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Rapid or Normal Gastric Emptying as New Supportive Criteria for Diagnosing Cyclic Vomiting Syndrome in Adults

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Background: Cyclic vomiting syndrome (CVS) in adults is a disorder characterized by recurrent and stereotypic episodes of severe nausea, vomiting and abdominal pain separated by symptom-free intervals. Our goal was to investigate gastric emptying (GE) in CVS patients.





Material/Methods: This was a retrospective study of 30 adult patients who met Rome III diagnostic criteria for CVS. Rapid GE was defined using two different predefined criteria as either <50% isotope retention or <65% isotope retention at 1st hour and/or <20% at 2nd hour.

Results: Of the 30 patients (25 had 4-hr GE) diagnosed with CVS, 22 were females and 8 males with a mean age of 39 years. Overall, 20 (80%) of the 25 CVS patients met the predefined criteria of <50% retention for rapid GE in the first hour. Fifteen (60%) met the 2-hour criteria for rapid emptying of <20% retention. Five (16.6%) patients of the 25 had a normal GE with a mean retention at the first hour of 65% (52–78%). Nine (36%) also met another predefined criteria of <35% retention for rapid GE in the first hour. Sixteen (64%) met criteria for normal GE.

Conclusions: (1) In adult CVS patients, GE is either rapid or normal, clearly distinguishing this entity from gastroparesis. (2) Cyclic vomiting syndrome is an important new etiology to explain the finding of rapid GE on a radionuclide test. (3) We suggest that rapid gastric emptying should be added as supportive criteria for diagnosing CVS in adults.

MeSH Keywords: **Gastric Emptying • Gastroparesis • Nausea • Vomiting**

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Background

Cyclic vomiting syndrome (CVS) is an idiopathic disorder that is characterized by relentless bouts of vomiting separated by symptom free intervals. The etiology and pathogenesis of CVS remain unknown. It was first described in children, but has increasingly been more recognized in adults. It has been estimated that up to 1.6% of children experience symptoms consistent with this disorder, but the prevalence in adults is unknown [1]. Recent referral patterns suggest a prevalence approximating 0.2% in the adult population. CVS has an average age of onset of 35 years old but these patients are not actually diagnosed until about 41 years old with no predilection for a specific gender.

Functional gastrointestinal (GI) disorders are comprised of symptoms arising in the GI tract that are not otherwise attributable to a known structural or biochemical explanation [2]. CVS is a functional gastrointestinal disorder in which the diagnosis is made clinically based on the criteria set forth by the consensus of expert opinion in the Rome III Criteria for Functional Gastrointestinal Disorder (Table 1) [3].

CVS consists of four phases: inter-episodic, prodromal, emetic and recovery phase. Recognition of this pattern of phases can help in making the diagnosis and in management. The inter-episodic phase is relatively symptom-free. The prodrome begins when the patient can sense the approach of an episode but can still tolerate oral intake. The vomiting or emetic phase is characterized by intense, persistent nausea, vomiting and other symptoms. The recovery phase begins with the remission of the nausea and vomiting and terminates when the patient has fully recovered [4]. The best treatment is to prevent the episodes of CVS by initiating a daily therapy regimen [5].

CVS can range from a mild disease with infrequent episodes to severe and debilitating disease that leads to frequent emergency department visits and hospitalizations. The frequency of CVS episodes averages about 12 episodes per year [6]. Over time without appropriate treatment the episodes begin to coalesce and then there is the perception of more chronic symptoms with few asymptomatic of "remission" days. The majority of cyclic vomiting attacks have been associated with a physiologic trigger mechanism. These include infection, psychological stress, physical stress, lack of sleep, poor diet and onset of menses. Migraine headaches, anxiety and depression are frequently reported to coexist with CVS [7]. Cyclic vomiting syndrome in adults has some different characteristics than children with the following hallmarks: 1) prominence of accompanying epigastric or diffuse abdominal pain; 2) increased prevalence of anxiety and depression; 3) normal or rapid gastric emptying and tachygastric electrogastragram (EGG) findings

Table 1. Rome III Diagnostic Criteria for CVS.

Must be at least three months, with the onset at least six months previously of:
1. Stereotypical episodes of vomiting regarding the acute onset and duration being <1 week
2. Three or more discrete episodes in the prior year
3. Absence of nausea and vomiting between episodes
4. Absence of any organic cause of vomiting
5. Supportive Criteria: Either a prior history or family history of migraine headaches

and 4) successful suppression of attacks by chronic amitriptyline therapy [8].

