ORIGINAL ARTICLE

Outcome for children with cyclical vomiting syndrome

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Objective: Cyclical vomiting syndrome (CVS) is a disorder that carries a significant burden of disease for children and their families. The aim of this study was to examine the outcome of a group of children diagnosed with CVS from 1993 to 2003.

Methods: Children diagnosed with CVS over a 10-year period were identified and a review of the clinical records was carried out to define demographic features and the spectrum of disease at presentation. The patient's parent was contacted to establish the child's current well-being. Ethical approval for the study was obtained.

Results: Fifty one children were diagnosed with CVS and 41 agreed to participate in follow-up. Mean age was 5.8 (SD 3.3) years at onset of CVS, 8.2 (SD 3.5) years at diagnosis, and 12.8 (SD 4.8) years at follow-up. Vomiting had resolved at the time of follow-up in 25/41 (61%) children. Sixteen of 41 (39%) children reported resolution of symptoms either immediately or within weeks of diagnosis. However, a large number of children from the group whose vomiting resolved and the group that were still vomiting continued to have somatic symptoms, with 42% of children suffering regular headaches and 37% having abdominal pain. 32 (78%) parents felt that the provision of a positive diagnosis and information made a significant impact on the severity of vomiting.

Conclusions: While 60% of children with CVS have resolution of symptoms, a significant proportion of both those in whom symptoms have resolved and those in whom vomiting persists continue to suffer from other somatic symptoms.

Although cyclical vomiting syndrome (CVS) was first described in 1883 by Samuel Gee,¹ it has only emerged as a topic of research interest in the last decade. CVS is characterised by periods of intense vomiting lasting hours to days with a symptom-free interval of weeks to months. The first international symposium on CVS in 1994 defined a set of criteria (outlined in table 1) to facilitate the diagnosis of CVS.² The diagnosis is often delayed as children undergo numerous investigations to rule out other causes of vomiting. While a variety of treatment options exist, which may be directed at one or more of the different phases of the syndrome,³ no definitive treatment has been shown to be effective in most children.

Community-based studies have estimated the prevalence of CVS to be between 0.03% and 2.3% in school-aged children.^{4–7} Only one prospective study to date has reported the outcome for children with CVS.⁸ This study reported that vomiting resolves in 60% of children. However, 46% of the group suffered migraine headaches at follow-up, compared to 12% of a control population. Fleisher suggests that individuals with CVS continue to experience CVS as adults and that CVS is an emerging disorder in adult gastroenterology.⁹

The aetiology and pathophysiology of CVS are poorly understood. A number of possible mechanisms are under investigation, including autonomic dysfunction,¹⁰ altered corticotropin-releasing factor and vasopressin release at a hypothalamic-pituitary level,¹¹ ion channelopathies seen in other periodic disorders,¹² and disorders of fatty acid and mitochondrial metabolism.^{13–15} Investigators have suggested that CVS is part of the spectrum of functional disorders. Anxiety and stress play a significant role in the onset and perpetuation of symptoms.⁹ Our own clinical experience would suggest that the provision of a diagnosis and information from the CVS Association greatly alleviate the burden of illness for these children and their families. As information on the outcome of CVS in children is limited, the aim of this study was therefore to examine the

outcome and current well-being of a group of children diagnosed with CVS between 1993 and 2003.

METHODS

Fifty one children who were diagnosed with CVS during the period 1993–2003 were identified from a CVS database maintained by the Department of Gastroenterology at Our Lady's Children's Hospital, Crumlin, Dublin. All children with CVS were diagnosed by a paediatric gastroenterologist according to the criteria outlined in table 1.

When a diagnosis of CVS was made, the condition was explained to the parents, and where possible, to the child. Possible trigger factors were discussed and an information sheet from the CVS Association was provided. Investigations and clinical management were tailored to the needs of individual children.

