Yield and Costs of Evaluating Children With Cyclic Vomiting Syndrome

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ABSTRACT

Background and Objectives: Cyclic vomiting syndrome (CVS) clinical guidelines recommend an algorithm of basic testing for standard patients, and more targeted testing, including laboratory and imaging studies, in the presence of specific red flags. The cost-effectiveness of this screening of children with suspected CVS is lacking. The objectives of this study are to determine whether screening studies in CVS patients results in diagnostic change and to estimate their healthcare cost.

Method: Charts of patients (1–18 years) with suspected CVS were retrospectively reviewed at a single center. Results and cost of laboratory and imaging studies were analyzed.

Results: A total of 503 charts were reviewed from electronic medical records with the International Classification of Diseases-9 (ICD-9) code 536.2 or search terms ''CVS, cyclic vomiting, persistent emesis/vomiting, hyperemesis, or intractable/ periodic vomiting.'' Of these, 165 (33%) had a diagnosis of CVS and 135 (82%) children (mean age 7.7 ± 4.3; 73 (54%) girls) met CVS criteria based on North American Society for Pediatric Gastroenterology, Hepatology and Nutrition diagnostic criteria. Of those meeting CVS criteria, 6 (4%) had a change in management based on the CVS screening evaluation. The mean cost of screening per patient that met CVS criteria was $6125.02 and the estimated total cost for all patients who met CVS criteria was $826,877.88.

Conclusions: The screening metabolic laboratory results, pelvic ultrasound, magnetic resonance imaging, and upper endoscopy resulted in a diagnosis change in few patients screened for CVS. Most children who met criteria for CVS did not benefit from screening evaluation as results did not change clinical diagnosis or management, and were associated with higher cost.

Key Words: cyclic vomiting syndrome, financial burden, management, pediatrics, recurrent vomiting, screening

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What Is Known

- Cyclic vomiting syndrome is a functional disorder characterized by recurrent stereotypical episodes of intense vomiting, which can present similar to patients with vomiting secondary to organic etiologies.
- There are North American Society for Pediatric Gastroenterology, Hepatology and Nutrition diagnostic criteria for evaluating patients with the likely diagnosis of cyclic vomiting syndrome to rule out organic etiologies. The cost of evaluating these patients with alarm symptoms is likely to be significant.

What Is New

- Few children with symptoms consistent with cyclic vomiting syndrome, who undergo various screening tests, are diagnosed with a disease other than cyclic vomiting syndrome.
- High healthcare cost were associated with the use of screening test for suspected cyclic vomiting syndrome and the diagnosis changed in few cases.

Cyclic vomiting syndrome (CVS) is a disorder defined by sudden, recurrent episodic attacks of nausea and vomiting, which can last from hours to days (1–4). It most commonly occurs in children with an incidence of 3.15/100,000 children (4). The CVS attacks recur in a similar pattern for each patient and patients are usually free of symptoms between episodes. Due to the intensity and severity of these episodes, patients often require hospital care and therefore school days or parental work is frequently missed and patients often require hospital care (5). This results in a reduced quality of life and a large cost of care is incurred annually (5). Consensus guidelines for the diagnosis and treatment of CVS have been formulated by a committee from the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) based on a systematic review of the medical literature, clinical experience, and expert opinion (6). Unfortunately, CVS patients can have a presentation similar to patients with vomiting secondary to organic etiologies (6,7). Diagnosable disorders that can mimic CVS affect 5 main systems: gastrointestinal, neurological, metabolic/mitochondrial, endocrinological, and urological. Gastrointestinal disorders that may mimic CVS include bowel obstruction, inflammatory diseases, pancreatic, and hepatobiliary disease. Neurological etiologies include: space-occupying central

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nervous system lesions, Chiari I malformation, familial dysautonomia, and epilepsy. Metabolic and mitochondrial disorders that may present with recurrent emesis include amino acidurias, organic acidurias; fatty acid oxidation defects; urea cycle defects; acute intermittent porphyria, Leigh disease, and mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) (8). Endocrinological disorders that mimic CVS include Addison disease, pheochromocytoma, and diabetes mellitus and urological disorders include obstructive uropathy and nephrolithiasis (6,9). Other etiologies to consider are drug abuse (chronic marijuana use, high-dose fat-soluble vitamins, nonsteroidal anti-inflammatory drugs, and laxatives), toxins (alcohol), and psychological (Munchausen syndrome by proxy) (10). Therefore, it is important to have laboratory and radiological evaluation done as recommended by the consensus guidelines. These recommended investigations can become extensive and costly. In addition, it is suggested that the laboratory evaluation be obtained during an acute attack and before initiation of intravenous fluids and treatment, which can result in delay of patient treatment. Due to the current environment of limiting healthcare costs, the value of obtaining the screening studies for CVS needs to be scrutinized. There has not been a study to date that evaluates the benefits and costs of these evaluations in diagnosing CVS. We aim to investigate the diagnostic practices, yield, and costs incurred while evaluating children with CVS. Furthermore, we plan to estimate the prevalence of other abnormalities in children referred for CVS evaluation at a tertiary care center.

