Rare disorders can be an underlying cause of cyclic vomiting: Familial Mediterranean fever, *Helicobacter pylori* gastritis, and cavernous transformation of the portal vein

**STOMACH**

Ödül Egritaş Gürkan, Aysel Ünlüsoy Aksu, Zeliha Demirtaş, Buket Dalgıç
Department of Pediatric Gastroenterology, Gazi University Faculty of Medicine, Ankara, Turkey

**ABSTRACT**

**Background/Aims:** Considering the etiology of cyclic vomiting syndrome (CVS) in childhood, a variety of underlying organic causes has been clearly identified in the literature. The aim of this study was to emphasize that endoscopic evaluation in the first step may help diagnosis and treatment in patients with CVS, unlike the CVS-related “North American Society for Pediatric Gastroenterology, Hepatology and Nutrition” (NASPGHAN) consensus statement in 2008.

**Materials and Methods:** The medical files of patients with vomiting complaints admitted to our tertiary center between the years 2007 and 2012 were analyzed retrospectively. Patients were identified according to the International Classification of Diseases (ICD) codes at their initial presentation, including vomiting.

**Results:** A total of 815 patients with vomiting complaints were evaluated. Of the 379 patients who presented with vomiting only, 336 patients were already being followed for chronic vomiting. Cyclic vomiting was detected in 31 out of 336 patients.

**Conclusion:** In our series, familial Mediterranean fever (FMF), cavernous transformation of the portal vein, and *Helicobacter pylori* (HP) gastritis presented with CVS for the first time in the pediatric age group. We emphasize that endoscopic evaluation in patients with CVS should be performed as the first step for appropriate diagnosis and treatment.

**Keywords:** Cyclic vomiting, familial Mediterranean fever, gastritis, cavernous transformation, children

**INTRODUCTION**

Cyclic vomiting is a chronic disease with relapsing vomiting attacks. The first pediatric descriptions of cyclic vomiting syndrome (CVS) were provided in the French literature by Heberden in 1806 and in the English literature by Gee in 1882 (1-3). CVS may be easily diagnosed from medical history; however, it is a complex disease for which physicians have to perform a variety of tests to illustrate accompanying organic pathology. Many diseases such as brain tumors, intestinal obstruction, pancreatitis, obstructive uropathy, metabolic disorders, and familial dysautonomia may mimic CVS. Tests to be performed to identify an underlying etiology in CVS are clearly indicated in the “North American Society for Pediatric Gastroenterology, Hepatology and Nutrition” (NASPGHAN) consensus statement in 2008 (4). According to the consensus statement, diagnostic endoscopic evaluation is necessary in patients with CVS in the presence of warning symptoms. Unlike the NASPGHAN consensus statement in 2008, according to our study results, we believe that performing endoscopic evaluation as the first step may help in the diagnosis and treatment, even in the absence of warning symptoms. Also, we emphasized the presence of cyclic vomiting association with familial Mediterranean fever (FMF), cavernous transformation of the portal vein, and *Helicobacter pylori* (HP) gastritis for the first time in a pediatric age group in the literature.

**MATERIALS AND METHODS**

The medical files of patients with vomiting complaints admitted to our tertiary center between the years 2007 and 2012 were analyzed retrospectively. Patients were identified according to the International Classification of Diseases (ICD) codes at their initial presentation. Patients were derived from the hospital information system with the following diagnosis and ICD codes: nausea and vomiting, R11; vomiting associated with other
psychological disturbances, F50.5; Vomiting following gastrointestinal surgery, K91.0; and vomiting in newborn, P92.0; Patients having other ICD codes in addition to the reference codes were excluded.

If the vomiting complaint lasts for more than a month, it was defined as chronic vomiting. To elucidate the etiology of chronic vomiting, the following analyses were performed for the patients according to their age, medical history, and physical examinations with changing priorities: urine analysis, urine culture, complete blood count (CBC), liver enzymes, kidney function tests, serum electrolytes, creatinine phosphokinase, arterial blood gases, amylase, lipase, thyroid function tests, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and metabolic tests (urine blood amino acids, urine organic acids, tandem mass, reductant substance in urine, ammonia, lactic acid/pyruvic acid), total IgA, Celiac serology, abdominal ultrasound/computed tomography (CT), upper gastrointestinal series, endoscopy, electroencephalography (EEG), cranial magnetic resonance imaging (MRI) examinations, and FMF mutation analysis.