Each family was contacted by letter in order to obtain consent. Parents who were not willing to participate were asked to return a letter of regret. The clinical records of each child were reviewed and data were collected regarding demographics, symptom pattern and severity, associated symptoms, possible trigger factors, investigations, interventions and hospitalisations. Any family history of migraine, CVS, irritable bowel, cancer or depression was also recorded. A single investigator (EF) carried out a structured telephone interview over approximately 30–40 min with the child's parents. During the interview, we collected information on the child's current well-being, resolution or persistence of symptoms, other symptoms including migraine, and factors associated with a change in symptoms. The family's perception of the diagnosis of CVS was explored. We also sought their perception of the usefulness, if any, of having a specific diagnosis for their child's symptoms and the provision of written information on CVS. The study was

Abbreviations: CVS, cyclical vomiting syndrome; SD, standard deviation

Table 1 Diagnostic criteria and typical clinical features of CVS²

Diagnostic criteria	Typical clinical features
Essential	
Recurrent severe discrete episodes	>4 Emesis/hour
Various intervals, normal health in between	2–4-Week intervals
Duration of hours to days	
No apparent cause of vomiting	
Supportive	
Stereotypical onset, intensity and frequency	Rapid onset/offset
Self-limited, spontaneous resolution	Early morning onset
Associated symptoms: nausea, abdominal pain, headache, motion sickness, photophobia	Trigger factors present
Associated signs: fever, pallor, dehydration, excess salivation, social withdrawal	

approved by the Ethics Committee of Our Lady's Children's Hospital, Crumlin.

Statistical analysis

Data were expressed as means and standard deviation (SD). Means were compared using the Student t test and differences between the groups were compared using the χ^2 test or the Fisher exact test. Statistical significance was set at the 5% level.

RESULTS

Of 51 children diagnosed during the study period, 42 families were contacted and 41 agreed to participate (80% follow-up). The nine families who could not be contacted had either changed address or their contact details were unavailable.

Clinical data at presentation

Twenty six patients (63%) were male and 15 (37%) female. The mean age at onset of symptoms was 5.8 years (SD 3.3 years), mean age at diagnosis was 8.2 years (SD 3.5 years) and mean age at follow-up was 12.8 years (SD 4.8 years).

Severity

At the time of diagnosis, 17 (41%) children had at least one episode of vomiting every month, a further 15 (37%) had at least one episode every 3 months and in nine patients (22%) the interval between episodes was greater than 3 months. Although CVS episodes (from time of commencing vomiting to

waking up well) were short lived (<24 h) in 16 (39%) children, they lasted 1–3 days in 14 (34%) and seven (17%) patients vomited for more than 3 days. In four children the duration of the episode was variable.

When first seen at our institution, 50% per cent of the group had already been admitted to a hospital at least once for rehydration with 27% having had two or more admissions.

Triggers and prodrome

At diagnosis 71% (29/41) of patients were able to identify a trigger factor for their episodes. In 18/41 (44%) this was predominantly a non-noxious exciting event such as a birthday, holiday or Christmas. In 9/41 (22%) a noxious trigger such as family separation or school anxiety was identified. In 2/41 (5%) the trigger identified was a specific foodstuff. A prodrome, generally a feeling of uneasiness or abdominal pain, was reported by 43% of patients. One child described the prodromal period as "the monsters are coming".

Family history

Either a first or second-degree relative with migraine was reported for 66% (27/41) of children and in one child there was a possible family history of CVS.

Follow-up

At the time of follow-up, 25/41 (61%) children had been free of vomiting episodes for at least a year, while 16 (39%) continued to vomit. Among those in whom vomiting had ceased, resolution had occurred within weeks of diagnosis in 16 (39%). There were no differences in the age at onset of symptoms, age at diagnosis or duration of follow-up between those whose vomiting had resolved and those who continued to vomit (table 2). In order to determine if the severity of symptoms at diagnosis influenced the outcome for children with CVS, we classified vomiting in children having symptoms lasting >24 h and occurring more often than monthly as severe. Seven (28%) of those in whom symptoms had resolved had severe CVS, while three (19%) of those who continued to vomit had severe symptoms ($p = \text{NS}$).

Overall, 12 children (29%) were prescribed medication for CVS, including anti-migraine medication, anti-emetics, benzodiazepines and erythromycin. There was no difference in medication usage between those who had ceased vomiting and those who had not (table 2).

