Pediatric Neurology 50 (2014) 569–573

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Original Article

Approach to the Diagnosis and Treatment of Cyclic Vomiting Syndrome: A Large Single-Center Experience With 106 Patients

Jonathan Moses MD [a], Ashley Keilman MS [b], Sarah Worley MS [c], Kadakkal Radhakrishnan MD [a], A. David Rothner MD [d], Sumit Parikh MD [d,e,*]

[a] *Department of Pediatric Gastroenterology, The Cleveland Clinic, Cleveland, Ohio*
[b] *Case Western Reserve University, School of Medicine, Cleveland, Ohio*
[c] *Department of Quantitative Health Sciences, The Cleveland Clinic, Cleveland, Ohio*
[d] *Center for Pediatric Neurology and Neurosurgery, The Cleveland Clinic, Cleveland, Ohio*
[e] *Program for Pediatric Neurometabolism/Neurogenetics, The Cleveland Clinic, Cleveland, Ohio*

ABSTRACT

BACKGROUND: Cyclic vomiting syndrome is characterized by repeated, stereotypical vomiting episodes. The diagnosis is made by exclusion of other organic diseases, which can lead to extensive testing. It has been suggested that these patients can have mitochondrial dysfunction. The aim of the study was to examine the evaluation of our cyclic vomiting patients and to determine whether they had associated, undiagnosed metabolic abnormalities. **METHODS:** This retrospective study included 106 patients aged <21 years at diagnosis. Information regarding medical history, laboratory, and imaging studies were collected. Metabolic studies in plasma and urine were obtained when patients were well and when patients were in a vomiting cycle, including plasma amino acids, acylcarnitines, and urine organic acids. **RESULTS:** The mean age at diagnosis was 8.9 ± 5.0 years. Neuroimaging revealed previously unknown intracranial abnormalities in <10% of patients, none of whom explained the vomiting signs. Abdominal ultrasounds revealed abnormalities in 15% of patients during an acute episode and 7% of patients when well. Sixty-one patients had an upper gastrointestinal series, all of which were normal. A total of 92% of patients had laboratory testing with 38% indicating abnormalities possibly suggesting mitochondrial dysfunction. **CONCLUSIONS:** This large, single-center study further evaluated the need for more focused evaluation in patients with suspected cyclic vomiting syndrome. Thirty-eight percent of our patients had abnormalities in blood and/or urine suggesting mitochondrial dysfunction, which requires more detailed investigation in the future.

Keywords: pediatrics, vomiting, mitochondrial disorder, metabolic testing

Pediatr Neurol 2014; 50: 569-573

Introduction

Cyclic vomiting syndrome (CVS) is characterized by repeated, stereotypical vomiting episodes that are accompanied by debilitating nausea and/or severe headaches.[1] The prodrome, onset, nature, and duration of signs and the frequency of episodes are consistent within a single patient but may vary between patients.[1-3] CVS is a chronic disorder of unknown etiology and is a diagnosis made by exclusion of other organic diseases.[1,4] As such, the clinician must eliminate other conditions without using excessive testing. Multiple societies have described diagnostic criteria to simplify establishing the diagnosis for the clinician.[1,4,5] The treatment approach to CVS is twofold. Acute treatment, used to ameliorate or abort signs, can include a combination of antiemetics, antihistamines, benzodiazepines, and intravenous fluids.[1,5-7] Prophylactic medications are used to reduce the frequency of attacks.

It has been suggested that some CVS patients may have underlying mitochondrial dysfunction as a part of their clinical picture.[7,8] Evidence to support this theory includes

Article History:
Received December 18, 2013; Accepted in final form February 12, 2014
* Communications should be addressed to: Dr. Parikh; Department of Pediatric Neurometabolism/Neurogenetics; 9500 Euclid Avenue; Mail code: S60; Cleveland, OH 44195.
E-mail address: parikhs@ccf.org

0887-8994/$ - see front matter © 2014 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.pediatrneurol.2014.02.009

clinical improvement when treated with carnitine and/or coenzyme Q10 and a maternal inheritance of migrainous signs, along with the identification of certain polymorphisms in the mitochondrial DNA sequence of CVS patient vs control groups.[9,10] The aim of this study was to examine our single-center experience with a CVS patient population as it relates to their clinical presentation, the nature of their signs, and the diagnostic evaluation performed in establishing their CVS diagnosis. In addition, we aimed to examine results of metabolic testing in these patients and the clinical response to commonly used medications.

Methods

Study population

We conducted a retrospective, single-center study of 106 newly diagnosed patients followed for management of CVS. The patients were enrolled from The Cleveland Clinic Children's Hospital Departments of Pediatric Gastroenterology and Pediatric Neurology from January 2007 to July 2010. The Institutional Review Board at the Cleveland Clinic approved the study.

