Original Article

The Two Sides of Opioids in Cyclical Vomiting Syndrome

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Abstract

Background: Cyclical vomiting syndrome is increasingly recognized in adults, with recent reports suggesting 'coalescing attacks' in one third of the patients. We hypothesized that the common need for opioid treatment may contribute to coalescing attacks through development of opioid dependence and withdrawal, triggering cyclical vomiting syndrome. **Aim:** This study was to review iatrogenic opioid dependence as the potential cause for triggering cyclical vomiting syndrome. **Materials and Methods:** A retrospective review was performed to identify patients treated for cyclical vomiting syndrome by a single physician between Jan and December of 2010. Demographic data, clinical presentation, treatment, cumulative opioid prescription during hospitalizations and emergency room visits and days of inpatient stay were abstracted from the chart. **Results:** Forty-one patients (mean age 37.5.6 ± 2.6 years; 66% female) were seen within this timeframe. In eleven patients (27%) with ongoing opioid use, the initial cyclical illness had progressed and eventually coalesced. A cohort of 23 patients was followed for at least 6 months (12.3 ± 1.7 months). The best single predictor of repeat hospitalizations was the cumulative opioid dosage. **Conclusion:** Continued use of opioid therapy is a poor prognostic marker of cyclical vomiting syndrome and may contribute to disease coalescence, with dependence and withdrawal triggering recurrent episodes.

Keywords: Cyclical vomiting syndrome, Coalescing attacks, Opioids

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Introduction

Cyclical vomiting syndrome (CVS) is an increasingly recognized disorder characterized by recurrent and stereotypic episodes of repetitive vomiting and abdominal pain with complete resolution of symptoms between such attacks.[1]

Despite this characteristic pattern, the diagnosis is often delayed and patients often undergo repeated testing and a variety of treatments. Exacerbations typically present quite dramatically and require treatment in emergency rooms or even admission with intravenous fluids, analgesic and antiemetic agents.[1,2] Published case series suggest that the majority of patients will respond with a decrease in attack frequency and/or severity to a range of interventions from tricyclic antidepressants to anticonvulsive agents or psychological interventions.[2-8] However, a subset of individuals continue experiencing attacks with increasing frequency and at times even ongoing difficulties without distinct symptom-free intervals, which has been referred to as coalescing CVS.[1,2] Considering the importance of pain and analgesic therapy, we hypothesized that iatrogenic opioid dependence may develop and contribute to the development of coalescing CVS. To address this question, we retrospectively analyzed demographic and clinical characteristics of all CVS patients seen by a single physician within a 10-month timeframe.

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Materials and Methods

This study was designed as retrospective review of all patients with CVS seen by a single physician between January and October of 2010. Patients were seen for

the first time or for follow-up visits, thus potentially extending the observation period beyond 10 months used to capture individuals. The study has been approved by Institutional Review Board of University of Pittsburgh (*IRB Protocol # PRO10100329*).

Data abstraction

The electronic medical records were reviewed to extract demographics, age of symptom onset, symptom pattern and the duration of typical CVS episodes. Coexisting illnesses and relevant family history were recorded. The medication used at the time of the initial encounter and during follow up was noted. The cumulative amount of opioids prescribed and/or administered during emergency room and hospital treatment was recorded and expressed as morphine equivalents using publically available conversion tables.[9] Finally, the frequency of emergency room visits, days of inpatient treatment and use of diagnostic tests were abstracted.

Statistical study

Descriptive and analytical statistics were performed using Sigma Stat 2.0 (SPSS, Chicago). Unless specifically mentioned, data are given as mean + SEM. The cohort was subdivided based on the clinical presentation, into patients with disease progression defined by increasingly frequent emetic episodes with eventual emergence of symptom coalescence compared to persons with persistence of the characteristic asymptomatic intervals. In addition, we examined the clinical course in a subgroup followed for at least 6 months and separately analyzed individuals with frequent hospitalizations and/or emergency room visits. Subgroup comparisons were performed using rank-sum tests. To identify potential predictors of frequent hospitalizations, we performed univariate analyses using the Spearman correlation coefficients. A *P* level of less than 0.05 was considered statistically significant.

Results

A total of 41 unique patients were seen within the time frame of this study. Out of this cohort, 23 patients were followed for at least 6 months (12.3 ± 1.7 months). The average age at symptom onset was at 29.3 ± 2.6 years of age; 10 patients (24%) reported symptom begin during childhood or adolescent years. The diagnosis had been previously established in only 5 patients (12%). Consistent with the defining criteria for CVS, patients reported more than 10 episodes of vomiting during the initial 24 h of an attack. The mean duration of episodes was 3.4 ± 0.3 days. Patient characteristics associated with CVS are shown in Table 1.

