Cyclic Vomiting Syndrome in Thai Children

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Abstract

Cyclic vomiting syndrome (CVS) is a severe childhood vomiting disorder of unknown etiology and pathogenesis. Clinical manifestations and prophylactic therapy of vomiting have been described in the literature. The data were limited in Asian children. The aim of this study was to study the clinical manifestation, to evaluate using antimigraine prophylactic drugs and response in Thai children with CVS.

The medical records of children with a diagnosis of CVS in the Department of Pediatrics, Siriraj Hospital, Mahidol University from 1994 to 2001 were retrospectively reviewed. Demographic data, clinical manifestations, investigations, treatment and outcome were collected and analyzed. Twenty five patients were enrolled in this study including 13 females and 12 males. Their ages ranged from 2.3 years to 14 years (7.8 ± 3.4 years). The age of onset was 5.2 ± 3.2 years. They had 14.7 ± 6.5 episodes per year with a duration of each attack 4 ± 1.8 days. There were 8 mild, 10 moderate and 7 severe cases. There were only 6 patients (24%) who had headache and 50 per cent of these had a family history of migraine. Eight patients received pizotifen which had 3 good, 1 fair, and 4 poor responses. Of this group, in 3 patients pizotifen was changed to amitriptyline. Eighteen patients received amitriptyline and the result of treatments were 11 good, 4 fair, and 3 poor. The other 2 patients were on propranolol with one good and one poor responses. The efficacy of amitriptyline and pizotifen were compared (83.3% *vs* 50%) which revealed no statistical significance ($p = 0.14$). There was no side effect from any of the medication in this study. In conclusion, the present report showed similar data of clinical features, prophylactic treatment and outcome as previous reports, except for fewer migraine headaches in patients and their families. Amitriptyline and pizotifen were effective in prophylactic therapy of vomiting episodes.

Key word : Cyclic Vomiting, Children, Migraine Headache, Amitriptyline, Pizotifen

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Cyclic vomiting syndrome (CVS) is a disorder of unknown etiology characterized by stereotypical, self- limited episodes of intense nausea and vomiting that lasts hours to days and are separated by intervals during which patients are entirely free of symptoms[1,2]. There has been considerable interest in CVS and its relationship to migraine for several decades after Samuel Gee's original description of the disorder in 1882[3,4].

CVS is a disorder of the brain-gut axis, heightened by behavioral and physiological response, and may represent an over response of the natural defense mechanisms developed teleologically to protect against a toxin or toxic ingestion and stress[5].

Migraine headache, abdominal migraine, and CVS seem to be manifestations of the migraine diathesis; they are all functional, self-limited episodic disorders separated by symptom free intervals[6].

There are many reports of CVS describing clinical features, pathogenesis, management and response in children and adults from Western countries, but only one report from South- East Asian countries[7].

The objective of this study was to study the clinical manifestation, to evaluate antimigraine prophylactic drugs used and the response in children with CVS.

MATERIAL AND MEDTHOD

The medical records of children with a diagnosis of CVS in the Department of Pediatrics, Siriraj Hospital, Mahidol University from 1994 to 2001 were retrospectively reviewed. Children were diagnosed as CVS and included in the study using the following inclusion criteria : three or more discrete, stereotypic episodes of nausea and vomiting,

Table 1. Clinical data, treatment and outcome in children with CVS.

