Middle East J Dig Dis. January 2023;15(1):32-36

doi 10.34172/mejdd.2023.317 http://mejdd.org

Middle East Journal of Digestive Diseases MEJDD

Original Article

Relapse Rate of Clinical Symptoms After Stopping Treatment in Children with Cyclic Vomiting Syndrome

Mahmoud Haghighat[1], Maryam Gholami Shahrebabak[1], Seyed Mohsen Dehghani[1], Maryam Ataollahi[1], Nazanin Amin Farzaneh[1], Samaneh Hamzeloo Hoseinabadi[1], Hazhir Javaherizadeh[2*]

[1]Gastroenterohepatology Research Center, Nemazee Teaching Hospital, Shiraz University of Medical Sciences, Shiraz, Iran
[2]Clinical Sciences Research Institute, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

Abstract

Background: Cyclic vomiting syndrome (CVS) is a chronic functional gastrointestinal disorder. It is characterized by recurrent episodes of vomiting typically separated by periods of symptom-free or baseline health. The present study aimed at evaluating the effectiveness of propranolol and the relapse rate of clinical symptoms after stopping treatment in children suffering from CVS.

Methods: Records of 504 patients below the age of 18 years with CVS who were treated with propranolol from March 2008 to March 2018 were reviewed. The duration of follow-up was 10 years.

Results: The average age of CVS affliction was 4.3 years and the average age at the diagnosis was 5.8 years. All subjects were treated with propranolol (for an average of 10 months). 92% of treated subjects were cured, causing a dramatic decrease in the rate of vomiting ($P<0.001$). Only an average of 10.5% of the studied subjects (53 people) showed a relapse of symptoms after stopping the treatment. The results of a 10-year follow-up period of the patients showed that 24 had abdominal migraine and 6 had migraine headaches, all of whom lacked the symptoms of disease relapse (prognostic evaluation).

Conclusion: The findings of this investigation show that the duration of treating CVS with propranolol could be shortened to 10 months with a low percent of symptoms relapse and this shortening may be effective in preventing the undesirable side effects of the drug. The presence of abdominal migraine and migraine headaches in patients after treatment accomplishment and the lack of disease relapse can be prognostic measures for this disease, which require intensive attention.

Keywords: Cyclic vomiting syndrome, Children, Propranolol, Duration of treatment period

Cite this article as: Haghighat M, Gholami Shahrebabak M, Dehghani SM, Ataollahi M, Amin Farzaneh N, Hamzeloo Hoseinabadi S, et al. Relapse rate of clinical symptoms after stopping treatment in children with cyclic vomiting syndrome. *Middle East J Dig Dis* 2023;15(1):32-36. doi: 10.34172/mejdd.2023.317.

Received: March 10, 2022, Accepted: November 15, 2022, ePublished: January 30, 2023

Introduction

Cyclic vomiting syndrome (CVS) is a chronic functional gastrointestinal disorder with sudden and relapsing episodes of severe emesis and vomiting, followed by asymptomatic episodes.[1-6]

At the present, CVS diagnosis is based on clinical criteria and there is no available specific diagnostic test or biomarker. The strategy of the North American Society for Gastroenterology, Hepatology, and Nutrition (NASPGHAN) was designed for CVS diagnosis in children, which insisted on a stereotypic pattern and an asymptomatic inter-episodic period. Diagnostic criteria for CVS, based on NASPGHAN strategies include at least five attacks during any time interval or at least three attacks during six months; disease attacks appear as sudden vomiting with high severity, lasting from one hour to 10 days and at least a one-week interval, unique stereotypical symptoms for each patient; occurrence of vomiting in each attack at least four times in an hour and lasting at least for one hour; patient's baseline level between attacks, and lack of symptoms compatibility with other disorders.[7,8]

CVS is a disorder with unknown etiology and pathophysiology and its acute symptoms are disabling and often require medical care. If acute CVS symptoms are not prevented, it can negatively affect patients' lives. However, the types of different treatments and treatment duration are very controversial.[9] It is thought that CVS is a type of abdominal migraine [10] and often leads to migraine headaches since a familial history of migraine headaches has been usually observed.[11,12] Therefore, anti-migraine drugs could prevent CVS.[13] Propranolol is usually administered to avoid CVS attacks.[14] Previous studies with propranolol have proven that this drug should be considered a prophylactic agent to control the symptoms and prevent attacks.[15] On the other hand, this drug is mostly used in children, and comparison with the other treatment available has shown a moderate response rate in several studies including high numbers of patients treated. No patient stopped the treatment because of unwanted side effects.[15,16] Meanwhile, efficiency rate, lack of disease symptoms relapse after stopping treatment, and treatment duration (especially in children) are among important and unclear problems in previous reports and studies, which are the focus of the present study. Duration of the treatment period in children with CVS can also

