http:// ijp.mums.ac.ir
Case Report (Pages: 12069-12074)

Use of Amitriptyline to Improve Persistent Vomiting in Pediatrics: A Case Report

*Angela Grace[1]

[1] St. Rafael General Hospital, Cancar, Manggarai Regency, East Nusa Tenggara, Indonesia.

Abstract

Background
Cyclic Vomiting Syndrome (CVS) is a Functional Gastro-Intestinal Disorder (FGID) which remains under-recognized. In Indonesia, CVS has never been reported.

Case Presentation
A 10-year-old girl was frequently admitted due to her intense vomiting in a local, limited resource private hospital in Manggarai Regency, East Nusa Tenggara, Indonesia, and had always been diagnosed with Gastro-Esophageal Reflux Disease (GERD). Her episodes were characterized by vomiting every 30-60 minutes at first, gradually declining over 3-4 days, and recurring in about 6-7 days. All the available test results were unremarkable. Symptoms were resolved after the administration of amitriptyline. She was discharged with continuous amitriptyline for two weeks and went into remission.

Conclusion
CVS should always be considered in repeated vomiting among children regardless of the rarity in daily practice. Recognition of this disorder is important to establish the prompt diagnosis and timely intervention, thus improving the quality of life of the children.

Key Words: Amitriptyline, Cyclic Vomiting Syndrome, Pediatrics, Vomiting.

*Please, cite this article as Grace A. Use of Amitriptyline to Improve Persistent Vomiting in Pediatrics. Int J Pediatr 2020; 8(9): 12069-74. DOI: **10.22038/ijp.2020.46056.3755**

Corresponding Author:

Angela Grace, MD, St. Rafael General Hospital, Cancar, Manggarai Regency, East Nusa Tenggara, Indonesia. Ruteng-Labuan Bajo Road, Manggarai Regency, East Nusa Tenggara, 86551.

Email: angelangiegrace@gmail.com

Received date: Mar.14, 2020; Accepted date: Jun. 22, 2020

1- INTRODUCTION

Cyclic Vomiting Syndrome (CVS) is one of Functional Gastro-Intestinal Disorder (FGID), characterized by recurring episodes of intense vomiting accompanied by nausea and headache followed by the asymptomatic period between the episodes (1-3). This condition can be burdensome since children often require hospitalization to receive intravenous fluids (4). However, CVS remains under-recognized despite its known prevalence, which is 1.9% in school-age children worldwide (2, 4). Up to now, both the prevalence and the incidence of cyclic vomiting CVS have been situated in rural areas in Indonesia. The present study aimed to highlight the challenge of diagnosing persistent vomiting in children, especially in a limited resources setting.

2- CASE REPORTS

A 10-year-old girl, weighing 20kg, was admitted to the emergency ward in a local, limited-resource hospital in Manggarai Regency, East Nusa Tenggara, due to profuse vomiting in the past seven hours before admission. Upon arrival, she was retching and vomiting. This was the sixth episode of vomiting over the previous six weeks. Before vomiting, she complained about nausea and headache, but no fever and neck stiffness was observed. She had sucralfate and domperidone from her previous episode, which was administered at home to no avail, thus leading her to the emergency ward. According to her parents' statements, she ate enough servings regularly three times a day and denied eating spicy or acidic foods earlier. Neither her parents nor siblings had any history of similar symptoms. She was the second of three children, always been a happy kid, had many friends, and was the top of her class.

She had several episodes of severe vomiting previously, which compelled her to be hospitalized. The episodes were characterized by vomiting every 30-60 minutes at first, then gradually declined over 3-4 days, and repeated in about 6-7 days. She was diagnosed with Gastro-Esophageal Reflux Disease (GERD) up to her fifth episode. During every hospitalization, she received intravenous fluids, an antiemetic, proton-pump inhibitor, H2 blocker, and sucralfate. Previous in-vitro studies for this patient, reported normal blood count and liver enzymes, in addition to a slight increase in urea and creatinine that indicated severe dehydration. The present physical examination showed that the patient seemed unhealthy and slightly dehydrated. Her blood pressure was 100/60, with a heart rate of 120 times per minute and afebrile. Abdominal examination revealed normal bowel sounds on auscultation and soft abdomen on palpation; however, there was epigastric pain with dull percussion near the umbilicus, indicating impacted stool, as the patient had not defecated for two days. Repeated abdominal examination after stool passage exhibited tympanic percussion on all abdominal regions. Other physical examinations were unremarkable. In-vitro examinations revealed mild leukocytosis (white blood cell count: 12,200 cells/mm^3; range 4,300-10,000 cells/mm^3) with normal hemoglobin and platelet, normal blood glucose, normal albumin, and negative for hepatitis B. Plain abdominal X-Ray displayed lodged stool, which was consistent with the physical examination (**Figure.1**).