There were no differences between the groups in the number of hospital admissions or trigger factors identified. Of those

Table 2 Characteristics of children whose vomiting had and had not resolved

	Resolved	Still vomiting	p
Number of patients	25	16	
Male	17 (68%)	9 (56%)	0.44
Mean age at onset, years	6 (SD 3.3)	5.5 (SD 3.3)	0.64
Mean age at diagnosis, years	8.3 (SD 3.5)	8.1 (SD 3.6)	0.86
Mean age at follow-up, years	13.1 (SD 4.9)	12.3 (SD 4.8)	0.6
Mean interval between onset and diagnosis, years	2.2 (SD 1.7)	2.6 (SD 2.6)	0.55
Mean interval between diagnosis and follow-up, years	4.6 (SD 2.6)	4.1 (SD 2.9)	0.56
Severity*	7/25 (28%)	3/16 (19%)	0.71
Admitted to hospital	14/25 (56%)	7/16 (44%)	0.44
Medication prescribed	16/8/25 (32%)	4/16 (25%)	0.67
Trigger factor identified	25 (64%)	13/16 (81%)	0.24
Family history of migraine	16/25 (64%)	11/16 (69%)	0.75
Remembered receiving leaflet	20/25 (80%)	14/16 (88%)	0.53
Diagnosis reassured family	19/25 (76%)	13/16 (81%)	0.69
Regular abdominal pain	9/25 (36%)	8/16 (50%)	0.37
Regular headache	10/25 (40%)	7/16 (44%)	0.81
Regular diarrhoea	6/25 (24%)	7/16 (44%)	0.18
Travel sickness	13/25 (52%)	9/16 (56%)	0.79

*Severe classified as having episodes at least every 4 weeks lasting >24 h.

What is already known on this topic

- CVS is mainly a childhood disorder characterised by severe recurrent episodes of nausea and vomiting with periods of normal health in between.
- There is a significant burden of illness associated with CVS in terms of hospitalisation and school absenteeism.
- One previous follow-up study suggested that vomiting resolves in 60% of children.

What this study adds

- Vomiting resolves in 60% of children, often very quickly after diagnosis.
- A significant proportion of those whose symptoms resolve and those in whom vomiting persists continue to suffer other somatic symptoms at follow up.
- A biopsychosocial approach to the management of CVS with the provision of information and explanation may greatly alleviate the burden of illness.

children who were still vomiting, 80% had been absent from school due to symptoms within the previous year; the mean number of days absent was 10.4 (SD 7.4).

Most children continued to experience somatic symptoms regardless of the presence or absence of ongoing vomiting (table 2). Overall, 41% of the entire group still complained of headache (10 of 25 (40%) of those in whom vomiting had resolved and 7/16 (44%) of those who still vomited were affected by regular headaches). Seventeen (41%) children had frequent or occasional abdominal pain (36% of the resolved group, 50% of the still vomiting group). Overall, 32% of the group had intermittent diarrhoea and 54% experienced travel sickness at follow-up.

Although 39% of the children continued to vomit, the caregiver felt that the symptoms were easier to deal with after a diagnosis had been made and information about CVS had been provided. Overall, 83% of families remembered receiving written information at the time of diagnosis, 41% used the internet to access further information on CVS, and 78% of parents felt that information and a diagnostic label made the condition more manageable, both for their child and themselves.

DISCUSSION

Two thirds of children attending our institution no longer experienced episodes of cyclical vomiting at follow-up. This figure is similar to previous reports.^{8–16} Resolution of symptoms did not correlate with duration or severity of the disorder at presentation, or indeed with any of the other variables analysed (table 2). The male to female ratio in this study was higher than previously reported, however there was no difference in outcome between boys and girls.

The diagnosis of CVS was based on the criteria set down at the first international symposium on CVS and were the accepted criteria at the time of diagnosis for the children studied. All children in this study also fulfilled the criteria defined by Rome III.¹⁷

Despite a positive diagnosis and information on the condition, almost 40% of children (16/41) continued to experience episodes of vomiting. For these children, a mean of 4.1 years

(SD 2.9 years) after diagnosis, CVS represented a significant disability, with seven children (44%) missing more than 10 days of school in the previous year. Medication use was not a predictor of recovery, with vomiting resolving in 66% of those prescribed some form of medication versus 58% of those who were not prescribed medication (table 2).