*Corresponding Author: Hazhir Javaherizadeh, Email: hazhirja@yahoo.com

be useful in determining the duration of the effective treatment period, the prognosis of migraine headaches, and disease progression in older ages.

Materials and Methods

This was a retrospective study on 504 patients under 18 years old with CVS, who were referred to the Pediatric Gastroenterology Clinic affiliated with Shiraz University of Medical Sciences during 2008-2018. Medical history of motion sickness and familial history of migraine headaches and abdominal migraine were queried and the diagnosis was made by a pediatric gastroenterologist according to the NASPGHAN criteria and clinical symptoms without any additional diagnostic paraclinical methods such as radiography, ultrasonography, endoscopy, and so on.

Patients with risk factors indicative of other diagnoses different from CVS (such as severe headaches, neurological symptoms, altered level of consciousness, gastrointestinal bleeding, abdominal tenderness, progressive weight loss, biliary vomiting, etc.) were excluded from the study.

All patients were treated with a 1 mg/kg/d of propranolol and written consents were filled in by patients' parents. The study was approved by the official inspective committee of our research center before the subjects' participation. Patients' records were collected using their histories and cases and followed up through the serial follow-up method. The patients who did not refer for follow-ups were excluded from the study. The duration of follow-up was 10 years.

Demographic data such as patients' age at the time of symptoms, age at the time of diagnosis, sex, patients' weight before and after the beginning of treatment, and recurrence rate of symptoms in the patients investigated were gathered and recorded on specific forms and then were statistically analyzed by Statistical Package for the Social Sciences for Windows, version 16 (SPSS Inc., Chicago, Ill., USA). The correlation between statistical information and clinical characteristics of patients was analyzed using inferential statistics by two-sample independent t test, Chi-square test, and Pearson and Spearman correlation coefficients with a significance level less than 0.05.

Ethical considerations were respected according to the ethical codes of Shiraz University of Medical Sciences. Patients' information and results of the investigation were archived confidentially.

Results

Analysis of demographic data of 504 children with CVS showed that 234 patients (46.4%) were female and 270 (53.6%) were male. On average, the time interval from the presence of disease symptoms to diagnosis was 17.04 months with a minimum of 6 months and a maximum of 121 months. The average age of CVS affliction was 52 months (4.3y) and the average age at the diagnosis was 69.9 months (5.8y). The highest prevalence and CVS diagnosis rates were in the age group under 6 years old (Table 1). Analysis showed that from a total of 504 children, 116 (23%) had motion sickness, 320 (63.5%) had a family history of migraine headaches, and 22 (4.4%) had a familial history of abdominal migraine. Also, most subjects had the onset of disease symptoms at midnight (61.9%), followed by early morning (32.9%). The lowest frequency of symptoms onset was during the daytime (5.2%). The distribution of the disease symptoms by sex is presented in Figure 1.

All patients in the present study were treated with 1 mg/kg of propranolol for an average of 10 months (with a minimum of six months and a maximum of 24 months). No side effect of the drug was observed. Examination and follow-up of patients were also indicative of an 87% positive response to 1 mg/kg of propranolol. In the remaining patients, the drug dosage was then elevated to 2 mg/kg, which resulted in total curing of 92%, and the remaining patients were treated with a second-line drug (amitriptyline or cyproheptadine). The average recurrence time was 11 months after stopping treatment. It was also observed that the proportion of patients with vomiting markedly decreased. treatment with the drug (10.5% in comparison with 92%, $P<0.001$).

The data analysis results showed that relapsing disease symptoms occurred only in 10.5% of subjects studied (53 subjects, 29 male and 24 female), of which emesis and vomiting (53 subjects, 100%), abdominal pain (20 subjects, 37.7%), headache (5 subjects, 9.4%), diarrhea (6 subjects, 11.3%), and fever (2 subjects, 3.7%) could be mentioned. 282 patients with positive responses to propranolol treatment had a familial history of migraine headaches and 169 patients lacked a familial history of migraine headaches. This was a significant difference ($P<0.001$). While there was no significant correlation between mean recurrence and duration of treatment, there was also no significant association between recurrence and sex ($P>0.05$) (Table 1).