The diagnosis of CVS is primarily based on history and clinical presentation. Increased awareness of the condition and a high index of suspicion may help decrease delay in diagnosis after symptom onset [9]. Making a definitive diagnosis of CVS requires the exclusion of other disorders associated with recurrent vomiting. Many medications can cause nausea and vomiting and most recently chronic daily marijuana use has been identified as inducing cyclical hyperemesis [10]. Due to the frequent misdiagnosis of CVS, the patient can be exposed to many unnecessary diagnostic tests and is therefore not initially treated appropriately.

There is an emerging consensus that CVS appears to involve dysregulated central neural pathways and neuro-endocrine mediators involved in the afferent and efferent brain – gut pathways of nausea and vomiting [11]. CVS is a functional brain-gut disorder that involves peripheral gastrointestinal mediation and central neuroendocrine [12,13]. Venkatesan et al. revealed that 90% of CVS patient in their study had evidence of sympathetic dysfunction [14]. No patients were found to have parasympathetic dysfunction. Their study suggests that sympathetic dysfunction plays an important role in CVS. Understanding why CVS patients have a rapid gastric emptying study (GES) in the vomiting free period suggests that an underlying autonomic dysfunction exists. Humoral factors and hormones have also been postulated to explain the rapid GES.

There are reports suggesting that patients with CVS have either a rapid or normal gastric emptying result [3,15]. This finding is important in being able to differentiate the entity of CVS from gastroparesis because symptoms can become very similar as the CVS attacks become more frequent [15]. Hence our goal was to investigate gastric emptying in a population of CVS patients in order to further understand the spectrum and characteristics of gastric emptying in CVS patients.

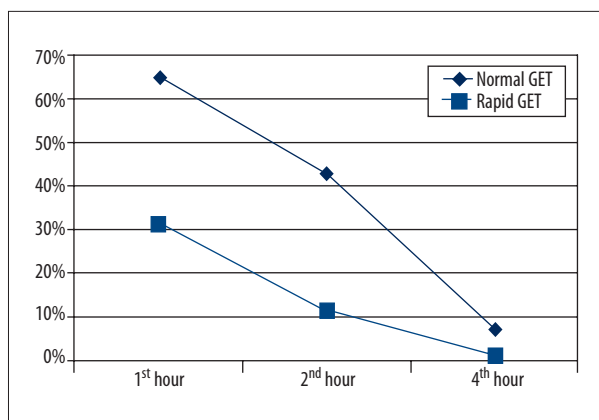


Figure 1. Mean GET for normal and rapid GE based on <50% retention criteria.

Material and Methods

Patients with the primary diagnosis of CVS were eligible for participation in the research study. For our retrospective study, thirty medical charts were reviewed of patients who met Rome III diagnostic criteria for CVS (Table 1) and presented for a new visit or follow up to Texas Tech University clinic of Gastroenterology in El Paso, Texas from 2009 to 2012. The study protocol was approved by the Institutional Review Board (IRB) of Texas Tech University Health Sciences Center of El Paso, Texas. Demographic data, comorbidities, GES results and amitriptyline dose were recorded.

Gastric emptying study

Gastric emptying time (GET) was assessed by standard 4-h scintigraphic method using a low fat solid meal. Scintigraphic GET was performed during the remission or quiescent stage of their disease. Patients were instructed to fast overnight and stop prokinetics and proton pump inhibitors (PPI) for at least 3 days and narcotic medication were withheld for more than 12 h. For diabetic patients, the glucose level had to be <250 mg/dL at the start of the meal or it was rescheduled unless glucose levels could be reduced. A standardized scintigraphic gastric emptying protocol involving a low fat (2%) isotope labeled egg white meal of 250 Kcal was performed. Anterior and posterior gastric images in the standing position were obtained at 0, 1, 2, 4 h after meal ingestion. During the 4 h of the assessment all patients remained upright, either walking or sitting. There was no reclining or sleep permitted.

Normal GE was defined as < 90% retention at 1 h, < 60% at 2 h, and <10% at 4 h. Rapid GE was defined using two different predefined criteria as either <50% isotope retention or <65% isotope retention at 1st hour and/or <20% at 2nd hour. Delayed gastric retention was defined as a delay of greater than 90% at 1 h, 60% at 2 h, and >10% at 4 h based on

Table 2. Summary of GET results (1, 2, 4 hours) based on the <50% retention criteria.

Mean GET% retention	Normal GET (n=5), mean (range)	Rapid GET (n=20), mean (range)
1 st hr	65% (52–78%)	31.3% (25–49%)
2 nd hr	43% (31–63%)	11.4% (5–17%)
4 th hr	7% (0–10%)	1% (0–9%)

Table 3. % Patients with rapid (<50% retention at 1st hour) or normal GE.