Metabolic tests and cranial imaging are indicated to all patients in presence of papilledema, motor and mental retardation and abnormal eye movements. In our series, fundus examinations in presence of papilledema, motor and mental retardation and metabolic tests and cranial imaging are indicated to all patients. In our series, endoscopy, electroencephalography (EEG), cranial ultrasound/computed tomography (CT), upper gastrointestinal series, endoscopy, electroencephalography (EEG), cranial magnetic resonance imaging (MRI) examinations, and FMF mutation analysis.

The diagnosis of CVS is made using the diagnostic criteria in 2008. Diagnostic criteria should include all of the following parameters: a) stereotypical episodes of vomiting regarding onset (acute) and duration (less than 1 week), b) three or more discrete episodes in the prior year, and c) absence of nausea and vomiting between episodes (4).

The files of patients diagnosed with CVS were examined retrospectively in detail. How many admittance were needed till the diagnosis, number of hospitalizations, social and economical status, presence of a loss prior to the start of attacks, presence of a documented failure in patient’s life, and decrease in the quality of life during vomiting attacks in out of hospital period (such as missing school, unable to watch television, unable to play games, continuous stay in bed) were noted from the files. Families of the patients who did not attend follow-up appointments were contacted by telephone calls. Patients who did not attend follow-up appointments were questioned for the following parameters: where and how do they continue their follow-ups, drug usage details, when the complaints subsided, additional complaints or diseases, and finally, continuance of follow-ups.

RESULTS
A total of 815 patients with vomiting complaints were admitted to our clinic between the years 2007 and 2012. Patients having additional ICD codes other than vomiting-related reference codes were excluded. Thus, a total of 379 patients were enrolled in the study, and patient files were analyzed retrospectively. In this group, there were 336 patients identified with CVS. The study flow chart of patients admitted with vomiting complaints is listed in Figure 1.

In the follow-up of the patients with CVS, the final diagnoses of the patients were as follows: gastroesophageal reflux (288 patients), erosive gastritis (2 patients), rotation anomaly (3 patients), eosinophilic esophagitis (3 patients), gluten allergy (1 patient), Celiac disease (1 patient), superior mesenteric artery syndrome (SMA) (1 patient), pyloric stenosis (1 patient), antral web (1 patient), paraduodenal pancreatic cysts (1 patient), intracranial mass (2 patients), and FMF disease with upper gastrointestinal involvement with esophagitis and gastritis (1 patient). There were 31 patients with CVS diagnosis.

The demographic characteristics, etiologies, and follow-ups of 31 patients diagnosed with CVS are shown in Table 1. In 6 of the 31 patients diagnosed with CVS, an underlying organic disease association was found during the follow-up period. Regarding the etiology of these 6 patients, the diagnoses were as follows: HP gastritis (3 patients), FMF (1 patient), portal hypertension (cavernous transformation of the portal vein) (1 patient), and duplication cyst (1 patient). The remaining 25 patients were diagnosed with idiopathic CVS.

The clinical and laboratory characteristics of the 6 patients who presented with CVS are given in Tables 2,3.
The Statistical Package for the Social Sciences (SPSS) v.16.0 software package for Windows (SPSS Inc., Chicago, Illinois, USA) was used for statistical analysis. Numerical data were expressed as a percentage, and measurement data were expressed as the mean±standard deviation (SD). Differences were evaluated with the χ2 test.

Parents and patients were informed about endoscopy, colonoscopy, and enteroscopy procedures, and the related written informed consents were obtained. The local ethics committee approved this retrospective study.