Ten-year follow-up results for patients showed that six subjects (1.3%) had migraine headaches and 24 (4.7%) had abdominal migraine, all of whom lacked symptoms indicative of previous disease relapse (Table 2).

Table 1. Age- and sex-categorized frequency of symptoms recurrence after stopping treatment

Parameters			Number	Percent
Age-categorized symptoms recurrence	<6 years old	Recurrence	26	10
		Total	260	100
	6-12 years old	Recurrence	24	10.9
		Total	221	100
	<12 years	Recurrence	3	13
		Total	23	100
Sex-categorized symptoms recurrence	Male	Recurrence	29	10.7
		Total	270	100
	Female	Recurrence	24	10.3
		Total	234	100

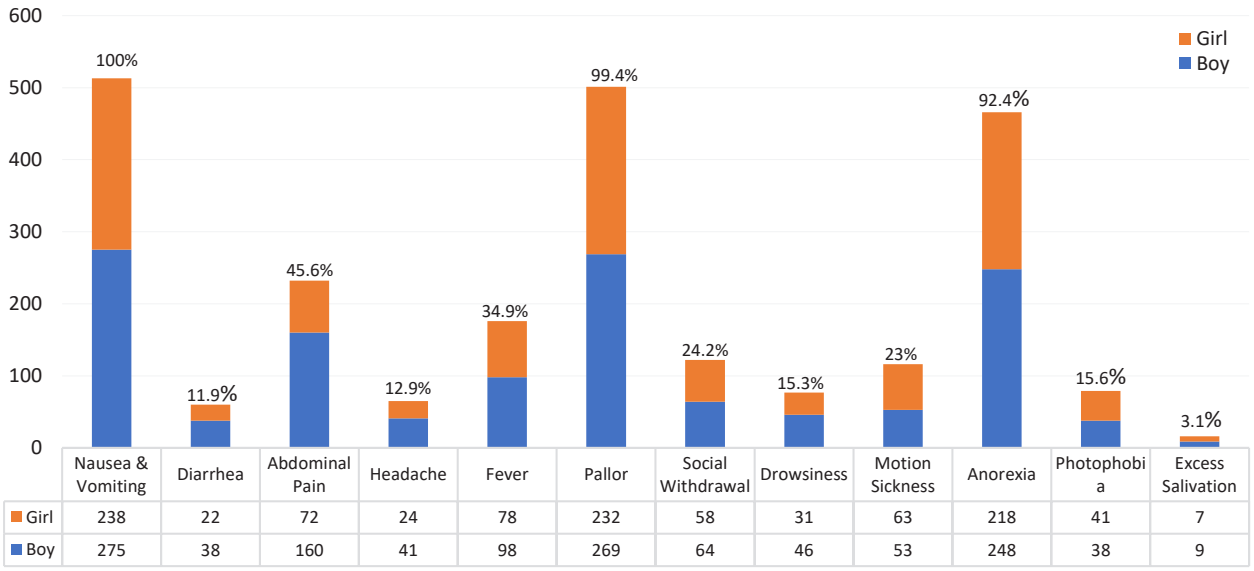

Figure 1. Frequency distribution of disease symptoms in the subjects studied

Table 2. frequency distribution of abdominal pain and migraine headache in the 10-year follow-up of the patients studied

Symptoms	Number	Percent
Abdominal migraine	24	4.7
Migraine headache	6	1.3

Discussion

CVS is a functional gastrointestinal disorder. It remains a disorder of unknown etiology and pathogenesis, characterized by recurrent episodes of vomiting typically separated by periods of symptom-free or baseline health. This disease usually affects children and younger adults and because of insufficient awareness about the disease, there is a remarkable delay in diagnosis. On the other hand, patients are subject to extensive examination and even unnecessary surgeries. This syndrome imposes dramatic damage on patients and their families.[4] Timely diagnosis and treatment with propranolol have been suggested in several studies.[15-17]

