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Original Article

Cyclic Vomiting Syndrome in Infants and Children: A Clinical Follow-Up Study

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ABSTRACT

BACKGROUND: Cyclic vomiting syndrome is characterized by recurrent vomiting that is associated with increased adrenocorticotropic hormone and antidiuretic hormone levels during cyclic vomiting syndrome attacks. However, both prognosis and treatment remain unclear. We therefore evaluated the clinical features, prognosis, and effectiveness of the prophylaxis of cyclic vomiting syndrome as well as the relationship between symptoms and adrenocorticotropic hormone/antidiuretic hormone levels. **METHODS:** We included 31 patients with cyclic vomiting syndrome who were admitted to Teikyo University between 1996 and 2008. All patients were diagnosed with cyclic vomiting syndrome based on the criteria of the second edition of the International Headache Classification. The patients (25 of 31) were followed until 2013. **RESULTS:** The median overall duration of the disorder was 66 (3-179) months. Follow-up was completed for 25 patients with cyclic vomiting syndrome, of whom 44% (n = 11) developed migraine. Valproic acid, valproic acid with phenobarbital, phenobarbital, and amitriptyline were effective in nine, four, three, and one patients, respectively. Abnormally high adrenocorticotropic hormone (n = 17) and antidiuretic hormone (n = 18) levels were found among the 25 patients for whom follow-up data were available. The following correlations were significant: attack duration and adrenocorticotropic hormone levels (correlation coefficient: 0.5153, $P = 0.0084$) and attack duration and antidiuretic hormone levels (correlation coefficient: 0.5666, $P = 0.0031$). Antidiuretic hormone levels in patients with bilious vomiting were higher than in those without bilious vomiting ($P = 0.048$). **CONCLUSIONS:** Most patients with cyclic vomiting syndrome recovered completely and benefited from prophylactic therapy, although half of them developed migraines.

Keywords: International Headache Classification, migraine, adrenocorticotropic hormone, antidiuretic hormone, prophylactic therapy

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Introduction

Cyclic vomiting syndrome (CVS) is a migraine variant characterized by recurrent, stereotypic episodes of various symptoms and is separated by intervals of comparative wellness.[1-3] It is included in the second edition of the International Classification of Headache Disorders (ICHD-2)[4] as a subgroup of childhood periodic syndromes that are common migraine precursors. It is also included in the subgroup of episodic syndromes associated with migraine in the third edition of ICHD.[5] However, its pathophysiology, prognosis, and natural history remain unclear.

A study reported a CVS prevalence of 1.9%, with 20%, 29%, and 29% patients diagnosed with migraine, travel sickness, and atopic diseases, respectively.[6] In another study[7] with 71 patients with CVS, 79% experienced vomiting at times specific to the individual, 60% were disturbed at night or had symptoms on waking, and 19% had episodes at characteristic times of the day. CVS often responds to migraine-directed prophylaxis with beta-blockers, amitriptyline, and cyproheptadine.[8-11] Valproate has been used in pediatric migraine prophylaxis since 2005.[12,13] We reported its effectiveness for CVS in 2009.[14]

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Although abnormally high adrenocorticotropic hormone (ACTH) and antidiuretic hormone (ADH) levels have been reported during CVS attacks,[15-20] the relationship between CVS symptoms and the hormone levels remains unclear. We evaluated this relationship as well as the clinical features, prognosis, and effectiveness of prophylaxis of CVS.

Methods

Study design and patient selection

Patients with CVS admitted for treatment at Teikyo University Hospital between 1996 and 2008 were included and followed up until 2013. All patients were diagnosed with CVS based on the ICHD-2 criteria.[4] They were hospitalized for intravenous rehydration because of severe vomiting and dehydration. All patients underwent diagnostic tests to eliminate the organic causes of the symptoms. The study was approved by the ethics committee of Teikyo University School of Medicine (No. 07-066) and was performed in accordance with the requirement of the Helsinki Declaration. Informed consent was obtained from patients and/or their parents.

Data collection

We collected the following data from all patients: age at onset, age at last CVS attack, overall duration of the disorder, interval of attack, number of vomiting episodes (per hour), and duration of attack as well as ACTH and ADH levels. We also evaluated the use of drugs for the prophylactic management of CVS for patients with CVS attacks occurring more than once a month and/or with particularly severe and disabling episodes. Effectiveness was evaluated as response or nonresponse: responders had less than two attacks per year, whereas nonresponders had more than three attacks per year.

Statistical analysis

Data were analyzed using the JMP software (SAS Institute, Cary, NC). Spearman rank correlation coefficients (ρ) were calculated for associations; those ≥ 0.7 were considered to be strong correlations, and those from >0.4 to <0.7 were considered to be significant correlations. Wilcoxon rank-sum test was used to compare age at the last attack and overall duration of the disorder with clinical features. The test was also used to compare ACTH and ADH levels with clinical symptoms. We considered P values of <0.05 to be statistically significant.

Results

Clinical features of patients with CVS

We initially included 31 patients with CVS, of whom 17 were males. The symptoms, temporal pattern, precipitating events, natural history, complications, and allergy history are described in Table 1.

The median age at onset was 48 (range: 3-177, n = 31) months, median age at last attack was 116.5 (42-310) months (n = 28), median overall duration of the disorder was 66 (3-179) months (n = 28), median interval between attacks was 8 (2-12)weeks (n = 31), median number of vomiting episodes per hour was 10 (4-30) (n = 31), and median duration of an attack was 3 (1-7) days (n = 31). Early morning vomiting was present in five of the 31 patients. Bilious vomiting, bloody vomiting, lethargy, pallor, abdominal pain, diarrhea, and headache were observed in five, eight, 11, 14, 23, 10, and 18 patients, respectively.

A family history of migraine was identified in the first or second degree relatives of 13 of the 31 patients (42%). Patients with salivation and allergic rhinitis were older at their last attack than those without (P = 0.0064 and 0.018, respectively). Patients with lethargy, salivation, anorexia, or a family history of CVS had longer durations of CVS than those without (P = 0.013, 0.0028, 0.0087, and 0.039, respectively). No significant difference in age at last attack or overall duration of the disorder existed with any other variable (gender, bilious vomiting, bloody vomiting, pallor, fever, nausea, abdominal pain, diarrhea, headache, photophobia, phonophobia, vertigo, different interval durations, early morning onset, stereotypical pattern, have precipitating events, complications, family history of migraine headache, allergy, atopic dermatitis, allergic conjunctivitis, bronchial asthma, and food allergy). However, the overall duration of the disorder was higher for patients with lethargy, salivation, anorexia, and a family history than for those

TABLE 1.
Clinical Characteristics

Parameters	Results
Male:female	17:14
Age of onset	3-177 (median 48) months
Symptoms	
Vomiting	4-30 (median 10) times/hour at peak, bilious (16%), bloody (28%)
Systemic	Lethargy (35%), pallor (45%), fever (55%), salivation (16%)
Gastrointestinal	Nausea (90%), abdominal pain (74%), anorexia (39%), diarrhea (32%)
Neurological	Headache (58%), photophobia (9.8%), phonophobia (3.2%), vertigo (12%)
Temporal pattern	
Duration	1-7 (median 3) days
Periodic	52% have regular intervals, generally. 2-4 weeks
Circadian	Early morning onset (12%)
Stereotypical	100%
Precipitating events	Psychological stress (13%), infection (16%), exhaustion (9.7%), dietary (6.5%), joyful event (9.7%) One or more triggers identified (45%)
Natural history	42-310 (median 116.5) months (n = 28), 41% + progress to migraine headache (n = 27)
Complications	Mental retardation (16%), after gastrointestinal surgical treatment (9.7%)
Family history of migraine	Cyclic vomiting syndrome (13%), migraine headache (42%)
History of allergy	Allergy (61%), allergic rhinitis (39%), atopic dermatitis (13%), allergic conjunctivitis (9.7%), bronchial asthma (6.5%), food allergy (6.5%)