for metabolic diseases obtained at the beginning of the episode before i.v. fluid	• Glucose • Electrolytes for anion gap • Urine ketones • Lactate • Ammonia • Serum amino acids • Urine organic acids • Plasma carnitine and acylcarnitine
Ultrasound of the abdomen and pelvis	Normal findings
Brain MRI	Normal findings
Esophagogastroduodenoscopy	Acute esophagitis

Table 3: *Diagnostic approach.*

By the end of the menstrual period the adolescent's condition was gradually restored.

Results and Analysis

Based on the latest guidelines of NASPGHAN the patient was diagnosed with cyclic vomiting syndrome.

Treatment is individualized, because there is no approved medication. Initially in the precursor stage NSAIDs and ondansetron were administered. Unfortunately, the patient relapsed and therefore prophylactic treatment with antidepressants (SSRIs) begun. We discussed the addition of carnitine, coenzyme Q10 and contraceptive medication with low estrogen content. Decline of the intensity of symptoms and reduction in frequency of the episodes were observed.

Discussion

The pathogenesis and etiology of CVS are unknown. Migraine, metabolic disorders, autonomous nervous system (ANS) disorders, hypothalamus-pituitary axis disorders, food allergies, menstruation and cannabis have been associated with the pathogenesis of CVS [8,14,16-21].

The fact that the CVS episodes are vigorous, circular and discrete, the evolution of CVS in migraine, the existence of a positive family history of migraine (80% in children with CVS vs. 14% in controls) and the positive response of CVS patients to migraine treatment are indications of a strong correlation between these two periodical syndromes, CVS and migraine [4,22].

As far as the metabolic disorders is concerned, two mRNA polymorphisms have been found in children with CVS, the 16519T and the 3010A [17]. The 16519T polymorphism is found six times more often in children with CVS than the control group. The 3010A polymorphism increases seventeen times the probability of CVS in children that also have the 16519T polymorphism [23]. These polymorphism have no correlation with the CVS of the adults [24].

Related to the ANS symptoms that are found in patients with CVS are: pallor, flushing, fever, lethargy, salivation and diarrhea [25-27]. Moreover, increased sympathetic cardiovascular tone has been found in children with CVS [20,22]. The above correlation is enhanced by the fact that dexmedetomidine - an α2 adrenergic agonist - has been proven successful in the treatment of CVS [28].

The response to stress, mediated by the hypothalamus-pituitary-adrenal axis (HPA), may also potentially induce CVS episodes [29,30]. Elevated ACTH and cortisol levels have been associated with lethargy and hypertension before the onset of vomiting [31]. Animal studies have demonstrated that CRF induces gastric stasis, vomiting or both [15].

Foods that may be associated with CVS are: cow's milk, soy, egg, chocolate, cheese, monosodium glutamate (msg - dairy products, meat, fish and vegetables). There have been found more elevated IgE levels in patients with CVS from control group for these foods [8].

Some girls develop menstrual CVS at the onset of their menstrual cycles. Some respond to low doses of estrogen or the "next day" pill (progesterone only). The PO contraceptives and other steroids can emit vomiting episodes [16].

The endocannabinoid system (ECS) consists of cannabinoid receptors CB1 and CB2 and the endogenous agonists of these, the 2-AG and anandamide. The ECS is believed to play a role in nausea and vomiting (and anxiety). There is considerable evidence that the activation of the central and peripheral CB1 receptors inhibits nausea and vomiting. Both nausea and vomiting are common side effects that accompany the use of CB1 receptor antagonists [32,33]. Patients who make frequent cannabis use, are more likely to experience hyperemesis syndrome cannabis rather CVS. Thus, the CVS may not be diagnosed until patients stop cannabis [34].

As trigger factors for CVS have been characterized the following [9]:

1. Infections, mainly chronic sinusitis (41%)
2. Mental stress (34%)
3. Foods, e.g. MSG, cheese, chocolate
4. Positive stimuli, e.g. excursions, celebrations etc.
5. Fatigue or lack of sleep (18%)
6. Atopic events (13%)
7. Menstruation (13%).

Because of the unknown pathophysiology of the disease, the treatment remains empirical. Treatment goals are the avoidance of triggers, preventive and deterrent therapy, supportive therapy during acute episodes and family support [35].

The empirical clinical care and treatment of CVS can be seen on table 4.