METHODS

The present, retrospective, single-center study was based on existing administrative and clinical data from Ann and Robert H Lurie Children's Hospital of Chicago (LCH) (Illinois). The electronic database (EPIC) of LCH expedited the retrieval of medical records and provided pertinent information for the study, which included the history of all patient encounters in the hospital and outpatient clinics, as well as laboratory, imaging and endoscopy results from all children cared for in the institution. Records of patients, ages 1 to 18 years old, from January 2008 to December 2014 were searched in EPIC for the International Classification of Diseases-9 code 536.2 or search terms ''cyclic vomiting syndrome, cyclic vomiting, persistent emesis, persistent vomiting, hyperemesis, intractable vomiting, or periodic vomiting.'' Only patients who had the screening laboratory tests performed at LCH were included.

Data were manually reviewed to determine if each patient met criteria for CVS based on NASPGHAN clinical guidelines (6). This included at least 5 attacks in any interval or a minimum of 3 attacks during a 6-month period, episodic attacks of intense nausea and vomiting lasting 1 hour to 10 days and occurring at least 1-week apart, stereotypical pattern and symptoms in the individual patient, vomiting during attacks occurring at least 4 times per hour or at least 1 per hour, returning to baseline health between episodes, and finally vomiting not attributed to another disorder.

Data regarding demographic characteristics, laboratory studies, imaging and endoscopic evaluations of each patient were manually abstracted. Further history was manually reviewed to determine whether the patient had alarm symptoms such as bilious emesis, abdominal pain or tenderness, hematemesis, attacks precipitated by fasting, attacks precipitated by intercurrent illness, or attacks precipitated by a high-protein meal. Physical examinations were also manually reviewed to determine whether each patient had any red flag symptoms, which include severe altered mental status, abnormal eye movements, papilledema, motor asymmetry, or a gait abnormality to suggest another etiology for their vomiting. Laboratory evaluations that were manually reviewed included a basic metabolic panel, which has sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose, and subsequent anion gap. Complete metabolic panel, which includes all the tests in the basic metabolic panel in addition to alanine transaminase, aspartate transaminase, total protein, albumin, alkaline phosphatase, and bilirubin was also reviewed. Other laboratory values reviewed included amylase, lipase, urine ketones, lactate, ammonia, serum amino acids, urine amino acids, plasma carnitine, acylcarnitine, and a gamma glutamyl transferase. Abnormal values were based on the normal ranges provided at the LCH laboratory. Imaging reports that were studied included an upper gastrointestinal (UGI) series (also called barium swallow/meal/follow through), brain magnetic resonance imaging (MRI), and ultrasound of the abdomen and pelvis. Results of endoscopic biopsies were examined as well.

Costs for the diagnostic tests and consultations were estimated using the amounts charged by the hospital to the payer in 2015. Costs for endoscopies included operating and recovery room charges, medications and supplies, anesthesia, pathology, and physician procedure fees. The present study was approved by the institutional review board of LCH.

RESULTS

A total of 503 charts were reviewed from electronic medical records with the International Classification of Diseases-9 code 536.2 or search terms ''cyclic vomiting syndrome (n = 89), cyclic vomiting (n = 37), persistent emesis (n = 28), persistent vomiting (n = 343), hyperemesis (n = 1), intractable vomiting (n = 1), or periodic vomiting (n = 4).'' There were 165 patients with a primary diagnosis or chief complaint of CVS. Of the 165 patients, 135 (82%) met CVS criteria based on NASPGHAN clinical guidelines (Fig. 1). The other 30 (18%) patients did not meet the criteria of CVS as they had another diagnosis, which could be contributing to their symptoms which included seizure disorder, migraine, gastroparesis, uretero-pelvic junction (UPJ) obstruction, cerebral palsy,