Table 1: Characteristics of patients with CVS

Characteristics	*N* (%)
Total number of patients	41
Male: Female	14:27
Abdominal pain	36 (88)
Diarrhea	10 (24)
Trigger factors	17 (41)
Prodromal	10 (24)
Early morning attacks	19 (46)
Anxiety	21 (51)
Depression	18 (44)
History of migraine	13 (32)
Dysautonomia	5 (12)
History of cholecystectomy	15 (37)
Marijuna consumption	13 (32)
Family history of CVS	3 (7)

Beyond unrelenting nausea and repetitive emesis, 36 patients reported severe abdominal pain during CVS attacks. The pain was located in the epigastric area (n = 13), left (n = 4) or right (n = 2) upper abdomen, diffusely across the abdomen (n = 9), peri-umbillical (n = 2) or in the lower abdomen (n = 6). Patients mostly focused on the intensity of the pain and labeled the pain as deep, pressure-like (n = 16), sharp or stabbing (n = 13), cramps or spasm (n = 4), punching or fist-like (n = 2), burning (n = 1), dull (n = 1) or squeezing (n = 1). About one quarter of our sample (n = 10) also developed severe diarrhea in the context of CVS exacerbations. When asked about triggering events, 14 individuals identified potential culprits, including stress (n = 6), hormonal changes with menstruation, menarche, or child birth (n = 5), sleep deprivation (n = 3), certain foods (n = 1), alcohol (n = 1) or seasonal changes with worsening depression due to seasonal affective disorder (n = 1).

While all patients described a highly dichotomous symptom pattern with emetic episodes and often prolonged asymptomatic periods at the onset of their illness, attack frequency increased overtime and residual symptoms, mostly nausea and a less intense abdominal pain persisted in 11 cases. Despite the emergence of daily symptoms, persons with coalescing illness continued to experience episodic exacerbation with repetitive vomiting, following a fairly stereotypic cause and typically requiring emergency medical care. Consistent with the defining characteristics, patients with symptom coalescence had more frequent emetic attacks compared to the rest of the group and had higher prevalence of anxiety and opioid consumption. This is described in Table 2.

Patients followed for at least 6 months (n = 23) were seen in the emergency room 5.5 ± 1.8 times and spent 13.2 ± 5.4 days in the hospital due to their CVS. All of them received intravenous fluids, antiemetics and

centrally analgesic medication. During these episodes, these patients underwent testing with 40 endoscopies and 51 abdominal CT scans.

The distribution of hospital days was skewed, with 8 patients not requiring hospitalizations during the study period and 5 patients accounting for 88% of the inpatient days. All of these patients had a typical history of cyclical vomiting syndrome with distinct and initially prolonged asymptomatic intervals, but eventually developed symptom coalescence. All of them also received daily opioids, with one patient being on chronic opioid therapy for chronic back pain and the remaining four showing a progressive increase in opioid therapy with eventual initiation of daily opioid use for the gastrointestinal symptoms. Compared to the remainder of the group, the calculated daily morphine equivalents based on prescribed opioids during this time frame was 278.0 ± 145.0 mg/day *versus* 36.8 ± 9.9 mg/day ($P < 0.01$). Consistent with this subgroup comparison, there was a significant correlation between opioid use and inpatient days [Figure 1].

Table 2: Patient characteristics in patients with worsening symptoms

Total number of patients		41	
CVS	**Coalescing illness**	**Stable disease**	***P* value (< 0.05 -significant)**
Number of patients	11	30	
Gender	3 (male) *vs* 8 (female)	11 (male) *vs* 19 (female)	NS
Age (years)	32.1++/−2.4	39.5+/−4.5	NS
Age of onset (years)	26.4+/−2.5	30.4+/−3.5	NS
Anxiety	10 (91%)	11 (37%)	<0.05
Opioid medications	11 (100%)	15 (50%)	<0.01
Interval between attacks	0.05+/−0.1	1.8+/−0.3	<0.05
Duration of attack	3.5+/−0.5	3.4+/−0.4	NS

