Reviewer's report

Title: Cyclic Vomiting Syndrome (CVS): is there a difference based on onset; pediatric vs. adult?

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Reviewer: David Fleisher

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Review of manuscript "Cyclic Vomiting Syndrome (CVS): is there a difference based on onset; pediatric vs adult? Thangham Venkatesan, Corresponding Author. Reviewer: David Fleisher, MD

This is a well-written contribution to the all-too-sparse body of literature on CVS, and especially adult CVS.

Suggestions to the authors:

1. "Matrilineal inheritance patterns were noted...to be...different...with pediatric-onset patients having a higher likelihood of...a matrilineal inheritance pattern..."

   Do the authors refer to the inheritance pattern of CVS per se, or to the inheritance pattern of migraine diathesis and its many presentations, including migraine headache?

2. "...but some patients developed coalescence of symptoms after several months/years after they were not treated appropriately."

   The hypothesis advanced in the 2005 paper on adult CVS (cit. #7) is that coalescence results from the patient's despairing sense of being out of control of an illness that no one understands, is willing to assume clinical responsibility for, or knows how to manage. Therefore, based on the hypothesis that anxiety and despair promote nausea, it follows that "appropriate" management involves more than medications. It should also include an emotionally supportive component implemented by caring clinicians who are expert in the disorder and have individualized, rational and effective management protocols for each CVS patient.

3. "Results of a gastric emptying study..." Please make clear whether the GES was done while the patient was entirely symptom-free or having inter-episodic dyspeptic nausea. Also, since a patient's emotional state (e.g., trait and/or state anxiety) may affect the EGG and Gastric emptying, it would have been a valuable contribution to have correlated the GES results with the patient's emotional state at the time the study was done.

4. "The incidence of chronic opiate use was significantly higher amongst non-responders..." Opiates are used by many adult CVS patients. Why? Are they employed solely for analgesia in the 67% of patients whose symptoms include
abdominal pain? Were that so, I would expect the use of opiates to be confined to that 67% and no opiate use by the other 33%. But, my experience has been that some patients who use opiates do not have abdominal pain. If this is true, then there must be another reason for the use of opiates. Butorphanol, morphine and Dilaudid all dramatically ameliorate panic anxiety, an experience more horrific than isolated abdominal pain itself. The problem of opiate use by CVS patients is that the majority of adult CVS patients have anxiety complicated by panic attacks (See cit # 7 and also Olden, Keate & Shapiro, 1999, AJG 94,9 2614). And panic attacks trigger their CVS episodes. This causes some chronically and severely anxious patients to rely on anxiolytic opiates to the extent that they become chemically dependent. It often becomes difficult to distinguish panic-induced CVS episodes from "Cyclic Withdrawal Syndrome." They have a very similar clinical appearance and, of course, both are relieved by a dose of Dilaudid. (My approach to sorting this out is to engage an addiction expert to protect the patient from opiate withdrawal symptoms by use of, say, methadone, which helps to distinguish CVS episode and panic vs. opiate withdrawal symptoms.

5. The "significantly longer delay in diagnosis of CVS in the pediatric-onset group..." should be appreciated in light of the history of CVS. CVS was written about only rarely between its initial description in 1882 and the early 1990's. Most pediatricians and pediatric gastroenterologists either didn't know of it or didn't recognize it and treat it for what it was. That was the reason the report of 71 pediatric cases in JPGN in 1993 was given such prominent placement in that issue (cit.# 3). A thoroughgoing description of adult CVS wasn't published until 2005 (cit # 7). I still encounter gastroenterologists who fail to recognize the diagnosis. Therefore, unlike a study of appendicitis, CVS should be viewed in light of the history of CVS awareness over the past several decades.

6. Regarding the use of marijuana: a) it does alleviate nausea; and b) it does stimulate appetite during the recovery phase. However, the authors left out mentioning marijuana's anxiolytic properties which, as in the case of opiates, does contribute to marijuana's chronic use by some patients. Again, dealing with CVS management is optimized by sophisticated appreciation of the emotional components of patients and their illnesses. That's the basis of the Bio-Psycho-Social model of clinical practice.

This paper is worthy of publication, even in its present form.

David Fleisher, MD