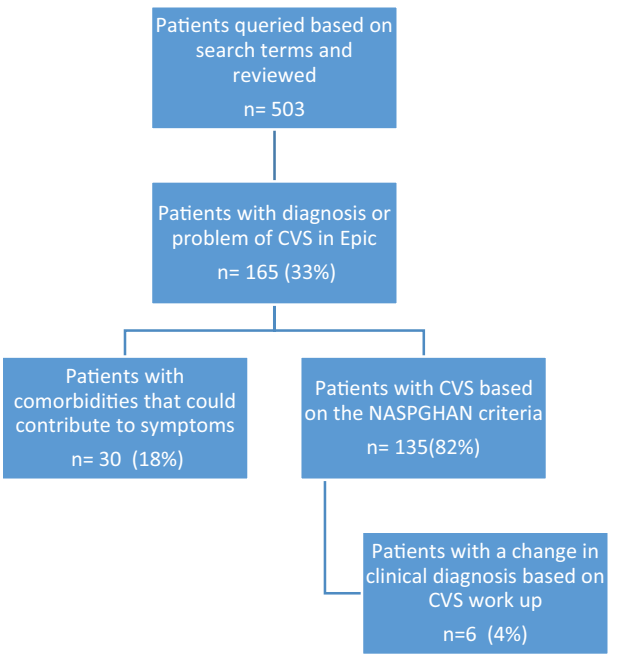

FIGURE 1. Results of screening patients who met cyclic vomiting syndrome (CVS) criteria.

TABLE 1. Abnormal clinical symptoms or physical examination findings

	Abnormal symptoms or signs, n (%)	Total number of patients
Bilious emesis	9 (7)	135
Abdominal pain or tenderness	67 (50)	135
Hematemesis	7 (5)	135
Attacks precipitated by fasting	1 (1)	135
Attacks precipitated by inter-current illness	6 (4)	135
Attacks precipitated by high protein meal	0 (0)	135
Neurological abnormalities	3 (2)	135
Papilledema	0 (0)	49

Angelman syndrome, Gitelman syndrome, rumination, irritable bowel syndrome, Ehlers-Danlos, postural orthostatic tachycardia syndrome, holoprosencephaly, Vertebral-Anal-Tracheo-Esophageal-Renal (VATER) syndrome, myofascial pain syndrome, Lennox-Gastaut, migraines, left hydronephrosis, intestinal failure, autism, and hydrocephalus. Table 1 describes abnormal clinical symptoms or physical exam findings from the 135 patients who met criteria of CVS. Abnormal laboratory, imaging, and endoscopic results are described in Table 2.

There were 135 children, mean age was 7.7 ± 4.3; and 73 (54%) were girls, who met CVS criteria. 6 (4.4%) of the 135 children had a change in medical management based on the CVS screening work up. In these 6 patients, the diagnosis changed to unspecified metabolic condition, carnitine deficiency, UPJ obstruction, increased intracranial pressure (ICP), lactose intolerance, and eosinophilic esophagitis (EoE).

Screening laboratory results such as basic metabolic panel, comprehensive metabolic panel, amylase, lipase, and gamma glutamyl transferase did not change management. Metabolic laboratory results (urine ketones, lactate, urine organic acids, and carnitine) were beneficial in detecting an unspecified metabolic condition and carnitine deficiency in 2 patients (1.4%) who presented with lethargy, failure to thrive, and recurrent emesis. Of the 135 patients who met CVS criteria, an UGI series was performed in 76 patients with 5 (7%) being abnormal. There was no change in management based on the abnormal results from a patient with a prior history of Ladd procedure secondary to malrotation, redundancy of duodenum, and superior mesenteric artery syndrome, who concurrently had CVS and gastroesophageal reflux. Abdominal and pelvic ultrasound was performed in 61 patients with 5 (8%) having abnormal findings. Pelvic ultrasound changed management in 1 patient (0.7%) who had UPJ obstruction. The other 4 abnormal ultrasounds did not change management with their findings of pelviectasis and 1 with superior mesenteric artery syndrome in a patient that concurrently had CVS. Brain MRI was performed in 68 patients with 10 (15%) reported as abnormal. Of those that were abnormal, management was changed in 1 patient (0.7%) who had increased ICP, but this patient also had a prior history of hydrocephalus with a ventriculo-peritoneal shunt with recent normal shunt series. The other patients with abnormal brain MRI findings were secondary to patients with seizure disorder, cerebral cyst, macrocephaly, Chiari I malformation, and unmyelinated white matter of the periventricular region. Upper endoscopy with biopsy performed in 36 patients with 7 (19%) being abnormal. Upper endoscopy with biopsy changed diagnosis in 2 patients (1.4%) from CVS to lactose intolerance and EoE. The diagnosis of lactose intolerance was based on low lactase enzyme level in duodenal mucosal biopsies. One patient had *Helicobacter pylori* gastritis that was treated but the underlying primary diagnosis of CVS remained unchanged. The other 4 patients had non-specific abnormal biopsy findings, which did not result in change in management.