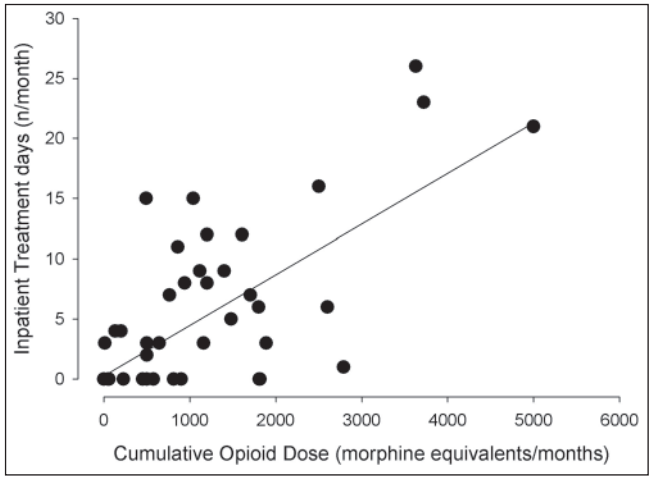

Figure 1: Correlation between opioid use and inpatient days

A more detailed examination of this patient group supports this close relationship between hospitalizations and opioid use. Hospitalizations were often clustered [see Figure 2], which triggered concerns about opioid dependence and development of withdrawal symptoms, mimicking and/or triggering CVS attacks. All 5 patients were counseled about the potential role of opioids in their disease and were offered a multi-disciplinary treatment

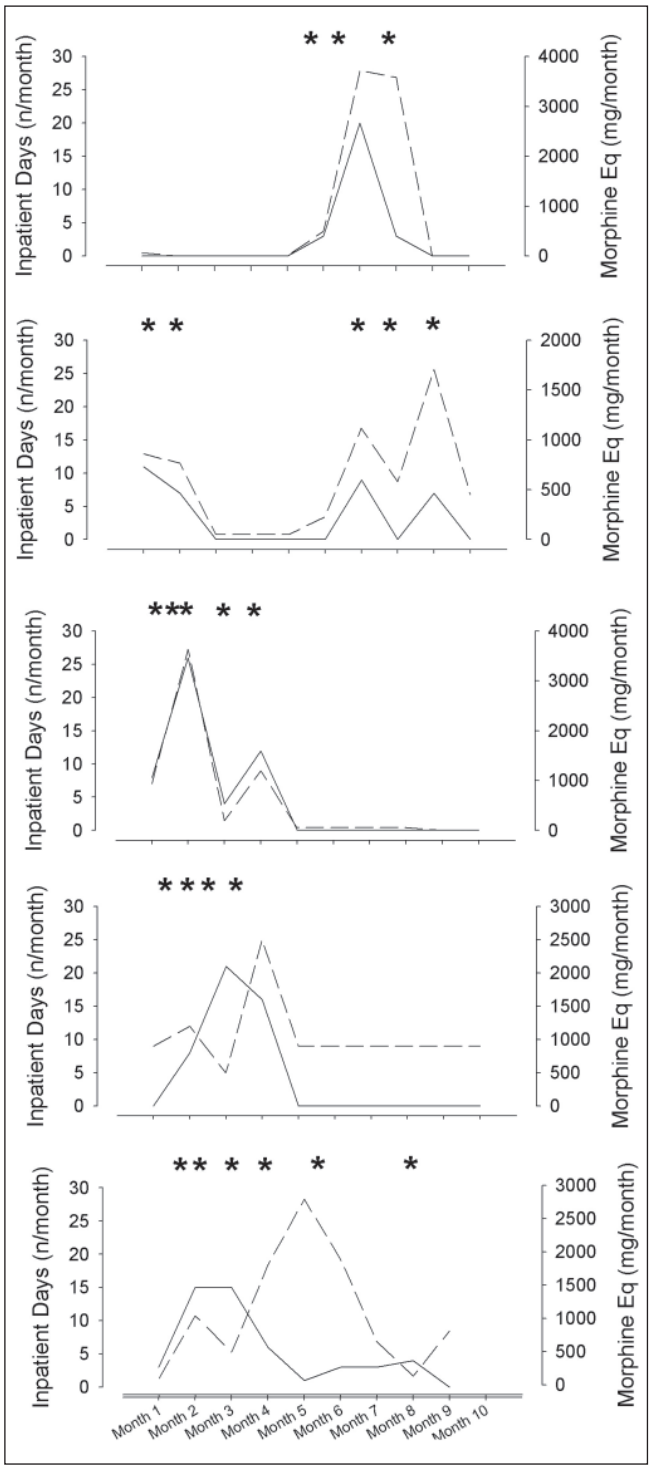

Figure 2: Relationship between hospitalization and opioid use

approach with medical and psychiatric support. One patient successfully completed treatment with inpatient treatment days dropping from 37 per year to 0. A second patient enrolled in an outpatient program to undergo rapid detoxification and suffered a hemorrhagic stroke due to a hypertensive crisis. She eventually recovered without residual symptoms, but continues to use opioids and marijuana. One patient was able to eliminate opioid use, avoided hospitalizations for 6 months, with recurrent opioid use and repeat hospitalizations after that time. Two additional patients did not attempt opioid tapers and instead sought care in other area hospitals.

