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Cyclic nausea and vomiting in childhood

Background
Cyclic vomiting syndrome (CVS) is an under-recognised functional gastrointestinal disorder of childhood. Despite failure of recognition by many health practitioners, it is relatively common and frequently disabling.

Objective
This article describes the clinical features, differential diagnosis, treatment and outcomes of CVS.

Discussion
Cyclic vomiting syndrome is a functional disorder in childhood with a prevalence of around 2%. It consists of recurrent paroxysms of severe nausea and vomiting separated by symptom free periods. Associations include migraine, genetic factors, autonomic dysregulation, neuromuscular disorders and a tendency to anxiety. Cyclic vomiting syndrome may be triggered by stress and anticipatory anxiety as well as infection, exercise, trauma, menstruation and foods. Diagnosis requires exclusion of other causes of nausea and vomiting. Management focuses on the phases of the illness: prevention of attacks, termination of vomiting, sedation and prevention of complications. Children may outgrow symptoms, develop migraine or continue to have episodes into adulthood.

The functional disorders are a group of syndromes in which symptoms of disease exist in the absence of significant biochemical or structural abnormalities. These include infant regurgitation, toddler's diarrhoea, constipation, irritable bowel syndrome and chronic abdominal pain.[1,2] Despite the absence of 'hard' laboratory or radiographic findings, these symptom complexes can result in difficulties for both the patient and their family. Frequent and repeated school absences may occur and affect academic and social functioning. Frustration with the medical system may result from delayed or incorrect diagnoses.

What is CVS?

Cyclic vomiting syndrome (CVS) consists of recurrent paroxysms of severe nausea and vomiting separated by symptom free periods.[1] The episodes occur at variable intervals, with an average of 12 per year. There is often a prodromal phase of nausea and pallor. Affected children may vomit up to 12 times per hour and may continue to have symptoms for days. Onset generally occurs before 5 years of age.

Vomiting episodes have been described as stereotypic for a child. That is, each episode resembles others in terms of duration, intensity of vomiting and features such as time of onset, prodromal features, and the duration of time between attacks.[3] The vomiting is typically accompanied by abdominal pain, nausea, anorexia, pallor and lethargy. Affected children may also exhibit migraine-like symptoms such as headache, photophobia, phonophobia and vertigo.

Children can appear very unwell, often more so than their counterparts with infective gastroenteritis. The paroxysms often end abruptly. Between episodes children appear completely well and are free from gastrointestinal symptoms.

There are a related group of children who have many of the features of CVS, without the vomiting episodes, but are still disabled by their intense nausea. These children are less commonly recognised. Children with CVS may have other functional gastrointestinal syndromes such as recurrent abdominal pain, but the phenotype is so distinct that it is usually easy to distinguish between them.

Causative factors

Several factors contributing to the cause of CVS have been identified. A genetic factor has been confirmed with the demonstration of maternally inherited mitochondrial DNA abnormalities.[4]

Cyclic vomiting syndrome shares characteristics with migraine and may be considered a migraine variant for many sufferers.[5–7] Both conditions are recurrent in nature, have a prodromal phase and may be precipitated by similar events. There is an increased incidence of migraine in patients (and their relatives) with CVS. Antimigraine medications are of use in the treatment of CVS.

Children with CVS have autonomic dysregulation,[8] with exaggerated cardiovascular responses to postural change and other stimuli, which may be associated with the onset of gastrointestinal symptoms.

A number of children with associated neuromuscular disorders, earlier onset of CVS and poor response to antimigraine therapies, have been labelled 'CVS-plus'.[9] They are thought to have an underlying brain abnormality. Children with the 'CVS-plus' pattern have an 8-fold increased rate of dysautonomic related features.

The psychological profile of children with CVS is characterised by a tendency to anxiety. There has been speculation regarding the role of serotonin in functional gastrointestinal disorders, including CVS. Although there is evidence of such a role in some disorders, this has not yet been confirmed in CVS.

The role of triggers

Many patients and their families can identify one or more triggers of vomiting episodes.[5] Stress and anticipatory anxiety related to school examinations, family conflict, and birthday parties are common precipitants. Other triggers include infection, exercise, trauma, menstruation, and foods, particularly cheese and chocolate.

These associations and experimental evidence allow speculation regarding a model of cyclic nausea and vomiting.[10,11] A range of triggers associated with physical or psychological stress causes release of corticotrophin releasing factor which stimulates vagal brain stem receptors, inducing gastric stasis or emesis. The lack of an effective negative feedback response that terminates the central and gastrointestinal changes may be related to defects in brain energy metabolism that have been documented in a few individuals with dysautonomic features.

Prevalence

Cyclic vomiting syndrome affects approximately 2% of the paediatric population; the prevalence in adults is not known. A 1963 study of children in Western Australia identified a prevalence of 2.3%,[12] and a 1994 cross sectional school study in Scotland found a prevalence of 1.9% in children aged 5–15 years.[13]

Differential diagnosis

Differential diagnosis includes both gastrointestinal and nongastrointestinal illness (*Table 1*).[11,14] It is essential to assess and investigate patients with persistent vomiting to exclude life threatening diagnoses such as malrotation with volvulus, neoplastic lesions of the central nervous system, and metabolic disorders.