DISCUSSION

The most important feature of CVS is the completely healthy state between episodes of vomiting (5). Each episode duration and recurrence interval varies according to the patient, generally in order (5). In 1995, Abu-Arafeh et al. (6) reported the incidence of CVS in the pediatric age group as 2.3% in their study. In 2006, Uc et al. (7) reported an incidence of 0.8% in African–American children. In 2008, Fitzpatrick et al. (8) reported an incidence of 3.15/100.000 in Ireland. Ertekin et al. (9) from Turkey reported the presence of CVS in 1263 school children (ages ranging from 7 to 14 years) and reported the prevalence as

| Table 1. Demographic characteristics, etiologies, and follow-ups of 31 patients diagnosed with cyclic vomiting syndrome |
|---|---|
| **Patients diagnosed with cyclic vomiting syndrome** | **n=31** |
| Gender | Female 14 (45.2%) Male 17 (54.8%) |
| Age at diagnosis (months) | Median: 84 (SD±56.84) (min: 18–max: 204) |
| Start of complaints (months) | Median: 48 (SD±46.62) (min: 6–max: 156) |
| Delay time until the diagnosis (months) | Median: 24 (SD±32.53) (min: 4–max: 132) |
| Vomiting frequency (during an attack) | |
| <10 times/day | 15 (48.4%) |
| >10 times/day | 10 (32.3%) |
| Too many to count | 6 (19.4%) |
| Attack duration (days) | Median: 2 (SD±2.56) (min: 1–max: 10) |
| Attack interval (days) | Median: 30 (SD±41.79) (min: 4–max: 110) |
| Family history for migraine | 12 (38.7%) |
| Presence of migraine | 1 (3.2%) |
| Family history for headache | 14 (45.2%) |
| Presence of headache | 3 (9.7%) |
| Aura period before attacks | 9 (29%) |
| Follow-up period of patients (months) | Median: 4 (SD±17.19) (Min: 1–max: 67) |

| Table 2. Demographic characteristics of the patients presented with cyclic vomiting syndrome |
|---|---|---|---|---|---|---|---|
| **Diagnoses of the patients presented with cyclic vomiting syndrome** | **Age at diagnosis/ gender** | **Age at onset of complaints** | **Body weight/ Percentile (pr)** | **Height/ Percentile (pr)** | **Pathologic findings in physical examination** | **Attack interval** | **Attack duration** | **Vomiting frequency** |
| Patient 1 | 3.5 years/ female | 3 years | 17.5 kg (10–25 pr) | 116 cm (50–75 pr) | Splenomegaly 4 cm under costal arc | In every 15 days | 4–5 days | <10 times/ day |
| Patient 2 | 14 years/ female | 13 years | 48 kg (25–50 pr) | 156 cm (25–50 pr) | None | Once in every 2 months | 1 day | >10 times / day |
| Patient 3 | 9 years/ male | 7 years | 24.1 kg (10–25 pr) | 126 cm (10–25 pr) | Epigastric tenderness | Once in a month | 10 days | <10 times / day |
| Patient 4 | 7 years/ female | 6 years | 25 kg (75–90 pr) | 126 cm (90–97 pr) | None | Once in every 3 months | 4 days | >10 times / day |
| Patient 5 | 10 years/ male | 5 years | 13.4 kg (10–25 pr) | 96 cm (25–50 pr) | Epigastric tenderness | Once in a month | 1 day | >10 times / day |
| Patient 6 | 14 years/ (duplication cyst) male | 13 years | 54 kg (50–75 pr) | 168 cm (75–90 pr) | None | Once in a week | 2 days | <10 times / day |

FMF: familial Mediterranean fever; HP: helicobacter pylori; HT: hypertension

Statistical analysis

The Statistical Package for the Social Sciences (SPSS) v.16.0 software package for Windows (SPSS Inc., Chicago, Illinois, USA) was used for statistical analysis. Numerical data were expressed as a percentage, and measurement data were expressed as the mean±standard deviation (SD). Differences were evaluated with the χ2 test.