Discussion

Our case series fits into a growing body of literature showing the problems patients and physicians encounter when dealing with cyclical vomiting syndrome. The often dramatic presentation stands in stark contrast with the essential normal findings on physical examination, laboratory testing or the often repeated imaging studies. The high rate of cholecystectomies performed in nearly 40% despite absence of gallstone disease shows steps physicians and patients are willing to take, hoping for some improvement in their situation. Consistent with current recommendations, essentially all patients were treated successfully during acute attacks using analgesics, antiemetics and intravenous fluids.[1] Most received tricyclic antidepressants or anticonvulsive agents to prevent recurrences, as are generally suggested based on the currently available data.[1,2,6,10] While most of the affected individuals responded to the treatment, a small but tangible number continued having frequent attacks with repeat hospitalizations, consistent with the described coalescence of this typically episodic illness.

Interestingly, the diagnosis of CVS had only been established in 10% of the patients, even though their symptoms had often started many years before the identifying encounter. These data are consistent with other reports showing a significant diagnostic delay with often repeated and typically negative diagnostic evaluations.[1,2,10] The importance of recognizing CVS goes beyond the resulting frustrations of repeat emergency room visits or hospitalizations and the expenses and risks related to unnecessary tests and treatments, as highlighted by the already mentioned cholecystectomies. While the acute management is largely symptomatic and thus does not necessarily differ from other disorders manifesting with pain, nausea and vomiting, long-term treatment of CVS should include strategies to decrease recurrent attacks. Such approaches are successful in reducing or even eliminating exacerbations in the majority of the affected individuals.[2-8,10,11] Thus, recognizing the pattern based on the defining criteria, identifying potential triggers and initiating appropriate preventative therapy is essential to decrease the need for emergency room visits or hospitalizations. It may also decrease the use of diagnostic tests that are often ordered, considering the at times dramatic presentation of CVS.

Our study also highlights a problem physicians face as they treat CVS patients. Consistent with a previously published report,[12] we noted a significant correlation between opioid use and hospitalization rates. This relationship may simply be a reflection of the need to treat the acute and often painful exacerbations, considering the common coexistence of repetitive vomiting and unrelenting pain that we found.[1,2,5,6,13] However, the repeated use of opioids may lead to iatrogenic opioid dependence with withdrawal symptoms developing soon after discharge and/or a rapid outpatient taper of analgesic medication. The associated emotional and/or autonomic arousal may suffice to trigger yet another CVS episode in susceptible individuals. Our data also fit into the larger picture, showing a relationship between recreational and — in our cohort also — prescribed drug use and the development of CVS.[14,15]

The opioid use with development of dependence and withdrawal may indeed be the key mechanism in patients with coalescent CVS. Our subgroup analysis supports the importance of withdrawal as a mechanism of disease, as all patients with emergence of disease coalescence used sedating drugs or medications. While prospective and larger studies will be needed to systematically test this hypothesis, we see potentially important implications and have implemented a strategy that systematically tapers opioid use in the outpatient environment, if patients have been admitted more than twice with less than 14 days between hospitalizations. While successful in some individuals, our preliminary results and data on the management of the narcotic bowel demonstrate ongoing narcotic or substance use in a substantial number of individuals and a high relapse rate.[16]

Overall, our case series shows the spectrum of CVS with several patients requiring hospitalizations. While acute therapy is typically quite effective in controlling symptoms, a subgroup of difficult patients may develop opioid dependence, potentially contributing to a cycle of repeated admissions due to recurrent attacks as a manifestation of withdrawal. Recognizing the typical patterns of CVS and instituting appropriate pre-emptive therapy early on may decrease repeat admissions and the associated increase in opioid use, thus avoiding the development of dependence. Probing for drug use, be it in the form of marijuana, benzodiazepines or opioids, is essential as it may provide clues into mechanisms and opportunities for lasting improvement through effective rehabilitation. Especially for the small subgroup with refractory and/or

coalescing symptoms, a multidisciplinary approach with substance abuse counseling, a tapering and elimination rather than escalation of narcotics is essential to achieve long-term remission.

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