TABLE 2. Abnormalities in laboratory, imaging or endoscopic results (n = 135)

	Abnormal results, n (%)	Test performed	Abnormal results that changed management (%)
Sodium	5 (5)	94	0 (0)
Potassium	13 (14)	94	0 (0)
Chloride	9 (10)	94	0 (0)
Bicarbonate	27 (29)	94	0 (0)
BUN	15 (16)	94	0 (0)
Creatinine	16 (17)	94	0 (0)
Glucose	31 (33)	94	0 (0)
Amylase	4 (6)	63	0 (0)
Lipase	1 (1)	72	0 (0)
Alanine transaminase	5 (6)	87	0 (0)
Aspartate transaminase	5 (6)	87	0 (0)
Total bilirubin	6 (7)	87	0 (0)
Direct bilirubin	0 (0)	64	0 (0)
Total protein	10 (12)	87	0 (0)
Albumin	26 (30)	87	0 (0)
Alkaline phosphatase	7 (27)	26	0 (0)
Gamma glutamyl transferase	0 (0)	16	0 (0)
Anion gap	1 (1)	72	0 (0)
Urine ketones	23 (39)	59	2 (1.4)
Lactate	2 (5)	40	2 (1.4)
Ammonia	4 (11)	38	0 (0)
Serum amino acids	5 (12)	42	0 (0)
Urine organic acids	7 (19)	37	2 (1.4)
Plasma carnitine	8 (22)	37	2 (1.4)
Acylcarnitine	2 (5)	39	0 (0)
UGI series	5 (7)	76	0 (0)
Brain MRI	10 (15)	68	1 (0.7)
Abdominal and pelvic ultrasound	5 (8)	61	(0.7)
Upper endoscopy with biopsy	7 (19)	36	2 (1.4)

BUN = blood urea nitrogen; MRI = magnetic resonance imaging; UGI = upper gastrointestinal.

Financial Burden of Testing

The total billed charges for all investigations performed for patients that met CVS criteria was $826,877.88 (Table 3) and $307,445.61 for patients who had a diagnosis of CVS but did not meet CVS criteria based on NASPGHAN clinical guidelines, totaling cost of $1,134,323.49. The mean (± SD) charge to evaluate 1 patient with CVS was $6125.02. The mean charges incurred in discovering a newly diagnosed patient with unspecified metabolic condition and carnitine deficiency $5303.28, UPJ obstruction $1986.48, increased ICP $3586.68, and lactose intolerance and EoE $23,000.

DISCUSSION

CVS is a functional disorder characterized by recurrent stereotypical episodes of intense nausea and vomiting, lasting for hours to days, with symptom-free intervals between the episodes (6). Strict clinical criteria have been developed to diagnose CVS (6).

TABLE 3. Cost of evaluating children with diagnosis of cyclic vomiting syndrome (n = 165)

Test	Number of tests performed of children that met criteria for CVS (n = 135)	Number of tests performed on children who did not meet CVS criteria (n = 30)	Charge per test (charges, $USD)
Basic metabolic panel	94	26	235.59
Hepatic function panel	87	24	299.06
Gamma glutamyl transferase	16	7	179.28
Direct bilirubin	64	17	137.25
Amylase	63	16	213.00
Lipase	72	19	196.70
Lactate	40	9	476.00
Ammonia	38	10	259.37
Urine ketones	59	18	58.14
Urine organic acids	37	10	630.34
Serum amino acids	42	10	788.10
Plasma carnitine	37	9	538.10
Acylcarnitine	39	9	142.00
UGI	76	18	1569.00
Brain MRI	68	19	3586.68
US abdomen and pelvis	61	19	1986.48
Endoscopy	36	10	11,500.00
Total cost of 135 children who met CVS criteria			826,877.88
Total cost of 30 children who did not meet CVS criteria			307,445.61
Total cost of 165 children with diagnosis of CVS			1,134,323.49

CVS = cyclic vomiting syndrome; MRI = magnetic resonance imaging; UGI = upper gastrointestinal.