All of the 504 children had emesis and vomiting, which consistent with other studies in the field, is characteristic of the disease.[18,19] The results indicated that the average incidence age was 52 months (4.3 years) and the average age at diagnosis was 69.9 months (5.8 years). The highest frequency of CVS patients concerning incidence and diagnosis ages was related to the group under 6 years old. Similar to our results, Fitzpatrick and colleagues in their study on the Irish population reported an average CVS diagnosis age of 7.42 years (ranging from 1.8 to 15 years). The average age at the CVS onset was 4 years (ranging from 0.4 to 14 years).[20] Through examination of school-age children in Aberdeen City, Scotland, Abu-Arafeh and Russell reported that children suffering from CVS were 9.6 years old on average and the average age of symptoms onset was 5.3 years (ranging from 1 to 13 years).[21]

Disease symptoms included emesis and vomiting (100%), and abdominal pain (45.6%). 63.5% of subjects had a family history of migraine headaches and 23% suffered from motion sickness. The examined symptoms are among the common complaints of sufferers and the symptoms observed in studies related to this field. Emesis and abdominal pain are among the most common complaints reported in some studies.[11,22,23] By examining 214 children with CVS, Li et al proved that based on either criterion of familial migraine history or progression after migraine headaches, 82% of subjects had migraine-associated CVS. Common symptoms such as abdominal pain, headache, social withdrawal, photophobia, physical fatigue, and motion sickness were also observed.[11] In a study on school-age children with CVS in Turkey (2006), Ertekin and colleagues reported that all subjects had weakness and anesthesia.[24] In a regional study in Ireland and Taiwan, it was demonstrated that 71% of patients had abdominal pain as the main complaint.[20,25] The studies in Scotland [21] and Turkey [24] suggest that migraine prevalence in children with CVS is 21% and 25%, respectively. Hadibarhaghtalab and colleagues also reported that 44.2% of patients with CVS in southern Iran had headaches and 11.6% suffered from abdominal migraine.[26] In our study in 2007, 23% of patients had a history of motion sickness, which was compatible with the results of the present study.[19]

Data analysis for the time of symptoms onset showed that for most of the subjects, this had occurred at midnight (61.9%), followed by early morning (32.9%). Fleisher and Matar indicated that the common times of attack bursts were between midnight to early morning.[27] Following our findings, Shin et al also reported that repeated vomiting usually began late at night and was associated with severe epigastric pain.[28] Tack et al reported similar findings with vomiting commonly beginning during the night or early morning.[29]

From the total of 504 children studied, all were treated with a 1 mg/kg dose of propranolol for an average of 10

months (minimum of 6 and maximum of 24 months) with no drug-originated side effects. Follow-ups of patients indicated an 87% positive response to 1 mg/kg of propranolol. Drug dosage was then elevated to 2 mg/kg with a total curative rate of 92% in the subjects. The ratio of patients with vomiting decreased significantly after drug therapy. Based on NASPGHAN's guidelines, propranolol is a second-line agent for preventing CVS.[8] However, the efficiency of this drug was very high in the present study. It is while in our other study on 181 CVS patients, 94% of patients had an acceptable response after propranolol administration.[19] Our previous studies on 206 patients with CVS in 2017 also established that as a prophylactic agent, propranolol had an acceptable response in 92.2% of such patients.[17] These results are comparable with those of other studies. In NASPGHAN Announcement it has been stated that propranolol has a moderate efficiency (35-75%) for CVS treatment in children.[8] Sunku also reported an efficiency rate of 52-65% in 2009.[30] In an investigation by Sezer and Sezer in 2016, 82% of the propranolol group showed a positive response to the treatment.[15]

Analysis of data gathered in the present work showed that only an average of 10.5% of the subjects (53 subjects) showed disease symptoms relapse after stopping the treatment and the sex had no effect on the drug's effect on these symptoms. Long-term follow-ups of patients in a 1- to 10-year time interval indicated that 24 subjects had abdominal migraine and 6 had migraine headaches of whom, all lacked symptoms of disease relapse. In another report, we followed up on 31% of patients with at least five years of drug withdrawal, and symptomatic relapses were observed in only 3.8% of subjects.[19] In another study, we also showed that during 9 months of treatment with propranolol, only 7.8% of subjects suffering from CVS had symptomatic relapses.[17] Therefore, noticing the successful treatment results with propranolol in our study and the lack of reports about effective remediation with propranolol, it is suggested that this drug can be administered for 8 to 10 months.

