Author's response to reviews

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

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Author's response to reviews: see over
Dear Editor,

We would like to thank you and the referees for their insightful comments. I have addressed your concerns with the appropriate revisions in the manuscript and have included our point-by-point response below.

Editors Comments -
1) The duration of follow-up and drop off rate should be mentioned-

Of 101 patients, adequate follow up data on response to therapy was present in 76 patients (75%) with an attrition rate of 25% and the mean duration of follow up was 11.2±6.2 months.

Please refer to - page 8; paragraph 1; line 3-5.

2) Why are there only 29 pediatric CVS patients in your cohort despite the center being a tertiary care referral center for CVS. Do the authors imply that adult onset CVS is more common than pediatric onset?

We would like to clarify that all patients in our study were adults > 18 years of age. The groups have been divided based on pediatric vs. adult onset of CVS. Patients were categorized as having pediatric onset CVS if they developed symptoms at < 18 years and as adult onset if symptoms developed ≥ 18 years of age. Given preliminary data suggesting that there may be genetic differences in patients based on onset of disease, we sought to examine if there were any differences in clinical characteristics and response to treatment amongst these two groups. We believe that the proportion of pediatric onset to adult onset CVS patients (30% to 70%) in our cohort is reasonable as the majority of children with cyclic vomiting syndrome are thought to outgrow their symptoms and develop migraine headaches as adults. The natural history of CVS has not been adequately studied in adults and we concur that this is a subject for future investigation.

Refer to page 4, paragraph 2

3) While response to treatment is an important outcome of the study, there is nothing mentioned as to how therapeutic response is defined- ? symptom questionnaire or visual analog scale- this data should be provided. Data as to the number of patients lost to follow up should also be provided as this is an important variable in the CVS population.

All patients seen in our clinic were asked standard questions about the frequency, duration and severity of episodes. In addition patients were also questioned about the need for ED visits, hospitalizations and visits to infusion clinics for CVS episodes. Complete response to therapy was defined as ≥ 80% amelioration in symptom duration or severity; partial response was at least a 50-80% reduction in symptom duration / severity. Non-responders had either no change in their disease status or < 50 % reduction in symptom
severity and frequency.
At the time of data analysis 25 (25%) of patients did not have data on response to follow-up.
Please refer to page 8, paragraph 1

4) The data analysis is interesting—why was the pediatric group not compared to the adult group when that was the aim of the study.

We would like to clarify that we sought to examine the differences between pediatric-onset and adult onset CVS patients and that all patients in the study were ≥ 18 years of age. The differences between these two groups of patients are depicted in Table 1.
We have included the information about response to treatment in the two groups in Table 1(last row).
There were some differences in clinical characteristics between patients who had pediatrics vs. adult onset of CVS but no significant difference in the response to therapy. We then performed a multiple regression analysis to identify predictors of response to therapy as this impacts management.
This has been included in the Aims section, page 5, paragraph 2.

5) Why was multivariate analysis of data not performed?

Initially we performed a univariate analysis on all dichotomous variables and a linear regression for all continuous variables. Only variables that had a p<0.1 were chosen for the multivariate regression model. On multivariate analysis, only compliance was found to be significant predictor of response to therapy. Given that only a single variable was found to be of statistical significance on multivariate analysis, we did not present this as a separate table but chose to incorporate the results into the body of the manuscript.
Please refer to page 8, paragraph 2, line 9-11.

Referee 1 Comments –
We appreciate the comments and feedback from Dr. Esfandyari.
We would like to clarify that all patients in our study were ≥18 years of age and patients were categorized as having adult onset CVS if they developed symptoms after 18 years of age and as having pediatric onset CVS if they developed symptoms at less than 18 years. We believe that the proportion of pediatric onset to adult onset CVS patients (30% to 70%) in our cohort is reasonable as the majority of children with cyclic vomiting syndrome are thought to outgrow their symptoms and develop migraine headaches as adults. We agree with Dr. Esfandyari that there is a need to study the natural history of CVS.
Regarding the statistical analysis, we performed a univariate analysis on the dichotomous variables and used Chi square exact test to compare treatment response between pediatric onset and adult-onset CVS patients and found no
difference with a $P$ value of 0.27 (included in table 1) While there is data on response rates in adults and children, the response patterns in pediatric and adult-onset patients is not known. Since this is a retrospective observational study our sample size was pre-determined. We acknowledge that further prospective validation of our findings should be performed. The power of the study would be determined by the effect size (Cohen’s $d$) that one wishes to detect at the outset and we concur with the reviewer that this should be considered in future prospective trials.

Referee 2 Comments -

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

As cited in the manuscript reference No 13 and 14, strong maternal inheritance of multiple disease manifestations and abnormal urine organic acids has been demonstrated in children with CVS, suggesting the presence of predisposing mitochondrial DNA (mtDNA) sequence polymorphisms. It has also been reported that pediatric-onset CVS have a higher proportion of maternal inheritance of functional symptomatology as ascertained by quantitative pedigree analysis. Please refer to page 4, paragraph 2-3

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

We agree with Dr. Fleisher’s observation on the pattern of coalescence in patients with CVS. As stated by him, we emphasize a multidisciplinary approach in CVS patients based on a bio-psycho-social model. Patients with underlying disorders such as anxiety and depression are often advised to seek cognitive behavioral therapy and we focus on both medical as well as behavioral management along with appropriate lifestyle changes.

We have emphasized this is the conclusion section of our manuscript. Please refer to page 11, paragraph 3, and page 12, paragraph 1.

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.

Most of the gastric scintigraphy scans were performed at other institutions and we were unable to ascertain the timing of the study with respect to the patient’s episode or verify if medications that interfered with the study were withheld. As is well known, there is considerable variation in the performance of gastric emptying studies between different institutions and we are thus
unable to comment on the quality of the studies that were performed at other institutions.

4. "The incidence of chronic opiate use was significantly higher amongst non-responders..."
We concur with Dr. Fleisher that several patients with CVS use narcotics on a chronic basis and this may be due to the associated anxiety and panic that they often experience. The author uses anti-emetics such as ondansetron and benzodiazepines as first-line therapy for management of acute symptoms. We usually reserve opiates for those with severe abdominal pain or refractory symptoms. We discourage chronic opiate use in our clinical practice as this may result in narcotic bowel syndrome and paradoxically cause visceral hypersensitivity/ hyperalgesia.

We really appreciate your comments and thoughtful insights of the referees. We have attempted to answer the questions and make changes in the manuscripts to the best of our ability. We would appreciate your consideration of this manuscript in your journal.

Regards,
Thangam Venkatesan