Case	Sex	Age (yr)	Onset (yr)	Episode/yr	Duration (day)	Severity	Treatment	Duration m	Result	Follow-up yr
1	Girl	2.3	1	12	5	Severe	Pizotifen	3	Poor	4
							Amitriptyline	7	Poor	
2	Boy	2.5	2	24	5	Moderate	Pizotifen	12	Good	3
3	Girl	3	1	24	5	Moderate	Amitryptyline	9	Fair	2
4	Girl	3.5	1.3	12	4	Moderate	Amitryptyline	15	Fair	1.3
5	Girl	3.5	2.5	24	3	Mild	Amitryptyline	32	Good	2.7
6	Girl	4.5	3	12	6	Severe	Propranolol	4	Fair	4.6
7	Boy	5	4	10	3	Mild	Amitryptyline	6	Good	2
8	Boy	5.5	3	12	4	Mild	Amitryptyline	3	Good	0.3
9	Girl	6	4	12	7	Mild	Amitryptyline	12	Good	1
10	Boy	6	5	15	2	Severe	Pizotifen	8	Poor	7
							Amitriptyline	8	Poor	
11	Girl	8	2	8	3	Moderate	Pizotifen	3	Poor	3.6
12	Girl	8.3	3	8	2	Moderate	Amitryptyline	3	Good	0.3
13	Boy	8.3	6	24	5	Mild	Amitryptyline	13	Fair	1.1
14	Girl	8.8	8	12	5	Severe	Amitryptyline	8	Good	0.7
15	Boy	9	5	6	7	Severe	Amitryptyline	10	Poor	0.8
16	Boy	10	7	12	3	Mild	Pizotifen	18	Good	4
17	Boy	10	8	8	2	Severe	Pizotifen	19	Poor	4
							Amitriptyline	12	Good	
18	Boy	10	3	24	3	Severe	Pizotifen	14	Fair	1.5
19	Girl	10.5	10	24	3	Moderate	Amitryptyline	28	Good	2.3
20	Boy	11	10.5	20	6	Moderate	Amitryptyline	28	Good	2.3
21	Girl	11	10	10	2	Mild	Amitryptyline	24	Fair	2
22	Boy	11	4	12	1	Moderate	Amitryptyline	17	Good	1.4
23	Girl	11.5	7	12	5	Moderate	Amitryptyline	7	Good	0.6
24	Boy	13	10	6	7	Moderate	Propranolol	8	Good	4.5
	Girl	14	10	24	2	Mild	Pizotifen	8	Good	3.5
mean ± SD			5.2 ± 3.2	14.7 ± 6.5	4 ± 1.8			12.1 ± 8		

each lasting more than 12 hours; more than 7 days between episodes; and no structural or metabolic explanation for the symptoms.

Evaluation included review of medical records and telephone interviews or letters of all the patients' parents. Demographic data, clinical manifestations, investigations, treatment and outcome were collected and analyzed. The patients were treated with prophylactic drugs including amitriptyline, pizotifen or propranolol. The severity of disease was classified as 1) mild (<10 emeses per day), moderate (10-20 emeses per day) and severe (>20 emeses per day).

All patients received prophylactic medication for prevention of vomiting attacks at least 3 months. Response to treatment was graded as 1) good (absence of vomiting or few episodes of vomiting), 2) fair (persistence of vomiting but improvement with less frequency and less intense episodes of vomiting and 3) poor (no response). In some cases with poor response, the medication was changed. The efficacy of prophylactic medication was evaluated as : effective (good and fair response) and not effective (poor).

Statistical

Data are reported as mean ± SD. Grouped data were compared using Fischer Exact Test. In all cases, $p<0.05$ was considered statistically significant.

RESULTS

The clinical presentations of individual patients are shown in Table 1. Twenty five patients were enrolled in this study including 13 females and 12 males. Their ages ranged from 2.3 years to 14 years (7.8 ± 3.4 years). The age of onset was 5.2 ± 3.2 years. They had 14.7 ± 6.5 episodes per year with duration of each attack of 4 ± 1.8 days. There were 8 mild, 10 moderate and 7 severe cases.

Clinical data of the children is summarized in Table 2. Uncertain onset in each episode was the most common time of onset (60%). Their symptoms during the episode included abdominal pain (100%), withdrawal (36%), hematemesis (28%), and headache (24%). Thirteen cases needed intravenous fluid (52%) The trigger of episodes was psychological stress (28%), infection (20%), and motion sickness (12%). Four cases had hypertension during the attack. Of 6 cases who had headache, 3 cases had a family history of migraine. Complete investigations for the diagnosis of CVS could not be performed in every case especially the inborn error of metabolism. However, the clinical manifestations and long term follow-up could exclude these diseases. Upper endoscopy were performed in 16 patients which revealed abnormal findings in 4 cases (3 esophagitis,1 gastritis). The other investigations were 17 GI follow through studies,14 EEG, and 18 blood ammonia whose results were normal.