Parents and patients were informed about endoscopy, colonoscopy, and enteroscopy procedures, and the related written informed consents were obtained. The local ethics committee approved this retrospective study.
Although the study method was different from our study, Hejazi et al. (10) diagnosed CVS in 17 out of 545 patients (3.1%) referred to their clinic with nausea, vomiting, and other motility disorders between 2004 and 2008. In our study, 31 out of 336 patients (9.22%), who were followed because of chronic vomiting in the last 5 years, were diagnosed with CVS. In our study, the incidence of CVS was found to be higher than other studies in the literature. This point may be related to the limited study group as chronic vomiting and also being a referral center as well.

If CVS comes to mind, it may be easily diagnosed with history. However, diagnoses such as urinary tract infections, food poisoning, gastroesophageal reflux, and psychogenic vomiting may delay diagnosis. Liao et al. (11) reported the diagnostic delay period as 2.1±2.2 years in their study of 24 children with CVS. Haghighat et al. (12) from southern Iran noted the diagnostic delay period as 2±1.81 years in their study of 181 patients with CVS. Similarly, Gokhale et al. (13) study showed the diagnostic delay period as 2.2 years. In our study, the median time for onset of complaints was determined as 48 months, while the median age at diagnosis was 84 months. We observed a diagnostic delay period of 3 years. We noted that the most common diagnosis in other centers as chronic vomiting and also being a referral center as well.

If CVS comes to mind, it may be easily diagnosed with history. However, diagnoses such as urinary tract infections, food poisoning, gastroesophageal reflux, and psychogenic vomiting may delay diagnosis. Liao et al. (11) reported the diagnostic delay period as 2.1±2.2 years in their study of 24 children with CVS. Haghighat et al. (12) from southern Iran noted the diagnostic delay period as 2±1.81 years in their study of 181 patients with CVS. Similarly, Gokhale et al. (13) study showed the diagnostic delay period as 2.2 years. In our study, the median time for onset of complaints was determined as 48 months, while the median age at diagnosis was 84 months. We observed a diagnostic delay period of 3 years. We noted that the most common diagnosis in other centers before admittance to our hospital was medical treatment-resistant reflux. On the other hand, urinary tract infection or somatization diagnoses were also present other than treatment-resistant reflux. The most striking example of this phenomenon was a 16-year-old female patient whose vomiting was thought to be due to somatization and was being followed in a psychiatric ward. The frequency of her vomiting attacks was described as once a month, particularly during menstrual periods, and severe enough to visit the emergency room, lasting up to 1 week. The patient had failed to attend school for over a year, and the absence of a psychogenic cause led to a gastroenterology consultation. The patient was diagnosed with CVS and received benefit from treatment after the initiation of propranolol. Currently, the patient has completed her college education.

Thorough investigations are required to distinguish CVS from various organic disorders presented with CVS. Cyclic vomiting occurs not only in CVS patients but also in other organic diseases clinically mimicking CVS. Thus, all possible organic causes of CVS have to be ruled out for the accurate diagnosis of CVS. The following diseases and disorders have to be considered for the differential diagnosis of CVS: bowel obstruction (14,15), pancreatic diseases (16,17), parasitic infestations (18), migraine (19), epilepsy (20), space-occupying central nervous system lesions (21,22), diabetes mellitus (23), Addison’s disease (24), pheochromocytoma (25), aminoaciduria, organic aciduria, fatty acid oxidation disorders, mitochondrial disorders, metabolic diseases such as urea cycle defects and porphyrias (26-30), and pelvi-ureteric junction obstruction (31,32).

In our study, etiologic organic causes for CVS were observed in 6 out of 31 patients (19.3%). Elimination of the underlying pathology resulted in a decline in the cyclic vomiting state. The most important feature of these pediatric age group patients is the fact that cavernous transformations of the portal vein and FMF related to the etiology of CVS have not been highlighted in the literature. The demographic and laboratory data of patients presented with CVS and having etiologic organic causes are shown in Tables 2, 3.