She was administered intravenous fluid, ranitidine, and ondansetron, together with sucralfate per oral. Nonetheless, the symptoms only had minor improvement. At this point, CVS was suspected; therefore, amitriptyline 12.5 mg was administered every 12 hours orally. Subsequently, the resolution of symptoms was reached by 24 hours, and she was discharged with continuous amitriptyline for two weeks. A follow-up after hospitalization reported that she had no episodes of vomiting after this admission.

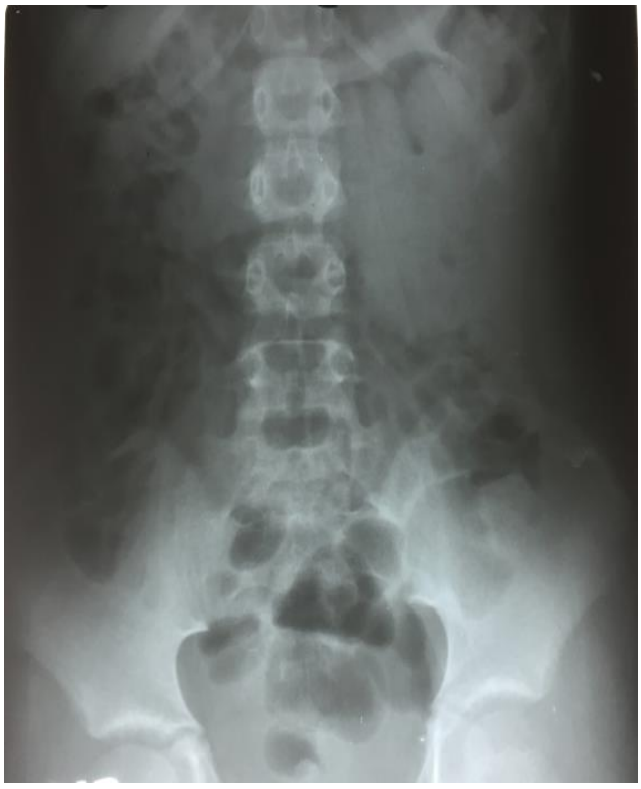

Fig.1: Plain abdominal X-Ray of current episode.

3- DISCUSSION

CVS is classified as pediatric and adult based on the age of symptoms onset (4-7). Symptoms in pediatric-onset CVS occur earlier than 18 years old, while symptoms in adult-onset CVS occur after 18 years old (7). CVS is more common among females, especially in pediatric-onset CVS, which is consistent with our case (4, 5, 7). CVS is more typical in Caucasian (79%), supported by Lewis et al. (8), which discovered that FGID in children was prevalent in the United States (7). Neither the Indonesian Basic Health Research has reported, nor has the Indonesian literature mentioned the prevalence or incidence of CVS (9). This fact suggests the invisibility reason in Indonesia. As a result, this patient was previously misdiagnosed as GERD. Nevertheless, several studies proposed that following GERD, CVS is the second cause of recurrent vomiting among children (10, 11). Lack of awareness of this disorder frequently causes misdiagnosis as GERD or peptic ulcer and therefore deferring the true diagnosis for up to 2.5-3 years among children (3, 4, 6, 12). Unexpectedly, the study conducted by Kumar et al. (7) revealed that the diagnosis of CVS was significantly delayed despite the comprehension of this disorder among Caucasians. Moreover, the mean age of onset of CVS is reported to be 4.8-5.2 years, while the mean age at diagnosis is 8.2-9.5 years (5). The patient, in this case, was diagnosed at ten years old, which is consistent with previous studies. CVS is diagnosed based on history, clinical presentation, and to a great degree: exclusion of other diseases (4, 5). There are two diagnostic criteria commonly used for CVS, including the International Classification of Headache Disorder 2004 (ICHD-II) or Rome III diagnostic criteria, as shown in **Table.1** (3, 5). The patient, in this case, fulfilled ICHD-II criteria, leading to the suspicion toward CVS. There are various tests to be conducted to exclude other diseases and diagnose of CVS, which are summarized in **Table.2** (4, 6, 7).

Table-1: International Classification of Headache Disorder 2004 (ICHD-II) Criteria and Rome III Criteria for CVS (3, 5).