During the attack some patients were admitted and received treatments including intravenous fluid and anti-emetic drugs (metoclopramide, ondansetron) without effective results. All patients received prophylactic medication including either pizotifen, amitriptyline or propranolol (Table 3). Eight patients received pizotifen which had 3 good, 1 fair, and 4 poor responses. Of this group, in 3 patients pizotifen had been changed to amitriptyline. Eighteen patients received amitriptyline and the results of treatment were 11 good, 4 fair, and 3 poor. The other 2 patients were on propranolol with one good and one poor response. The efficacy of amitriptyline and pizotifen were compared (83.3% *vs* 50%) which revealed no statistical significance ($p = 0.14$). No side effects of the medications were reported

Table 2. Clinical manifestations and investigations in children with CVS.

	Case	%
Onset of attack		
Uncertain time	15	60
Certain time	10	40
Abdominal pain	25	100
Withdrawal	9	36
Hematemesis	7	28
Headache	6	24
Hypertension	4	16
Need IV. Fluid	13	52
Trigger factor		
Psychological stress	7	28
Infection	5	20
Motion sickness	3	12
Family history of migraine	3	12
Investigations		
Gastroduodenoscopy	16	
Positive findings	4	
Negative findings	12	
GI follow through (normal findings)	17	
EEG (normal findings)	14	
Blood ammonia (normal findings)	18	

Table 3. Treatments and responses to different medications.

Medication	Severity	Response		
		Good	Fair	Poor
*Pizotifen	Mild	2	-	-
	Moderate	1	-	-
	Severe	-	1	3
*Amitriptyline	Mild	4	2	-
	Moderate	5	2	-
	Severe	2	-	3
Propranolol	Mild	-	-	-
	Moderate	1	-	-
	Severe	-	-	1

* Comparing efficacy between pizotifen and amitriptyline, Fischer Exact Test (P = 0.14)

DISCUSSION

Cyclic vomiting syndrome is not commonly found in Thai children, but during the last 10 years more cases have been diagnosed. Because knowledge of CVS is not widely known, wrong diagnoses such as gut obstruction, peptic ulcer disease and psychogenic disorders are commonly made.

Data from Western countries showed that CVS was slighlty more common in females than males and the onset often occurred in preschool or early school years(1). The onset of CVS ranged from 6 months to 18 years of age, with the mean of 6.9 years. The frequency of episodes ranged from 1 to 70 per year, averaging 12 per year. The present report showed similar data.

The different data in this present report showed that uncertain onset of each episode was common. Fleiser DR reported that vomiting began at characteristic times of the day in 76 per cent of patients and the most common times of onset were the middle of the night and/ or on arising in the early morning(1).

The other different data in this study were headache symptom and family history of migraine headache. There were only 6 patients (24%) who had headache and 50 per cent of these had family history of migraine. Headache, migraine headache and family history of migraine headache were more common in previous reports(6,8,9). Li BU studied 214 children with CVS in which 82 per cent of these were migraine - related CVS(9). The migraine subgroup tended to have milder, shorter episodes with fewer emeses and less dehydration. In addition, this group had a twofold higher response rate to antimigraine therapy.

Prophylactic treatment is appropriate during symptom-free intervals. Agents commonly prescribed are those used in prophylaxis of migraine headaches such as cyproheptadine, amitriptyline, and propranolol. Prophylaxis should also include amelioration of factors that may predispose to or trigger attacks.

Pizotifen is the 5- hydroxy tryptamine receptor antagonist that has been suggested for CVS because of its usefulness in the prophylaxis of migraine headache and abdominal migraine in children. Symon D studied the efficacy of pizotifen in treatment of abdominal migraine(10). The results showed pizotifen to be superior to placebo in the prophylaxis of abdominal migraine.

Tricyclic antidepressants have been used in the prophylaxis and treatment of migraine(11). Anderson JM, et al studied the effective prophylactic therapy for cyclic vomiting syndrome in children by using amitriptyline or cyproheptadine(8). Of the 22 patients receiving amitriptyline, 73 per cent had a complete response and 18 per cent had a partial response. Prakash C studied the efficacy of amitriptyline in adults with CVS which appeared beneficial for some patients but less effective in CVS than chronic, persistent functional nausea and vomiting(12).