Phase	I Baseline state of health	II Prodrome	III Acute vomiting	IV Recovery
Symptoms	None	- Nausea - Anorexia - Epigastric pain	- Vomiting > 4/h - Salivation - Epigastric pain - Pallor - Photophobia - Withdrawal - Lethargy	Vomiting ceases
Therapeutic Goal	Prophylaxis	Prevention of acute vomiting	Supportive interventions	Baseline state of health
Treatment	- Amitriptyline 0,25mg/kg/day/bid - Psychotherapy (personal and family) - Avoidance of identified triggers - L - carnitine 50mg/kg/day/bid - Coenzyme Q10 10 mg/kg/day/bid - Low estrogen, oral Contraceptives	- Ondansetron supp or po - Darkened, quiet room - PPIs po	- Fluid, electrolyte and nutritional management - Ondansetron 0,3-0,4 mg/Kg/dose iv every 4-6h - PPIs iv - Sedatives - - Analgesics	Refeeding

Table 4: *The clinical care and treatment of CVS.*

Cyproheptadine is the first-line preventive treatment in < 5 year-old children. It is a first-generation antihistamine with additional anticholinergic, anti0serotoninergic and local anesthetic properties. It causes increased appetite, which can lead to weight gain. Amitriptyline is the first-line preventive treatment in > 5 year-old children. It is a tricyclic antidepressant drug and it reduces the clinical status in 88% of the patients that comply with the treatment for 1 - 2 years [9,36].

The coenzyme Q10 can lead to 50% reduction of the clinical status in approximately 70% of the patients that comply with the treatment with no adverse effects, while 50% of the patients that are treated with amitriptyline have reported adverse effects that have led to the withdrawal from therapy the 21% of these patients [36].

Ondansetron, a 5-HT3 antagonist is a potent and effective antiemetic agent that acts on chemoreceptors in the brainstem. In CVS, it is more effective at high doses of 0,3 - 0,4 mg/kg every 6 hours and can be more effective in severe episodes when a benzodiazepine or diphenhydramine as adjuvant against nausea are co-administered. Ondansetron alleviates the episodes more than it prevents them [10].

Conclusion

1. In the prodromal phase of the disease increased prolactin levels can be found.
2. The preventive treatment usually involves amitriptyline and coenzyme Q10.
3. Failure to control the episodes with preventive treatment should be followed by a review of the diagnosis.
4. Treatment in all phases is empirical and individualized.
5. The intervention of the child psychiatrist, family and individual psychotherapy is important.
6. Even though cyclic vomiting syndrome is not a frequent disease entity, it should not be omitted from our differential diagnosis thought.

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Bibliography

1. Li BU., *et al*. "Is cyclic vomiting syndrome related to migraine?" *Journal of Pediatrics* 134.5 (1999): 567-572.

2. Lombard HC. "Névrose de la digestion, caractérise par des crises periodiques de vomissements et une profonde modification de l'assimilation". *Gazette Medicale de Paris* (1861): 312.

3. Gee S. "On fitful or recurrent vomiting". St Bartholomew Hospital Reports 18.1 (1882).

4. Li BU., *et al*. "North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition consensus statement on the diagnosis and management of cyclic vomiting syndrome". *Journal of Pediatric Gastroenterology and Nutrition* 47.3 (2008): 379-393.

5. Fitzpatrick E., *et al*. "The incidence of cyclic vomiting syndrome in children: population-based study". *American Journal of Gastroenterology* 103.4 (2008): 991-996.

6. Abu-Arafeh I and G Russell. "Cyclical vomiting syndrome in children: a population-based study". *Journal of Pediatric Gastroenterology and Nutrition* 21.4 (1995): 454-458.

7. Lee WS., *et al*. "Cyclic vomiting syndrome in South-East Asian children". *Journal of Paediatrics and Child Health* 34.6 (1998): 568-570.

8. Lucarelli S., *et al*. "Cyclic vomiting syndrome and food allergy/intolerance in seven children: a possible association". *European Journal of Pediatrics* 159.5 (2000): 360-363.

9. Li BU and JP Balint. "Cyclic vomiting syndrome: evolution in our understanding of a brain-gut disorder". *Advances in Pediatrics* 47 (2000): 117-160.

10. Li BU and L Misiewicz. "Cyclic vomiting syndrome: a brain-gut disorder". *Gastroenterology Clinics of North America* 32.3 (2003): 997-1019.

11. Sreedharan R and CA Liacouras. "Major Symptoms and Signs of Digestive Tract Disorders". 20th edition. Nelson textbook of pediatrics, ed. Kliegman., *et al*. Volume 1. ELSEVIER (2015): 306.

12. Tarbell SE and BU Li. "Anxiety Measures Predict Health-Related Quality of Life in Children and Adolescents with Cyclic Vomiting Syndrome". *Journal of Pediatrics* 167.3 (2015): 633-638.e1.

