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RAPID COMMUNICATION

Cyclic vomiting syndrome in children: Experience with 181 cases from southern Iran

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Abstract

AIM: To evaluate the clinical presentation, response to prophylactic therapy and outcome of children with cyclic vomiting syndrome (CVS) in Shiraz, Iran.

METHODS: During a period of 11 years (March 1994 to March 2005), 181 consecutive children with a final diagnosis of CVS were evaluated, treated and followed in our center. Patients were randomized to receive either amitriptyline or propranolol as prophylactic treatments.

RESULTS: There were 88 boys and 93 girls with mean age of onset of symptoms of 4.9 ± 3.3 years (range, neonatal period to 14 years), the mean age at final diagnosis was 6.9 years (range, 1.5 to 14), and the mean duration between the onset of the first attack and the final diagnosis of CVS was 2 ± 1.81 years (range, 1/6 to 8). The mean duration of each attack was 4.26 days (range, from few hours to 10 d) and the mean interval between the attacks was 1.8 mo (range, 1 wk to 12 mo). The time of onset of the attacks was midnight to early morning in about 70% of cases. Amitriptyline was effective in 46 out of 81 (56%) patients ($P < 0.001$). Propranolol appeared to have a superior action and was effective in 74 out of 83 (92%) patients ($P < 0.0001$).

CONCLUSION: There is a significant lag time between the onset of clinical symptoms and the final diagnosis of CVS in our area. In patients with typical clinical presentations of CVS, who are examined by an experienced physician, invasive workup is not necessary. Propranolol appears more effective than amitriptyline for prophylactic use in children with CVS.

Key words: Cyclic vomiting syndrome; Children; Propranolol; Amitriptyline

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INTRODUCTION

Cystic vomiting syndrome (CVS) is an idiopathic disorder, which presents with stereotypic episodes of severe, intractable non-bilious vomiting[1]. The episodes have a rapid onset, persist for several hours to days, and are separated by symptom-free intervals[1,2]. Although many consider CVS to be a migraine equivalent, little is known about its etiology or pathogenesis[2-7]. After gastroesophageal reflux (GER), CVS is the second most common cause of recurrent vomiting in children[8]. The disorder usually begins in childhood, mainly in preschool age children[9-13].

The vomiting is self-limited, and resolves spontaneously if left untreated, but severe, prolonged attacks can lead to dehydration and electrolyte disturbances and related complications. CVS has no specific diagnostic test and no specific treatment, or generally accepted management[1,2]. The diagnosis of CVS is based on a typical clinical presentation, and by exclusion of other possible causes with a similar presentation[1,2,5,14-16]. Consensus diagnostic criteria proposed in 1994 suggested four essential clinical features of cyctic vomiting syndrome[17-19]: (1) three or more recurrent episodes of vomiting; (2) varying intervals of completely normal health between episodes; (3) stereotypical episodes that are repetitive with regard to symptom onset and duration; (4) absence of laboratory or radiographic findings of an alternative diagnosis (absence of an organic cause).

Supportive criteria for the diagnosis of CVS are: self-limited nature of the attacks; accompanying symptoms of nausea, abdominal pain, headache, motion sickness, photophobia and lethargy; and with associated signs of fever, pallor, dehydration, excessive salivation and social withdrawal. In children, nausea and possibly lethargy are considered to be key diagnostic features[17]. The most controversial and challenging aspects of this disorder are the types of effective treatment, and the duration of medical therapy. No specific therapy has been proven to be effective for CVS in controlled trials. However, despite these controversies, medical therapy remains the only possible and promising tool to prevent, suppress or shorten the attacks[2,7]. Several empiric treatments have been shown to be effective in case series[18]. Treatment can be considered as abortive, supportive and prophylactic.

Agents that have been used empirically (with variable success) in children include: sumatriptan, erythromycin, carnitine, propranolol, cyproheptadine and tricyclic antidepressant. The aim of this prospective study was to evaluate the clinical presentation, response to prophylactic medical therapy, and outcome in children with CVS in southern Iran.