Our results recommend that the highest frequency of disease incidence and diagnosis was in the age group under 6 years old and preschool ages. CVS treatment period could also shorten via propranolol administration, which would be along with helpfulness in preventing from drug's side effects. The occurrence of abdominal migraine and migraine headache symptoms in patients after full healing and lack of disease relapse can act as a prognostic agent for this disease, which requires paying more attention.

Our data about relapse need further studies. The recent guidelines recommend other drugs for the prophylaxis of CVS, but the availability and low cost of propranolol and experiences with propranolol can be beneficial in some cases with CVS.

Study limitations

Single center study, patents incompliance, and loss of some data during follow up.

Acknowledgments

The authors would like to thank the Center for Development of Clinical Research of Nemazee Hospital and Dr. Zarei for editorial assistance. The present article was from the special thesis written by Maryam Gholami Shahrebabak.

Competing Interests

The authors declare no conflict of interest related to this work.

Funding

None.

References

1. Hayes WJ, VanGilder D, Berendse J, Lemon MD, Kappes JA. Cyclic vomiting syndrome: diagnostic approach and current management strategies. *Clin Exp Gastroenterol* 2018;11:77-84. doi: 10.2147/ceg.s136420
2. Hejazi RA, McCallum RW. Review article: cyclic vomiting syndrome in adults--rediscovering and redefining an old entity. *Aliment Pharmacol Ther* 2011;34(3):263-73. doi: 10.1111/j.1365-2036.2011.04721.x
3. Stanghellini V, Chan FK, Hasler WL, Malagelada JR, Suzuki H, Tack J, et al. Gastroduodenal disorders. *Gastroenterology* 2016;150(6):1380-92. doi: 10.1053/j.gastro.2016.02.011
4. Venkatesan T, Samuel EA. Cyclic vomiting syndrome. In: Rao SSC, Parkman HP, McCallum RW, eds. *Handbook of Gastrointestinal and Motility Disorders*. Thorofare: SLACK Incorporated; 2015.
5. Abell TL, Adams KA, Boles RG, Bousvaros A, Chong SKF, Fleisher DR, et al. Cyclic vomiting syndrome in adults. *Neurogastroenterol Motil* 2008;20(4):269-84. doi: 10.1111/j.1365-2982.2008.01113.x
6. Yang HR. Recent concepts on cyclic vomiting syndrome in children. *J Neurogastroenterol Motil* 2010;16(2):139-47. doi: 10.5056/jnm.2010.16.2.139
7. Sato T, Igarashi N, Minami S, Okabe T, Hashimoto H, Hasui M, et al. Recurrent attacks of vomiting, hypertension and psychotic depression: a syndrome of periodic catecholamine and prostaglandin discharge. *Acta Endocrinol (Copenh)* 1988;117(2):189-97. doi: 10.1530/acta.0.1170189
8. Li BU, Lefevre F, Chelimsky GG, Boles RG, Nelson SP, Lewis DW, et al. North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition consensus statement on the diagnosis and management of cyclic vomiting syndrome. *J Pediatr Gastroenterol Nutr* 2008;47(3):379-93. doi: 10.1097/MPG.0b013e318173ed39
9. Sudel B, Li BU. Treatment options for cyclic vomiting syndrome. *Curr Treat Options Gastroenterol* 2005;8(5):387-95. doi: 10.1007/s11938-005-0041-9
10. Paul SP, Barnard P, Soondrum K, Candy DC. Antimigraine (low-amine) diet may be helpful in children with cyclic vomiting syndrome. *J Pediatr Gastroenterol Nutr* 2012;54(5):698-9. doi: 10.1097/MPG.0b013e31824ca0a2
11. Li BU, Murray RD, Heitlinger LA, Robbins JL, Hayes JR. Is cyclic vomiting syndrome related to migraine? *J Pediatr* 1999;134(5):567-72. doi: 10.1016/s0022-3476(99)70242-8
12. Stickler GB. Relationship between cyclic vomiting syndrome and migraine. *Clin Pediatr (Phila)* 2005;44(6):505-8. doi: 10.1177/000992280504400606
13. Hikita T, Kodama H, Kaneko S, Amakata K, Ogita K, Mochizuki D, et al. Sumatriptan as a treatment for cyclic vomiting syndrome: a clinical trial. *Cephalalgia* 2011;31(4):504-7. doi: 10.1177/0333102410390398
14. Lee LY, Abbott L, Mahlangu B, Moodie SJ, Anderson S. The management of cyclic vomiting syndrome: a systematic