Perhaps the most remarkable finding in this study is that even in those children whose vomiting had resolved, 40% continued to suffer from other somatic complaints including headache and abdominal pain. This suggests that for some children at least, CVS represents part of the spectrum of functional disorders. The short time between diagnosis and resolution of CVS (immediately or within weeks) in 39% of children is also notable. This lends further support to the idea that CVS may be, in fact, a functional disorder which responds well to identification of key stressors or triggers.¹⁸ Forbes *et al* have suggested that CVS is more commonly seen in anxious children with high internalising scores on the Achenbach Child Behaviour Checklist,¹⁹ while Fleisher *et al* found that 70% of patients in his series of adults with CVS had features characteristic of one or more anxiety disorders.⁹ Therefore, a biopsychosocial approach to the management of CVS may greatly improve the outcome. The formation of a therapeutic relationship between the child, family and physician is key in managing all functional disorders. Facilitating the understanding that both biological and psychosocial factors contribute to symptoms and illness behaviour may lead to the resolution of symptoms and greatly alleviate the burden of illness.^{20–21}

It is important not to underestimate the impact that CVS has on the family and the relief associated with its resolution. Although the follow-up interview was in some cases up to 10 years after diagnosis, recollection of the period of illness was startlingly vivid. This is illustrated by the fact that 83% of parents remembered receiving the information leaflet at the time of initial consultation. The provision of a definite diagnosis and information on CVS made the symptoms more manageable for half of those who continue to vomit. We feel that this is because the perception of the parents and the child is integral to the management of CVS. While the retrospective nature of this follow-up study limits the conclusions we can draw, the rapid resolution of symptoms in many of these children suggests that CVS may fall into the spectrum of functional disorders. A biopsychosocial approach to the management of CVS, focusing on appropriate explanation and reassurance could have a significant effect on coping and illness behaviour.

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ARCHIVIST

Prognosis in childhood multiple sclerosis

The proportion of patients with multiple sclerosis (MS) who develop symptoms before 16 years of age has been variously estimated at between 0.4% and 10.5%. There have been few studies of the course of childhood-onset MS and how it may differ from adult-onset disease. Now data from the European Database for Multiple Sclerosis (EDMUS) network of adult neurology departments (Christel Renoux and colleagues. *New England Journal of Medicine* 2007;**356**:2603–13) have clarified the natural history of MS beginning in childhood.

Thirteen adult neurology departments in France and Belgium provided data on 394 patients with MS of childhood (age 16 years or younger) onset (COMS) and 1775 patients with MS of adult (>16 years) onset (AOMS). The proportion of the total cohort who had COMS was 2.2%. The female:male ratio was 2.8 in COMS and 1.8 in AOMS. In the COMS group, mean follow-up was for 17 years and 49% received at least one disease-modifying treatment (interferon β , azathioprine, mitoxantrone, cyclophosphamide, methotrexate, glatiramer acetate or mycophenolate mofetil) at some time. The mean age of onset of COMS was 13.7 years and 30 patients (7.6%) were aged 10 years or younger at disease onset. The first symptoms of COMS were isolated brain stem symptoms in 66 (17%), isolated long tract symptoms in 149 (38%), and other or combined symptoms in 87 (22%). The initial course was exacerbating-remitting in 385 patients and progressive in nine. The median time to the second episode was 2 years. Among patients with an initial exacerbating-remitting course, 110 (29%) converted to secondary progression during follow-up (estimated median time to conversion to secondary progression, 28 years and estimated median age at conversion, 41 years). The estimated median times to scores on the Kurtzke Disability Status Scale of 4 (walking limited but can walk >500 m without aid), 6 (walking up to 100 m with support) or 7 (walking up to 10 m with support) were 20, 29 and 37 years, respectively. Walking was preserved for longer with younger age at onset. Patients with progressive disease at onset had shorter times to irreversible disability. Compared with AOMS, COMS was more likely to begin with isolated optic neuritis or isolated brain stem symptoms and less likely to begin with long tract symptoms. Encephalitic symptoms occurred in 7% of patients with COMS but were rare in AOMS. An exacerbating-remitting initial course is more common in COMS (98% vs 84%) and the estimated times to conversion to secondary progression and to disability were 10 years longer in COMS than in AOMS. The estimated age at conversion or disability was about 10 years younger in COMS compared with AOMS.

Children with MS are more likely than adults to present with isolated optic neuritis or brain stem disorder and may present with an encephalopathic picture. They develop the disease about 20 years before adults and take about 10 years longer to progress to severe disability. They are therefore, on average, about 10 years younger than people with adult-onset disease on reaching severe disability.