ICHD-II Criteria	Rome III Criteria
At least 5 episodic, stereotypical attacks of intense nausea and vomiting lasting from an hour to 5 days	Acute, stereotypical episodes of vomiting and lasts less than a week.
Vomiting during attacks occurs at least 4 times in at least an hour.	Three or more separate episodes in the preceding year.
Asymptomatic period between attacks.	Absence of symptoms between episodes.
Not attributed to another disorder.	Happens for at least 3 months, with onset at least in the past 6 months.
	Gastrointestinal, metabolic, central nervous system structural or biochemical disorder are not identified.
	Additional criteria: personal or family history of migraine headaches.

CVS: Cyclic Vomiting Syndrome.

Table-2: Recommended Work Up in Case of Suspected Cyclic Vomiting Syndrome (4-6)

Recommended Work Up in Case of Suspected CVS		
Blood tests	Electrolytes	Blood ketones
	Glucose	Ammonia
	Blood urea nitrogen	Lactate
	Creatinine	Plasma amino acids
	ALT/GGT	Plasma organic acids
	Amylase	Plasma carnitine
	Lipase	Plasma acyl carnitine
	Celiac antibodies	Beta HCG
Urine analysis	Urine ketones	
	Urine organic acid profiles	
	Urine toxicology	
	Urine Porphobilinogen	
Imaging	Upper gastrointestinal series radiographic imaging	
	Abdominal ultrasound	
	Esophagogastroduodenoscopy	
	Colonoscopy	
	Brain MRI	
Other	Electroencephalogram (EEG)	

CVS: Cyclic Vomiting Syndrome, HCG: Human chorionic gonadotropin, ALT: Alanine Aminotransferase, GGT: Gamma-glutamyl transferase.

Due to the limited resources, apart from the routine blood tests, only tests for glucose, urea, creatinine, Alanine aminotransferase (ALT), albumin, and plain abdominal X-ray were carried out, which came back with unremarkable results. Consequently, trial and error treatment of amitriptyline was decided, and the improvement thereupon was unanticipated. Undoubtedly other differential diagnoses at that time were also considered, including peptic ulcer and gastroesophageal reflux, which were the previous diagnoses of this patient. Differential diagnoses for pediatric recurrent vomiting are outlined in **Table.3** (5, 6). Since all the available tests came back normal, FGID was suspected. The first suspicion was on the abdominal migraine, as it is the most frequent FGID among children reported by Lewis et al. (8), and Saps et al. (13) (9.2% and 1%, respectively). However, the episode of vomiting was stereotypical;

thus, the idea of abdominal migraine was then rejected. CVS was decided regardless of incomplete exclusion of other diseases due to the fulfillment of ICHD-II criteria and favorable response to amitriptyline. Amitriptyline is the first-line CVS for both pediatric and adult CVS (6). An initial lower dose is suggested (0.5-1 mg/kg/day or 10 mg at bedtime), then titrated and continued up to 2-3 weeks until a therapeutic effect is reached, usually around 1-2 mg/kg/day (1, 5). In this case, 12.5 milligrams of amitriptyline was administered every 12 hours and continued to two weeks after discharge, resulting in remission. Children with CVS who responded well to prophylactic medication were reported to have satisfying long-term outcomes (14). Patients with five years old or less are treated using cyproheptadine at 0.25-0.5 mg/kg/day divided into two or three doses (15). However, a randomized clinical trial discovered that both amitriptyline and cyproheptadine are both effective and no age-related effect on efficacy (10). As another option, when cyproheptadine is not available, or amitriptyline is not well-tolerated, propranolol is the second line of treatment at the dose of 0.25-1 mg/kg/day divided two or three times (4, 6). Adding erythromycin to propranolol for pediatric CVS treatment has also been recommended since the combination of both medicines offers a better response compared to propranolol (11). This suggestion can be applied in limited resources, in the condition where the first choice of the drug might not be available. Liao et al. suggested performing diagnostic therapy to minimize long-overdue diagnosis (16). Besides, the costs of fruitless tests can be reduced (6). Children with CVS have a lower health-related quality of life compared to children with other FGID (12). Therefore, awareness of this disorder, timely diagnosis, and early intervention can ease the burden of the patients and their families, improving their quality of life.