The present study showed that the majority of patients received amitriptyline (18 cases, 72%) had an effective response in 83 per cent. The other group was on pizotifen (8 cases,32%) which was effective in 50 per cent. However, when the effi-

cacy of amitriptyline and pizotifen was compared (83.3% *vs* 50%) it revealed no statistical significance ($p = 0.14$). Although the majority of patients in this study were not the migraine subgroup, both medications were effective in prevention of vomiting attack in CVS

In conclusion, this report described some similar data of clinical features, prophylactic treatment and outcome to previous reports, except for fewer migraine headaches in patients and families. Amitriptyline and pizotifen are effective agents for the prophylactic therapy of vomiting episodes.

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Cyclic Vomiting Syndrome ในเด็กไทย

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Cyclic vomiting syndrome เป็นกลุ่มอาการที่ผู้ป่วยมีอาการอาเจียนอย่างรุนแรงเป็นระยะเวลาไม่นานและเมื่อผู้ป่วยหายก็จะหายเป็นปกติ เมื่อถึงระยะเวลาหนึ่งผู้ป่วยจะกลับมามีอาเจียนเหมือนที่เคยเป็น สาเหตุของกลุ่มอาการนี้ยังไม่ทราบแน่ชัด อาการ อาการแสดง การดำเนินของโรค การรักษาโดยให้ยารักษาไมเกรน ในการป้องกันอาเจียน และผลการรักษาได้มีการรายงานไว้ในวารสารต่างประเทศ แต่ข้อมูลดังกล่าวในเด็กเอเชีย มีเพียง 1 รายงาน การศึกษานี้จึงมีจุดประสงค์เพื่อหาข้อมูลดังกล่าวโดยเปรียบเทียบกับข้อมูลเดิม การศึกษาเป็นการศึกษาย้อนหลังโดยดูการบันทึกรายงานในผู้ป่วยเด็กที่ภาควิชากุมารเวชศาสตร์ คณะแพทยศาสตร์ศิริราชพยาบาล ตั้งแต่ปี พ.ศ. 2537–2544 พบว่ามีผู้ป่วยที่ได้รับการวินิจฉัยจำนวน 25 รายเป็นเด็กหญิง 13 รายและเด็กชาย 12 ราย มีอายุเฉลี่ย 7.8 $\pm$ 3.4 ปี อายุที่เริ่มมีอาการอาเจียน 5.2 $\pm$ 3.2 ปี โดยมีอาเจียน 14.7 $\pm$ 6.5 ครั้งต่อปี ระยะเวลาที่เป็นแต่ละครั้งนาน 4 $\pm$ 1.8 วัน มีผู้ป่วยที่มีอาการรุนแรงน้อย 8 ราย รุนแรงปานกลาง 10 รายและรุนแรงมาก 7 ราย ข้อมูลที่ได้ แตกต่างจากรายงานเดิมคือจะไม่ค่อยพบประวัติปวดศีรษะผู้ป่วยและประวัติครอบครัวที่เป็นไมเกรน โดยพบเพียง 6 รายที่มีปวดศีรษะและผู้ป่วย 3 คนในกลุ่มนี้ที่มีพ่อหรือแม่เป็น migraine ในผู้ป่วย 8 รายที่ได้รับยา pizotifen มี 3 รายที่การรักษาได้ผลดี 1 ราย ได้ผลปานกลางและ 4 รายไม่ได้ผล ผู้ป่วย 18 รายที่ได้รับ amitriptyline ได้ผลการรักษาดี 11 ราย ผลดีปานกลาง 4 รายและไม่ได้ผล 3 ราย ผู้ป่วย 2 รายที่ได้รับ propranolol ผลการรักษาดี 1 ราย อีก 1 รายไม่ได้ผล ไม่พบภาวะแทรกซ้อนของการใช้ยา เมื่อเปรียบเทียบผลของยา pizotifen กับ amitriptyline ในการป้องอาเจียน (83.3% *vs* 50%) พบว่าไม่มีความแตกต่างทางสถิติ ($p = 0.14$)

คำสำคัญ : อาเจียนเรื้อรังเป็นช่วง ๆ, เด็ก, ปวดศีรษะไมเกรน, เอมิทริบทายรีน, พิโซทิเฟน

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