Rapid GES at 1 st hour	80%	(n=20)
Rapid GES at 2 nd hour	60%	(n=15)
Normal GES	16.6%	(n=5)

normal data established for this standardized GES. The GET results were interpreted by the Texas Tech University of El Paso Department of Nuclear Medicine. A medical chart review was required to obtain prior gastric emptying study results and any additional data.

Statistical analysis

Descriptive statistics are presented as means or percentage for variables measured on a continuous scale (e.g., age) and as proportions for variables measured on a discrete scale (e.g., gender).

Results

Overall, 30 patient medical charts were analyzed in those diagnosed with CVS between the years 2009–2012. This included 22 females and 8 males with a mean age of 39 years (19 to 68 years). All patients reported nausea, vomiting and mid-epigastric pain. The majority of patients reported monthly episodes of cyclic vomiting that lasted for at least 5 days. Comorbidities included diabetes mellitus (30%), hypertension (30%), hyperlipidemia (26.6%), anxiety (46.6%), depression (36.6%), migraines (36.6%), panic disorder (6.6%), and chronic daily marijuana use (30%) for more than 5 years.

Overall, 20 (80%) of the 25 CVS patients met the predefined criteria of <50% retention for rapid GE in the first hour with a mean retention of isotope at 1st hour of 31.3% (25–49%) (Figure 1, Tables 2, 3). Fifteen (60%) met the 2-hour criteria for rapid emptying with a mean retention of 11.4% (5–17%). Five (16.6%) patients of the 25 had a normal GE with a mean retention at the

Table 4. % Patients with rapid (<35% retention at 1st hour) or normal GE.

Rapid GES at 1 st hour	36%	(n=9)
Normal GES	64%	(n=16)

first hour of 65% (52–78%) (Table 4). Nine (36%) met the pre-defined criteria of <35% retention for rapid GE in the first hour. The remaining sixteen (64%) patients met criteria for normal GE. Interestingly 19 (70%) of the patients were being treated with amitriptyline in doses ranging from 10 mg to 200 mg at night at the same time of the GE study.

Discussion

Our study, demonstrates that up to 80% of our adult patients with CVS had a rapid GE accounting with 16.6% being normal when using the <50% retention criteria. When using the <35% retention criteria 36% had a rapid GE and 64% had a normal GE. This data signals that CVS is a new addition to the differential diagnosis of rapid GE. This observation is very relevant for clinicians who may already suspect the diagnosis of CVS when evaluating patients with a questionable vomiting presentation. Identifying rapid or normal GE would provide confirmatory evidence of CVS and set the stage for initiating appropriate medical treatment by defiantly excluding the possibility of gastroparesis. This is particularly relevant in diabetics or when cycles of vomiting are becoming more frequent and gastroparesis is raised as a differential diagnosis. Gastric emptying studies should be performed during the remission phase when there are minimal or no symptoms and no narcotic medications are being received [16]. Patients hospitalized with CVS that are given narcotics can have a falsely delayed GE. Understanding why there is a rapid GE during a vomiting free period has led to speculation and support for an underlying autonomic dysfunction is

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these patients [1,17]. Cyclic vomiting syndrome is an uncommon diagnosis, however with improved awareness it is being recognized more in adults. However, there is still a significant delay between onset of symptoms and diagnosis in adults. CVS should be considered in the initial diagnostic evaluation for unrelenting nausea and vomiting and accompanying abdominal pain without another explanation. Increased awareness of this disorder can lead to a reduction in invasive and costly diagnostic workups. The clinical relevance of our study is that a rapid GE should alert the clinician to consider CVS in the differential diagnosis. We also recommend further prospective studies in larger populations and multiple centers with standard radionuclide 4-hour GET to better evaluate this observation. In adult CVS patients, GE is either rapid or normal, clearly distinguishing this entity from gastroparesis. The mechanism of why cyclic vomiting syndrome patients have a rapid GE is unknown but warrants future investigation.

Conclusions

Cyclic vomiting syndrome is an important new etiology to explain the finding of rapid GE on a radionuclide test. One hundred percent of CVS patients have either rapid or normal GE. This is a “signature” finding separating CVS from gastroparesis and hence we recommend that GE status be added as one of the criteria for the diagnosis of CVS.

Disclosures

All participated authors in this study declare no financial, professional or personal conflicts.

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All Authors were involved in manuscript preparation and literature review.

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