Table-3: Differential Diagnoses for Pediatric Recurrent Vomiting (5, 6)

Differential Diagnoses for Pediatric Recurrent Vomiting	
Gastrointestinal disorder	Peptic ulcer Gastroesophageal reflux Cholecystitis Gastrointestinal obstruction Inflammatory bowel disease Eosinophilic esophagitis
Neurological disorder	Autonomic epilepsy Intracranial mass lesions
Metabolic disorder	Inborn error of metabolism
Genetic disorder	Mitochondrial disease
Substance-related disorder	Cannabinoid hyperemesis syndrome
Functional disorder	Abdominal migraine

4- CONCLUSION

CVS should always be considered in persistent vomiting among children. When CVS is suspected, particularly in a limited resources setting, diagnostic therapy should immediately be performed. Recognition of this disorder is important to establish the prompt diagnosis and timely intervention; therefore, the quality of life of the children can be improved.

5- ACKNOWLEDGMENTS

The author would like to thank Kevin Dominique Tjandraprawira, MD for his kind assistance in editing this manuscript and Leonardus Wibowo Hidayat, MD for his convenient suggestions for this manuscript. The abstract of this manuscript was presented as a poster in 9th Europaediatrics 2019 in Dublin, Irlandia, and published as an abstract in Archives of Diseases in Childhood 2019;104**:**A197. The complete manuscript has never been published elsewhere.

6- CONFLICT OF INTEREST: None.

7- REFERENCES

1. Hejazi RA, McCallum RW. Cyclic vomiting syndrome: treatment options. Exp Brain Res 2014;232(8):2549-52.

2. Sagar RC, Sood R, Gracie DJ, Gold MJ, To N, Law GR, et al. Cyclic vomiting syndrome is a prevalent and under-recognized condition in the gastroenterology outpatient clinic. Neurogastroenterol Motil 2018;30(1):e13174.

3. Shearer J, Luthra P, Ford AC. Cyclic vomiting syndrome: a case series and review of the literature. Frontline Gastroenterol 2018;9(1):2-9.

4. Tan MLN, Liwanag MJ, Quak SH. Cyclical vomiting syndrome: Recognition, assessment and management. World J Clin Pediatr 2014;3(3):54.

5. Irwin S, Barmherzig R, Gelfand A. Recurrent gastrointestinal disturbance: abdominal migraine and cyclic vomiting syndrome. Curr Neurol Neurosci Rep 2017;17(3):21.

6. Kaul A, Kaul KK. Cyclic vomiting syndrome: a functional disorder. J Pediatr Gastroenterol Nutr 2015;18(4):224-9.

7. Kumar N, Bashar Q, Reddy N, Sengupta J, Ananthakrishnan A, Schroeder A, et al. Cyclic Vomiting Syndrome (CVS): is there a difference based on onset of symptoms - pediatric versus adult? BMC Gastroenterol 2012;12(1):52.

8. Lewis ML, Palsson OS, Whitehead WE, Van Tilburg MAL. Prevalence of functional gastrointestinal disorders in children and adolescents. J Pediatr 2016;177:39-43. e3.

9. Badan Penelitian dan Pengembangan Kesehatan. Hasil Utama Riskesdas 2018. Jakarta: Kementerian Kesehatan Republik Indonesia; 2018.

10. Badihian N, Saneian H, Badihian S, Yaghini O. Prophylactic therapy of cyclic vomiting syndrome in children: comparison of amitriptyline and cyproheptadine: a randomized clinical trial. Am J Gastroenterol 2018;113(1):135.

11. Haghighat M, Dehghani SM, Shahramian I, Imanieh MH, Teimouri A, Noori NM. Combination of erythromycin and propranolol for treatment of childhood cyclic vomiting syndrome: a novel regimen. Gastroenterol Hepatol Bed Bench 2015;8(4):270.

12. Tarbell SE, Li BU. Health-related quality of life in children and adolescents with cyclic vomiting syndrome: a comparison with published data on youth with irritable bowel syndrome and organic gastrointestinal disorders. J Pediatr 2013;163(2):493-7.

13. Saps M, Nichols-Vinueza DX, Rosen JM, Velasco-Benítez CA. Prevalence of functional gastrointestinal disorders in Colombian school children. J Pediatr 2014;164(3):542-5. e1.

14. Treepongkaruna S, Jarasvaraparn C, Tanpowpong P, Lertudomphonwanit C. Short- and long-term outcomes of children with cyclic vomiting syndrome. J Med Assoc Thail 2014;97(10):1077-83.

15. Moses J, Keilman A, Worley S, Radhakrishnan K, Rothner AD, Parikh S. Approach to the diagnosis and treatment of cyclic vomiting syndrome: a large single-center experience with 106 patients. Pediatr Neurol 2014;50(6):569-73.

16. Liao K-Y, Chang F-Y, Wu L-T, Wu T-C. Cyclic vomiting syndrome in Taiwanese children. J Formos Med Assoc 2011;110(1):14-8.