Study inclusion required a new diagnosis of CVS made at an age of <21 years. We defined CVS based on established standards in the published literature, most consistent with the Rome III criteria, as follows: (1) a pattern of vomiting episodes, with a duration of <1 week and a period of wellness between episodes, (2) a stereotypical pattern to the acute episodes, and (3) exclusion of other organic disease as a cause for their signs.[1,6,7] Clinicians used these guidelines and their expert opinion to determine the diagnosis in each patient. Children who were subsequently evident to have another etiology for their signs during the diagnostic evaluation were excluded from the study based on findings of history and physical examination (Table 1).

A standard protocol is in place at our institution for the evaluation of patients referred for vomiting with concern for CVS. A pediatric neurologist (S.P. or A.D.R.) and a pediatric gastroenterologist (K.R.) evaluated each patient. The evaluation consisted of a comprehensive history taken using a standard template in the electronic medical records, which included a detailed neurological and gastrointestinal physical examination, imaging studies, and laboratory testing using an internal protocol.

The data collection involved patient demographics, anthropometrics, past medical history, CVS characteristics, imaging findings, laboratory results, endoscopic procedures, and treatment response. Imaging studies included an abdominal ultrasound (US), upper gastrointestinal series (UGI), and brain magnetic resonance imaging (MRI). Laboratory studies included a hemogram, chemistry panel, and liver function tests. Metabolic laboratories included non-fasting plasma amino acids, acylcarnitine profile, lactate, pyruvate, ammonia, ketones, and urine organic acids. The abdominal US and laboratory tests were obtained when the patient was well and during an acute attack, when possible. Patients were not receiving intravenous fluids when metabolic tests were obtained and were typically performed in an outpatient setting. Specimens obtained during a vomiting cycle were not timed but rather dependent on when a family could take the child to the laboratory. Given the patients were actively vomiting at the time, it is possible these laboratories were fasting samples. An esophagogastroduodenoscopy was performed at the discretion of the evaluating pediatric gastroenterologist (K.R.).

Response to treatment with acute and prophylactic medications was assessed at follow-up. Response to acute medications was defined as any of the following: (1) decreased severity or duration of acute episodes, (2) complete resolution of acute episodes, or (3) avoidance of emergency department visit. Response to prophylactic medications was defined as any of the following: (1) resolution of abnormalities since initiating treatment, (2) decreased frequency or duration of acute episodes (within the last 6 months), or (3) decreased number of emergency department visits (within the last 1 year).

TABLE 1.
Alternate Diagnoses or Comorbidities Established During the Evaluation for CVS

- Frequent or chronic vomiting
- Progressive encephalopathy
- Chronic daily headaches
- Migraine without aura
- Postviral gastroparesis
- Gastoesophageal reflux disease
- Delayed gastric emptying
- Eosinophilic gastroenteritis
- Hydronephrosis

Statistics

Patient groups were described using means and standard deviations for continuous variables and counts and percentages for categorical variables and compared using *t* tests for continuous variables and chi-square or Fisher exact tests as appropriate for categorical variables. Sample sizes for individual variables reflect missing data. All analyses were performed on a complete-case basis. Study data were collected and managed using REDCap electronic data capture tools hosted at The Cleveland Clinic. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing (1) an intuitive interface for validated data entry, (2) audit trails for tracking data manipulation and export procedures, (3) automated export procedures for seamless data downloads to common statistical packages, and (4) procedures for importing data from external sources.[11] All tests were two tailed and performed at a significance level of 0.05. SAS 9.2 software (SAS Institute, Cary, NC) was used for all analyses.

Results

Patient characteristics

The demographics, past, and family medical history are described in Table 2. One hundred six patients were included in the study population. The mean age at diagnosis was 8.9 ± 5.0 years. Of the 106 patients, 58% were male patients and 79% were Caucasian. A personal history of migraine was present in 25% of the children and 72% had a family history of migraine. The characteristics of their CVS episodes are described in Table 2. The average duration of each cycle was 24 hours, with 18 episodes of vomiting per cycle and a peak vomiting intensity of five emeses per hour. Abnormalities completely resolved between episodes in 88% of patients. Episode triggers were identified in 66% of patients, as listed in Table 3. Autonomic signs, including fever and hypertension, were observed in 25% of patients.

TABLE 2.
Demographics, Past and Family Medical History, and CVS Characteristics

Factor	n = 106
Age at diagnosis (yr)	8.9 ± 5.0
Male, n (%)	61 (58)
Caucasian, n (%)	84 (79)
Personal history of migraines, n (%)	27 (25)
Family history of migraines, n (%)	76 (72)
Family history of epilepsy, n (%)	11 (10)
Median duration of cycles (in hr)	24 (1-336)
Episodes of vomiting (per cycle)	18 (1.5-600)
Peak number of emeses (per hr)	5 (1-20)
Complete resolution of abnormalities between cycles (%)	88