MATERIALS AND METHODS

Subjects

This prospective study included 181 consecutive children with a final diagnosis of CVS who were evaluated, managed and followed in our center between 1994 and 2005. All patients were evaluated by pediatric gastroenterologists and a neurologist (authors) and the diagnosis of CVS was based on typical clinical presentation (three or more episodes of intractable, self limited, non-bilious vomiting, separated by symptom-free intervals) and by exclusion of other possible causes with similar presentation (no identifiable organic cau
se). The initial assessment included a complete medical and family history, physical examination including evaluation of the patients' intellectual, motor, emotional and social development, and current level of functioning.

Methods

In addition to routine workup which was carried out at the time of the initial presentation, an upper gastrointestinal series (UGI) and small bowel follow through (SBFT) were performed in all patients. Sinus series and brain computed tomography (CT) were done in cases with suspicion of sinus or CNS problems. Endoscopy was carried out only in those patients with abnormal findings on UGI studies, and EEG in those with a history of seizure disorder. Patients were selected randomly for prophylactic treatment with either propranolol (1 mg/kg per day) or amitriptyline (1 mg/kg per day).

In non-responsive patients, the doses of drugs were increased to the maximum recommended level. If the symptoms did not improve, the medication was discontinued and was replaced with another drug. Patients were evaluated regularly in the pediatric GI clinic. The follow up period ranged from 6 mo to 12 years.

Table 1 Concomitant clinical symptoms in 181 children with CVS

Symptoms	*n* (%)
Abdominal pain	40 (22)
Abdominal pain + fever	33 (18)
Abdominal pain + fever + headache	45 (25)
Abdominal pain + headache	33 (18)
Abdominal pain + diarrhea	21 (12)
Fever	9 (5)

RESULTS

There were 88 boys and 93 girls. The mean age of onset of symptoms was 5 ± 3.3 years (range, neonatal period to 14), the mean age of diagnosis was 6.9 years (range, 1.5 to 14) and the mean time span between the onset of the first attack and diagnosis of CVS was 2 ± 1.8 years (range, 1/6 to 8). The mean duration of attacks was 4.25 d (range, few hours to 10 d) and the mean interval between attacks was 1.8 mo (range, 0.25 to 12). Eighty seven percent of patients had attacks of fairly uniform duration. Vomiting began at characteristic times specific for the individuals in 85% of cases, 70% patients were awakened during the night and/or had symptoms on arising in the morning and 15% patients had episodes beginning at other characteristic times of the day. Ninety percent of patients had attacks of fairly uniform duration and course. Most patients had concomitant symptoms in addition to vomiting (Table 1). Fever was usually of low grade and remitted spontaneously.

Abdominal pain was usually mild to moderate in intensity and was located in the periumbilical and/or epigastric area. About 40% of patients had history of identifiable specific conditions or events (i.e. parents' conflict, school examination, excitement, common cold) that seemed to trigger their episodes.

Forty one (25%) patients had a history of motion sickness and 8 (5%) had a history of seizures, which were controlled by anticonvulsant drugs. There was no temporal relation between the seizures and cyclic vomiting. About 55% of older children had history of recurrent headaches; in 20% the symptoms were typical of migraine. In 24% of cases, family history was positive for migraine. No patient had a positive family history of CVS. Barium studies and sinus series were normal in 97% and 95% patients respectively. Of the total of 181 patients, 164 (81 on propranolol and 83 on amitriptyline) had a regular follow-up. Of the 83 patients who received amitriptyline, 46 (56%) showed a good response, with decrease in the frequency and severity of attacks. A significant number of these cases had side effects of amitriptyline including: irritability, agitation, insomnia or lethargy.