review. *Eur J Gastroenterol Hepatol* 2012;24(9):1001-6. doi: 10.1097/MEG.0b013e328355638f
15. Sezer OB, Sezer T. A new approach to the prophylaxis of cyclic vomiting: topiramate. *J Neurogastroenterol Motil* 2016;22(4):656-60. doi: 10.5056/jnm16035
16. Haghighat M, Dehghani SM, Shahramian I, Imanieh MH, Teimouri A, Noori NM. Combination of erythromycin and propranolol for treatment of childhood cyclic vomiting syndrome: a novel regimen. *Gastroenterol Hepatol Bed Bench* 2015;8(4):270-7.
17. Haghighat M, Memari H, Honar N, Dehghani SM, Imanieh MH, Injoo SJ, et al. The efficacy and duration of treatment with propranolol in children with cyclic vomiting syndrome in southern Iran. *Prz Gastroenterol* 2017;12(4):291-5. doi: 10.5114/pg.2017.72105
18. Li BU, Misiewicz L. Cyclic vomiting syndrome: a brain-gut disorder. *Gastroenterol Clin North Am* 2003;32(3):997-1019. doi: 10.1016/s0889-8553(03)00045-1
19. Haghighat M, Rafie SM, Dehghani SM, Fallahi GH, Nejabat M. Cyclic vomiting syndrome in children: experience with 181 cases from southern Iran. *World J Gastroenterol* 2007;13(12):1833-6. doi: 10.3748/wjg.v13.i12.1833
20. Fitzpatrick E, Bourke B, Drumm B, Rowland M. The incidence of cyclic vomiting syndrome in children: population-based study. *Am J Gastroenterol* 2008;103(4):991-5. doi: 10.1111/j.1572-0241.2007.01668.x
21. Abu-Arafeh I, Russell G. Cyclical vomiting syndrome in children: a population-based study. *J Pediatr Gastroenterol Nutr* 1995;21(4):454-8. doi: 10.1097/00005176-199511000-00014
22. Prakash C, Staiano A, Rothbaum RJ, Clouse RE. Similarities in cyclic vomiting syndrome across age groups. *Am J Gastroenterol* 2001;96(3):684-8. doi: 10.1111/j.1572-0241.2001.03606.x
23. Fleisher DR, Matar M. The cyclic vomiting syndrome: a report of 71 cases and literature review. *J Pediatr Gastroenterol Nutr* 1993;17(4):361-9.
24. Ertekin V, Selimoğlu MA, Altnkaynak S. Prevalence of cyclic vomiting syndrome in a sample of Turkish school children in an urban area. *J Clin Gastroenterol* 2006;40(10):896-8. doi: 10.1097/01.mcg.0000212627.83746.0b
25. Liao KY, Chang FY, Wu LT, Wu TC. Cyclic vomiting syndrome in Taiwanese children. *J Formos Med Assoc* 2011;110(1):14-8. doi: 10.1016/s0929-6646(11)60003-x
26. Hadibarhaghtalab M, Hadibarhaghtalab N, Manafi AR. Clinical characteristics of pediatric patients with cyclic vomiting syndrome in southern Iran. *Galen Med J* 2012;1(1):29-34. doi: 10.31661/gmj.v1i1.8
27. Fleisher DR, Gornowicz B, Adams K, Burch R, Feldman EJ. Cyclic vomiting syndrome in 41 adults: the illness, the patients, and problems of management. *BMC Med* 2005;3:20. doi: 10.1186/1741-7015-3-20
28. Shin YK, Kwon JG, Kim KY, Park JB, Han SJ, Cheon JW, et al. A case of cyclic vomiting syndrome responding to gonadotropin-releasing hormone analogue. *J Neurogastroenterol Motil* 2010;16(1):77-82. doi: 10.5056/jnm.2010.16.1.77
29. Tack J, Talley NJ, Camilleri M, Holtmann G, Hu P, Malagelada JR, et al. Functional gastroduodenal disorders. *Gastroenterology* 2006;130(5):1466-79. doi: 10.1053/j.gastro.2005.11.059
30. Sunku B. Cyclic vomiting syndrome: a disorder of all ages. *Gastroenterol Hepatol (N Y)* 2009;5(7):507-15.