We evaluated the CVS patients with an organic etiology. Our first patient was a 3.5-year-old girl who was referred because...
of episodes of vomiting in every 15 days in the last 6 months. The patient's medical history revealed a 6-month therapy for gastroesophageal reflux refractory to treatment in a different center. CVS diagnosis was defined after medical history. Upon detection of splenomegaly in physical examination, further tests lead to portal hypertension diagnosis, secondary to cavernous transformation of the portal vein. Esophageal varices were present in the endoscopic evaluation, and propranolol treatment was initiated for both portal hypertension and cyclic vomiting. The patient received propranolol treatment till the operation and did not encounter any vomiting attacks. Treatment was stopped after shunt operation, and the patient has no vomiting attacks at present.

Our second patient was a 14-year-old female who was followed in the pediatric nephrology department for 4 years with FMF disease diagnosis. The patient was under colchicine treatment, and had 10 or more vomiting attacks per day, generally lasting for a day, in a cycle of every 2 months for the last year. After obtaining more in-depth details of the patient’s medical history, it was learned that the patient had irregular colchicine usage in the last 2 years and even discontinuation of usage in recent months. CBC, biochemistry tests, metabolic tests, endoscopy, upper gastrointestinal series, and fundus examination were performed for the exclusion of organic pathology accompanying cyclic vomiting. Physical examination and laboratory investigations revealed no pathological findings. Vomiting attacks did not occur with the regular usage of colchicine in an appropriate dose during follow-up for 2.5 years. The patient was diagnosed with FMF disease who presented with CVS. The emergence of cyclic vomiting after interruption in colchicine usage and disappearance in regular usage in addition to the absence of any accompanying etiologic factors for cyclic vomiting reminded us once again that FMF disease may be present in many different forms. FMF may present itself with vomiting (33,34).

The third, fourth, and fifth patients were at ages 9, 7, and 10 years, respectively and did not have classical dyspeptic complaints such as halitosis, abdominal pain, bitter taste, and early satiety. CBC, biochemical panel, urine culture, metabolic tests, upper gastrointestinal series, and fundus examinations were performed, and no pathological findings were present. Endoscopic views of all three patients were compatible with antral nodular gastritis, and biopsies were reported as HP+ gastritis. Treatment using antibiotics and proton pump inhibitors (PPIs) was initiated, and no complaints were seen. It was observed that patients failed to comply with follow-up appointments as the complaints disappeared. Parents were contacted by telephone calls after appointment breaks for 2 years, 19 months, and 1 year respectively. The response of the parents revealed that the patients had not been followed in any other center as their complaints disappeared.

In 2011, Koletzko et al. (35) clearly defined treatment and follow-up protocols for HP infections in childhood. The HP work-
signs were observed in 2 patients during endoscopy (nodular gastritis, megabulbus). Etiological factors were identified only through these pathological endoscopic appearances. To evaluate the results of our study, CBC, biochemical panel, and upper gastrointestinal series were performed for all patients as the first step. However, in our study, additional endoscopic evaluations were performed for all patients, unlike the 2008 NASPGHAN consensus statement. Based on our own study, we believe that performing endoscopic evaluation as the first step may help in the diagnosis and treatment, even in the absence of warning symptoms.

As a result, CVS may be easily diagnosed from a patient’s medical history; however, it may be defined as a complex disease. Physicians may be forced to perform a variety of tests to identify an accompanying organic pathology and attempt to administer various medications during follow-up. After reviewing the literature, we learned that many diseases may manifest themselves as CVS in the pediatric age group. In our series, apart from the literature, we observed that FMF disease, cavernous transformation of the portal vein, and HP gastritis presented with CVS for the first time in the pediatric age group. HP gastritis may manifest itself as cyclic vomiting, and even without additional dyspeptic complaints, treatment of HP may be useful. Contrary to the NASPGHAN consensus statement, endoscopic evaluation may be performed in the first step even without the presence of warning symptoms. In our study, three patients without warning symptoms were diagnosed through endoscopic findings. To the best of our knowledge, based on the studies and presented case reports in the literature, demonstrating underlying etiology and determining the appropriate treatment for the patient is more challenging than diagnosing the disease.

Ethics Committee Approval: Ethics committee approval was received for this study.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.


Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES