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Original Article

Cyclic Vomiting Syndrome and Migraine in Children

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Background: Cyclic vomiting syndrome (CVS) is an episodic nausea and non-bilious vomiting disorder characterized by recurrent stereotypic symptoms with disease-free intervals. CVS in children is associated with a high prevalence of migraine, and is commonly considered a precursor to migraine. This study aimed to investigate the clinical manifestations of pediatric CVS and its prognosis, and to clarify its relationship with the risk of migraine development in children.

Methods: The clinical features of children diagnosed with CVS before the age of 18 years at the designated hospital were retrospectively studied over the past 30 years (1976 – 2006) based on the Rome III or ICHD II criteria. Clinical evaluations, including age of onset, sex, family history, symptoms and duration during attacks, frequency, trigger events, electroencephalogram, treatment and subsequent development of migraine were assessed from chart records and telephone interviews.

Results: Thirty-five children (17 males and 18 females) were enrolled. Their age of onset ranged from 2 to 17 years (mean, 6.8 ± 3.1 years) and frequency of attacks ranged from once to 36 times per year (mean, 8.2 ± 7.6 times). Duration of symptoms during each attack ranged from 1 to 45 days (mean, 5.9 ± 7.3 days). Of 20 children assessed for migraine development, seven subsequently developed typical migraine symptoms. There was younger onset age in the migraine-positive subgroup (5 ± 1.7 years) than in the migraine-negative subgroup (8.9 ± 3 years; $p = 0.001$). Co-morbid headache during CVS attack was also more evident in the migraine-positive subgroup (28.6% *vs.* 0%).

Conclusion: Results of the study show that younger onset age and headache during CVS attacks may have increased risk of migraine development. Large-scale prospective studies are warranted to further clarify the relationship between CVS and migraine.

Key Words: children, cyclic vomiting syndrome, migraine, migraine equivalents

Cyclic vomiting syndrome (CVS) is an episodic nausea and non-bilious vomiting disorder characterized by recurrent stereotypic symptoms with disease-free intervals in otherwise healthy children.[1–4] Patients usually have rapid onset relentless vomiting, abdominal pain, and fatigue lasting for hours to days. Factors that trigger attacks are commonly identified, and symptoms are

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self-limited and resolve spontaneously without special treatment.[5,6] Diagnosis is based on history, clinical presentation, and exclusion of any metabolic, gastro-intestinal, or central nervous system structural or biochemical disorders.[7–9] The International Classification of Headache Disorder 2004 (ICHD-II) or Rome III diagnostic criteria are mostly used for CVS diagnosis (Table 1).

CVS often begins in childhood and is a common cause of recurrent vomiting in children.[10,11] Although its etiology is still undefined, it is commonly considered a precursor of migraine or migraine equivalent. Migraine, abdominal migraine, and CVS have similar clinical courses, with episodic attacks separated by symptom-free intervals.[12] There are also some similarities in their symptomatology, such that CVS patients may have headache or abdominal pain during vomiting attacks.[7]

Patients with CVS have higher prevalence of migraine than the general population (22% and 5%, respectively).[13,14] Despite the lack of specific laboratory tests for diagnosing CVS and migraine, there are some links between CVS and subsequent migraine. The present study retrospectively investigated the correlation between clinical manifestations of CVS and risks of migraine development in children to determine some clinical patterns indicative of a stronger relationship.

Patients and Methods

Children aged < 18 years diagnosed to have CVS at the designated hospital in the past 30 years (1976 – 2006) were all reviewed retrospectively and evaluated by pediatric neurologists and pediatric gastroenterologists. The diagnosis of CVS was based on clinical presentations, physical examination, and exclusion of any metabolic, gastro-intestinal, or central nervous system structural or biochemical disorders by serial work-up on admission. Thirty-five patients were enrolled in the present study based on the Rome III or ICHD II criteria.

Clinical evaluations, including age of onset, sex, family history, symptoms and duration during attacks, frequency of attacks, trigger events, electroencephalogram, and treatment during attacks, were performed by chart review. Clinical follow-up information, including subsequent development of migraine, was obtained from the outpatient clinics and by telephone interviews. The diagnosis of migraine was made using the

Table 1. Diagnostic criteria of cyclic vomiting syndrome

ICHD II Criteria for CVS

1. At least 5 attacks fulfilling criteria 2 and 3
2. Episodic attacks, stereotypical in the individual patient, of intense nausea and vomiting lasting from 1 hr to 5 d
3. Vomiting during attacks occurs at least 4 times hr for at least 1 hr
4. Symptom-free between attacks
5. Not attributed to another disorder

Rome III Criteria for CVS

At least 3 mo, with onset at least 6 mo previously of

1. Stereotypical episodes of vomiting regarding onset (acute) and duration (< 1 wk)
2. Three or more discrete episodes in the prior year
3. Absence of nausea and vomiting in between the episodes
4. There are no metabolic, gastrointestinal, or central nervous system structural or biochemical disorders
5. Supportive criteria: personal or family history of migraine headaches

CVS = cyclic vomiting syndrome. hr = hour(s); mo = month(s); yr = year(s).

ICHD-II criteria (international classification of headache disorder, 2nd).[15]

Statistical analysis

Statistical analysis was performed with STATA Version 10.0. Gender, symptoms during attacks, electroencephalography, and family history of migraine were compared between the migraine-positive and migraine-negative groups using Fisher's exact test. Mann-Whitney test was used for continuous variables, including age, frequency, and duration. A $p < 0.05$ was considered statistically significant.

Results

Of the 35 children (17 males and 18 females) enrolled, the age of onset ranged from 2 to 17 years (mean, 6.8 ± 3.1 years). The frequency of attacks ranged from 1 to 36 times per year (mean, 8.2 ± 7.6 times) while the duration of CVS symptoms during each attack ranged from 1 to 45 days (mean, 5.9 ± 7.3 days).

During vomiting episodes, 71% and 11% of patients had abdominal pain and headache, respectively. Triggering events, including stress, fever, and upper respiratory tract infection, occurred in 11 cases (31%). No cases had a family history of CVS, although seven cases (20%) had migraine history on their maternal side and one (3%) on the paternal side.

Electroencephalography was performed in 33 patients, and 16 (46%) showed slow background activity, while four (11%) showed focal epileptiform discharges (Table 2). All 35 received supportive treatment of parenteral fluid, electrolyte replacement, and anti-emetic agents. Six received prophylactic therapy of flunarizine upon discharge, but were lost to follow-up.

Twenty patients were followed up in the hospital or by telephone interviews. Their average follow-up period was 7.5 years (range, 2–12 years). They were classified into two groups. Seven patients subsequently developed typical migraine symptoms that met the ICHD-II for migraine in an average follow-up period of 6.7 years (range: 2–12 years) and were defined as the migraine-positive group. The other 13 patients did not develop migraine in an average follow-up period of 7.8 years (range: 2–12 years) and

Table 2. Clinical manifestations of patients[a]

	CVS patients ($n = 35$)
Gender	
Male	17 (48)
Female	18 (52)
Onset age (yr)	
Mean ± SD	6.8 ± 3.1
Range	2 – 17
Family history of migraine	
Maternal	7 (20)
Paternal	1 (3)
No family history	28 (77)
Symptoms during attack	
Vomiting	35 (100)
Abdominal pain	25 (71)
Headache	4 (11)
Others (dizziness, lethargy, diarrhea)	2 (5)
Frequency (times/yr)	
Mean ± SD	8.2 ± 7.6
Range	1–36
Duration of CVS attack (d)	
Mean ± SD	5.9 ± 7.3
Range	1–45
Trigger events	
Yes	11 (31)
No	24 (69)
EEG pattern	
Slow wave	16 (46)
Focal/Diffuse	8(23)/8(23)
Focal epileptiform discharges	4 (11)
14 and 6 positive spikes	6 (17)
Negative finding	11 (31)
Not done	2 (6)
Migraine development	
Yes	7 (20)
No	13 (37)
Lost to follow-up	15 (43)

[a]*Data are presented as n (%), mean ± SD or range. EEG = electroencephalography; CVS = cyclic vomiting syndrome; SD = standard deviation.*

Table 3. Development of migraine and clinical characteristics ($n = 20$)

	Migraine (+) ($n = 7$)	Migraine (–) ($n = 13$)	p
Gender (n)			0.356
Male	3	9	
Female	4	4	
Mean onset age (yr)	5 ± 1.7	8.9 ± 3.3	0.001
Frequency (Mean, times/yr)	4.5	9.4	0.498
Duration (Mean, d)	5.9	7.6	0.523
Symptoms during attack (n)			
Abdominal pain			0.613
Yes	3	3	
No	4	10	
Headache during CVS attack			0.111
Yes	2	0	
No	5	13	
EEG pattern (n)			0.876
Slow wave	5	6	
Focal spikes	1	1	
14 and 6 positive spikes	0	2	
Negative finding	1	2	
Family history of migraine (n)			1.000
Maternal	2	3	
Paternal	0	0	
No family history	5	10	

EEG = electroencephalography; CVS = cyclic vomiting syndrome.

were defined as the migraine-negative group (Table 3).

Through follow-up (average, 7.5 years; range, 2–12 years) by telephone or outpatient clinics interviews conducted by pediatric neurologists, there was note of younger onset age of CVS in the migraine-positive group (5 ± 1.7 years) than in the migraine-negative group (8.9 ± 3 years; $p = 0.001$). The incidence of headache during CVS attack was not significantly different between the two groups (2/7 *vs*. 0/13, $p = 0.111$), which may be due to a small number of patients. Patients with subsequent migraine tended to have higher incidence of headache during CVS attack compared with the migraine-negative group (28.6% *vs*. 0%). Gender, duration and frequency of attacks, electroencephalogram, and family history of migraine did not differ between the two groups.

Discussion

Although the direct correlation between CVS and migraine has not been confirmed, their relationship has been investigated in previous studies.[13,14] Li et al in 1999 found some differences in the clinical parameters between migraine-associated and non-migraine-associated CVS patients. Milder vomiting episodes, more typical migraine symptoms (i.e. abdominal pain, headache during attacks, social withdrawal, photophobia, and more triggering events) are more common in migraine-associated patients. They also had higher response rates to anti-migraine therapy.[14]

In the present study, there is a higher incidence (35%) of subsequent migraine compared with previous studies, which may be related to a longer follow-up period in this study. The average

follow-up period was 7.5 years (range, 2–12 years). As such, the incidence of subsequent migraine development may be more accurate. The age of the study patients is also relatively young, and some may not have reached adolescence at the time of enrollment. It may thus underestimate the incidence of subsequent migraine development.

The results here show younger onset age of CVS in the migraine-positive group, which is different from previous studies. Li et al showed that there is no significant difference in the age of onset between the two study groups used in their investigation. They defined patients without migraine symptoms but with family history of migraine as the migraine-associated group. By contrast, the criteria for patients enrolled in the current study are more exact than Li's in searching for risk factors of migraine development in CVS patients.[14] This study indicates that younger age of onset in CVS may have stronger correlation with subsequent migraine development ($p = 0.001$).

The incidence of associated symptoms in the study patients, including abdominal pain and headache (71% and 11%), is remarkably lower than in previous studies.[1,14,16] Although the incidence of headache during CVS episodes was low in the present study, there is a higher incidence of comorbid headache in the migraine-positive group (28.6%) than in the migraine-negative group (0%), although not statistically significant. Patients with headache during cyclic vomiting attack tend to develop subsequent migraine more often than patients without headache. Thus, headache during attacks may indicate a migraine character of CVS patients and disclose the relationship between migraine and CVS.

However, significant differences between migraine- and non-migraine-associated CVS in previous studies, including family history of migraine, number of episodes, clinical manifestations with abdominal pain, photophobia, withdrawal symptoms, and more triggering events, are not noted in the current study. Triggering events, occurring in 11 cases (31%), are slightly lower than a previous study.[1,3] The majority have episodes triggered by infection (mostly by upper airway infection) and stress. According to previous literature, various events like infection, psychologic stress, diet, lack of sleep, physical exhaustion, atopic events, motion sickness, and menses can trigger episodes.[16] Such trigger events are difficult to determine in a retrospective study.

Maternal inheritance of CVS has been described in many reports, with mitochondrial inheritance as a sensible hypothesis because of a higher degree of maternal inheritance in CVS and migraine.[13,14,16,17] Although only 20% of patients here have maternal family history of migraine, maternal inheritance remains evident in this study, as previously.

Although abnormal results of electroencephalography have been emphasized in previous literature, the role of EEG in diagnosing migraine is controversial.[18–20] Few studies mention the relationship between electroencephalography results and CVS. Several small quantitative EEG studies of headache and cyclic vomiting reveal increased delta activities during an episodic attack.[18,21] In the current study, 33 patients received an electroencephalogram exam during the CVS attack. Their results included focal or diffuse slow waves in 16 patients (46%), focal spikes in four patients (11%), and 14 and six positive spikes in six patients (17%; Table 2). These observations show a high incidence of slow activities (46%) during CVS attack in this study. There is difficulty comparing our findings with previous data due to scarcity of literature. Focal or generalized slow activities may be a particular pattern of CVS but more cases are needed to confirm this. Wang et al found that 14 and six positive spikes were more common in patients with abdominal pain, headache, and other autonomic symptoms.[22] Only six patients (17%) have 14 and six positive spikes in EEG during an acute episode of CVS. The present study did not find 14 and six positive spikes as a significant risk factor in migraine development.

A previous study mentions a higher response rate to anti-migraine treatment in the migraine-associated group.[14] In the present study, 35 cases

received supportive treatment during CVS attacks. Six had prophylactic therapy with flunarizine as a discharge medicine, but were lost to follow-up. However, because of a limited case number and the retrospective design in this study, it is difficult to establish a definitive relationship between treatment response and migraine development.

In conclusion, there is a significant correlation between clinical manifestations of CVS and subsequent migraine development. Despite the small case number and the retrospective design, results here showed that younger onset age of CVS and headache during attacks may indicate increased risk of migraine. These results provide a new insight regarding subsequent migraine development in children with CVS, particularly if there is an earlier onset age or headache during CVS attack. Large-scale prospective studies are warranted to further clarify the relationship between CVS and migraine.

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