13. Hikita T., *et al*. "Cyclic Vomiting Syndrome in Infants and Children: A Clinical Follow-Up Study". *Pediatric Neurology* 57 (2016): 29-33.

14. Rashed H., *et al*. "Autonomic function in cyclic vomiting syndrome and classic migraine". *Digestive Diseases and Sciences* 44.8 (1999): 74S-78S.

15. Tache Y. "Cyclic vomiting syndrome: the corticotropin-releasing-factor hypothesis". *Digestive Diseases and Sciences* 44.8 (1999): 79S-86S.

16. Prakash C and RE Clouse. "Cyclic vomiting syndrome in adults: clinical features and response to tricyclic antidepressants". *American Journal of Gastroenterology* 94.10 (1999): 2855-2860.

17. Venkatesan T., *et al*. "Quantitative pedigree analysis and mitochondrial DNA sequence variants in adults with cyclic vomiting syndrome". *BMC Gastroenterology* 14 (2014): 181.

18. Gordan N. "Recurrent vomiting in childhood, especially of neurological origin". *Developmental Medicine and Child Neurology* 36.5 (1994): 463-467.

19. Jernigan SA and LM Ware. "Reversible quantitative EEG changes in a case of cyclic vomiting: evidence for migraine equivalent". *Developmental Medicine and Child Neurology* 33.1 (1991): 80-85.

20. Li BU and DR Fleisher. "Cyclic vomiting syndrome: features to be explained by a pathophysiologic model". *Digestive Diseases and Sciences* 44.8 (1999): 13S-18S.

21. Simonetto DA., *et al*. "Cannabinoid hyperemesis: a case series of 98 patients". *Mayo Clinic Proceedings* 87.2 (2012): 114-119.

22. To J., *et al*. "Evaluation of neurocardiac signals in pediatric patients with cyclic vomiting syndrome through power spectral analysis of heart rate variability". *Journal of Pediatrics* 135.3 (1999): 363-366.

23. Zaki EA., *et al*. "Two common mitochondrial DNA polymorphisms are highly associated with migraine headache and cyclic vomiting syndrome". *Cephalalgia* 29.7 (2009): 719-728.

24. Boles RG., *et al*. "Are pediatric and adult-onset cyclic vomiting syndrome (CVS) biologically different conditions? Relationship of adult-onset CVS with the migraine and pediatric CVS-associated common mtDNA polymorphisms 16519T and 3010A". *Neurogastroenterology and Motility* 21.9 (2009): 936-936.e72.

25. Cullen KJ and WB MaCdonald. "The periodic syndrome: its nature and prevalence". *Medical Journal of Australia* 50.2 (1963): 167-173.

26. Fleisher DR. "The cyclic vomiting syndrome described". *Journal of Pediatric Gastroenterology and Nutrition* 21.1 (1995): S1-S5.

27. Fleisher DR., *et al*. "Cyclic Vomiting Syndrome in 41 adults: the illness, the patients, and problems of management". *BMC Medicine* 3 (2005): 20.

28. Khasawinah TA., *et al*. "Preliminary experience with dexmedetomidine in the treatment of cyclic vomiting syndrome". *American Journal of Therapeutics* 10.4 (2003): 303-307.

29. Fleisher DR and M Matar. "The cyclic vomiting syndrome: a report of 71 cases and literature review". *Journal of Pediatric Gastroenterology and Nutrition* 17.4 (1993): 361-369.

30. Li BU. "Cyclic vomiting syndrome: light emerging from the black box". *Journal of Pediatrics* 135.3 (1999): 276-277.

31. Sato T., *et al*. "Recurrent attacks of vomiting, hypertension and psychotic depression: a syndrome of periodic catecholamine and prostaglandin discharge". *Acta Endocrinologica (Copenhagen)* 117.2 (1988): 189-197.

32. Chouker A., *et al*. "Motion sickness, stress and the endocannabinoid system". *PLoS One* 5.5 (2010): e10752.

33. Parker LA., *et al*. "Regulation of nausea and vomiting by cannabinoids". *British Journal of Pharmacology* 163.7 (2011): 1411-1422.

34. Allen JH., *et al*. "Cannabinoid hyperemesis: cyclical hyperemesis in association with chronic cannabis abuse". *Gut* 53.11 (2004): 1566-1570.

35. Lee LY., *et al*. "The management of cyclic vomiting syndrome: a systematic review". *European Journal of Gastroenterology and Hepatology* 24.9 (2012): 1001-1006.

36. Hejazi RA., *et al*. "Efficacy of tricyclic antidepressant therapy in adults with cyclic vomiting syndrome: a two-year follow-up study". *Journal of Clinical Gastroenterology* 44.1 (2010): 18-21.

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