There are a many disorders that can present with symptoms of recurrent vomiting. Li et al (7) established diagnostic profile of 225 children presenting with cyclic vomiting and 88% were felt to have CVS based on either the absence of any laboratory findings or an incomplete response to treatment of an identified finding. It becomes a challenge to the practitioner to differentiate between CVS and more serious causes of vomiting.

Red flags that raise suspicion for a metabolic disorder include any degree of electroencephalogram abnormality, encephalopathy with attacks, and attacks triggered by fasting, illness, or high-protein, carbohydrate, or high-fat foods. The diagnostic yield of metabolic testing is higher if performed during an acute symptomatic exacerbation (8). UPJ obstruction may present at any age, with symptoms including nausea, vomiting, epigastric pain, periumbilical pain, more localized flank pain, unilateral back pain, hematuria, urinary tract infection, palpable mass, or failure to thrive (11). In 1 case report, a diagnosis was delayed by 2 years as abdominal or flank pain was the only suggestive symptom and thus the child could only indicate its presence when older (9)

NASPGHAN clinical guidelines recommend a diagnostic approach that begins with a basic workup first to avoid ''shotgun'' testing. They recommend to instead use a strategy of targeted testing that varies with the presence of 4 red flags: abdominal signs (eg, bilious vomiting, tenderness), triggering events (eg, fasting, high protein meal), abnormal neurological examination (eg, altered mental status, papilledema), and progressive worsening or a changing pattern of vomiting episodes. Olson and Li (12) previously found the most cost effective therapy in the management of CVS to be UGI with small bowel follow through (SBFT) with empiric treatment for CVS.

Our study showed that only a few children with symptoms consistent with CVS, who underwent laboratory testing at our tertiary referral center, were diagnosed with a disease other than CVS.

These diagnoses made by laboratory testing were not confirmed by clinical response to treatment. In the patients diagnosed with lactase deficiency and EoE, both conditions are unlikely to lead to episodic vomiting. Therefore, it is possible that both diagnosis were incidental findings in addition to the presence of CVS. Physicians in tertiary centers tend to test for rare conditions, which is sometimes driven by the parent's desire to make sure that all possible organic etiologies are ruled out. This practice of testing for everything possible likely leads to a lower yield of screening tests in tertiary centers.

There have been no studies that estimate the total cost involved in the management of patients that undergo the workup following the NASPGHAN guideline algorithm. The utility of laboratory investigations needs to be considered, especially in times of limited resources when physicians should be aware of the costs and yield of testing. Our study indicates that the cost related to CVS in children in the United States is substantial. The average cost of evaluating each child in our center was $6125.02. This represents 99.5% of the annual per capital health care expenditure in the United States for 2012 ($9900.00 per capita) (13). Endoscopy was the largest cost in diagnostic workup with charge per test costing $11,500.00 and a cumulative cost for those with a diagnosis of CVS $414,000.00. Given the cost of endoscopy, it is important to consider the diagnostic yield when evaluating a patient for CVS. The low yield of these screening tests should prompt the medical community to conduct prospective studies specifically designed to assess common practices and analyze the costs and yield of each medical action.

The limitations of our study include its retrospective nature, being conducted in a single tertiary care center and the possible lack of submission of all prior investigations by referring physicians. Due to the retrospective design, we were unable to determine exact algorithm for patients' workup or determine whether there were other functional associations to their vomiting. Therefore, our study results are indicative of the practice in our tertiary center and are not strictly reflective of the NASPGHAN consensus–driven practice. We were also not able to determine causality between NASPGHAN guidelines and amount of testing performed. Patients were not

followed longitudinally and therefore, long-term outcomes of reduced cost could not be determined. We cannot affirm that the results of our study represent the practice variations of the whole pediatric GI community across the United States; however, it probably reflects the common practice of care. The study includes physicians and nurse practitioners with different levels of training and expertise. Our study only assessed the costs directly related to the evaluation of CVS. The cost of the prescribed medications and the indirect expenses related to missed parental work, childcare for other children, and transportation costs for the appointment were not calculated. This study does not contradict current NASPGHAN guidelines but suggests that further studies are warranted to determine whether we need to modify the NASPGHAN guidelines to minimize the initial screening performed on patients with suspected CVS.

CONCLUSIONS

The screening metabolic laboratory results, pelvic ultrasound, MRI, and upper endoscopy resulted in a change of diagnosis in few patients screened for suspected CVS. Most children who met criteria for CVS did not benefit from screening laboratory results or studies, as results did not change clinical management. High healthcare costs were associated with the use of screening tests for suspected CVS.

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