Seventy four out of 81 (92%) patients who received propranolol had a good response ($P < 0.0001$), without any significant side effects. Patients who were non responsive to amitriptyline, were treated with propranolol, and most of them had a satisfactory response. A few patients who were non-responsive to both drugs, had repeated, severe attacks with frequent hospital admissions. This group was non-responsive to other medications as well including phenobarbital and cyproheptadine. There

was no explanation for the lack of response in this group.

The medication was discontinued in 52 (31%) patients. These subjects were > 10 years of age and were symptom free on prophylactic medication for at least 5 years. They were followed for one year or more, and only two cases had recurrence of symptoms.

DISCUSSION

The present report represents one of the largest studies of CVS in the literature. Although our findings do not provide further information on the etiology or pathogenesis of this disorders, it does supplement previous observations concerning the stereotypic nature of attacks, their precipitants, duration of illness, the time span between attacks and the time span between symptom onset and the final diagnosis[1,2]. The overall gender ratio in our series was equal. A similar gender distribution has been reported by Abu-Arafeh[9], although many have suggested a higher frequency in girls[10-12,19,20].

The mean age of onset of symptoms in our series was 5 ± 3.3 years, which is the same as that reported by Abu-Arafeh[9], but younger than that reported by Fleisher (6.75 years)[2] and older than that reported by Hoyt and Stickler (3.8 years)[11]. In present series, the first attack began during the neonatal period in 10 (5.5%) cases and at 14 years of age in 5 cases. In the series reported by Fleisher[2], the age range was 6 mo to 18 years. None of the patients reported in the previous series had disease onset in the neonatal period. Although CVS has been characterized as beginning in preschool and early school aged children, our data suggest that the onset in neonatal and pre-adolescent children is also possible. Adult onset cases have also been reported[21]. Therefore one cannot exclude the diagnosis of CVS on the basis of the age. In 85% of our cases the symptoms of CVS occurred from midnight to early morning. Further, 90% of the attacks had a uniform length, which is in agreement with previous studies[17].

Forty percent of our patients had a history of triggering events, which is approximately one-half of the incidence reported by Fleisher *et al*[2]. Twenty percent of our cases had history of motion sickness in early childhood, which is approximately 50% lower than that reported by Fleisher *et al*[2]. Fifty eight percent of our patients had history of recurrent headaches and of these 20% were migraine-like, which compares well with previous findings[2,4].

None of our patients had a family history of CVS, indicating that CVS is unlikely to be hereditary. Upper gastrointestinal series (UGI) and small bowel follow through (SBFT) were normal in 97% of our cases, suggesting that a thorough history and physical examination by an experienced physician can detect most of the typical cases of CVS without the need for invasive investigations. Therefore, it is recommended that routine barium studies are not necessary in typical cases of CVS as suggested by some authorities[16] and they should only be done in atypical cases, or in those patients unresponsive to medical treatment.

A significant number of our patients with a typical presentation suffered from multiple attacks spread over several months and even years with repeated hospital admissions before they were referred to our center. They were usually misdiagnosed and received treatment for other conditions such as food poisoning, metabolic disorders or acid peptic disease. The significant lag time between the onset of symptoms and final diagnosis of CVS in our series indicates that this disorder is usually not considered in the differential diagnosis of children with recurrent vomiting in this area. About 92% of our cases were responsive to propranolol without significant side-effects, while 56% were responsive to amitriptyline with considerable side-effects. The present data indicates that propranolol is much more effective and safe in comparison with amitriptyline, therefore propranolol is recommended as the first drug of choice for prophylaxis in children with CVS. It is concluded that: (1) the age of onset, sex distribution and clinical presentations of patients in southern Iran with CVS are similar to those in other regions of the world; (2) there may be a significant lag time between the onset of clinical symptoms and final diagnosis of CVS in our area; (3) in patients with a typical clinical presentation of CVS, invasive investigations are not necessary; and (4) propranolol is much more effective and has fewer side effects than amitriptyline for prophylactic therapy of children with CVS.

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