The differential diagnosis is similar for patients with nausea as the main symptom, but with more emphasis on medications and toxins, mucosal abnormalities, liver disease and neuropsychiatric disturbance.[15] The lower overall frequency of attacks and the higher peak intensity of vomiting in CVS will usually allow its clear distinction from disorders such as bulimia nervosa.[3,10]

Investigations

Serum electrolytes may be assessed in the acute setting, before commencing intravenous fluid therapy, to seek evidence of underlying metabolic, endocrine or renal disorders. Plasma and urine amino acid profiles are indicated in vomiting associated with fasting to exclude inborn errors of metabolism. Bilious vomiting requires plain abdominal films of the abdomen to exclude obstructive causes of vomiting.

Early morning emesis and neurological findings on examination should prompt imaging of the central nervous system, and in general, children should undergo brain imaging studies. Stool and urine

Table 1. Differential diagnosis of cyclic nausea and vomiting

Medications and toxins
- Antibiotics
- NSAIDs
- High dose vitamins
- Hormonal preparations
- Laxatives

Infections
- Enteric agents
- Hepatitis
- Epstein-Barr virus
- Otitis media
- Chronic sinusitis

Gastrointestinal
- Bowel obstruction
  - malrotation with volvulus
  - iInternal hernias
  - duplication cysts
- Inflammatory lesions
  - peptic ulcer disease
  - gastritis
  - duodenitis
  - chronic appendicitis
  - inflammatory bowel disease
- Pancreatitis
- Hepatobiliary disease

Neuropsychiatric disorders
- Migraine
- Epilepsy
- Space occupying CNS lesions
  - hydrocephalus
  - posterior fossa tumours
  - subdural effusion
- Factitious illness
- Anxiety states
- Bulimia nervosa

Renal
- Pelvi-ureteric junction obstruction
- Nephrolithiasis

Metabolic and endocrine
- Pregnancy (in adolescents)
- Diabetes mellitus
- Addison disease
- Phaeochromocytoma
- Organic acidurias
- Fatty acid oxidation defects
- Mitochondrial disorders
- Urea cycle defects
- Aminoaciduri

microscopy and culture may exclude infectious causes of vomiting. Gastrointestinal endoscopy may be indicated in patients with symptoms of oesophagitis that persist beyond vomiting episodes.

While CVS can occur in infants and young children, a diagnosis should only ever be made after a period of observation and careful exclusion of other causes of recurrent vomiting.

Approaches to therapy

Therapeutic objectives need to be built around the different phases of CVS.[11,16,17]

Prevention

Prevention of symptomatic episodes should be the primary goal of therapy for all patients followed by switching off or aborting established episodes, and minimising distress and complications when this is not feasible.

The response of any individual to a particular, untried treatment is difficult to predict, therefore therapeutic trials must be undertaken to customise a solution for the individual. This typically will take a long period, and will require a supportive relationship and long term commitment from a family physician in what is a very challenging clinical scenario.

Prevention of episodes may be possible for patients who can identify avoidable precipitants such as stressful situations and certain foods. This may involve trials of dietary elimination. A dietician may be helpful in ensuring an adequate balanced diet is achieved in the face of dietary elimination and frequent hospitalisation. Consultation with a mental health professional can be beneficial in exploring psychological stressors and developing techniques for dealing with anticipatory anxiety.

Prophylaxis

Medical prophylaxis should be considered in patients with attacks occuring more frequently than once per month as continuing compliance is an issue for those with less frequent attacks. Prophylaxis is useful in those with features of migraine. Unfortunately, it is most likely to be effective in those whose illness is less severe; although in practice it will be attempted in all patients. A range of agents have been utilised, although the quality of evidence to support these decisions is limited to anecdotal reports and poorly controlled clinical trials.

Antimigraine medications pizotifen, propranolol and cyproheptadine may be effective in those with a family history of migraine. Anticonvulsants such as phenobarbitone, carbamazepine, valproate and topirimate have been utilised, as has amitriptyline.[11] Carnitine[18] and erythromycin[19] have both been reported as effective prophylactic agents in limited trials.

In practice, a sequential trial of agents over periods that will cover 2–3 attacks is appropriate, staring with the safest agents (pizotifen, cyproheptadine, propranolol, carnitine), before progressing to amitryptilene and anticonvulsants. Too rapid an assumption of lack of effectiveness may limit the use of some agents.

Table 2. Drug therapy in cyclic vomiting and nausea

Prophylaxis	
Propranolol	10 mg/day given in two doses
Cyproheptadine	0.3 mg/kg/day given in 1–2 doses
Erythromycin	20 mg/kg/day given in 2–4 doses
Pizotifen	0.5–1.0 mg at night
Sumatriptan*	Oral 25–50 mg, intranasal 10 mg, or subcutaneously 3–6 mg
Carbamazepine	5–10 mg/kg/day given in two doses
Amitriptyline	5–25 mg at night
Hospital based management	
Glucose 10%	≤ maintenance fluid volume IV
Ondansetron	0.3–0.4 mg/kg and then 0.1 mg/kg/hour IV
Omeprazole	1 mg/kg/day IV given in two doses
Lorazepam	0.05–0.1 mg/kg IV 2–4 times per day
Chlorpromazine	0.15–0.3 mg/kg IV 2–3 times per day

* Effect not proven in young children

Acute management

The most important facets of acute phase management are a management plan and a relationship with a health practitioner whom the parents can contact to expedite prompt care.[16] In rural settings, the general practitioner will undertake all aspects of management, while in urban settings the GP role may focus on liaison with hospital doctors. Children should not be waiting long periods for treatment if there is to be any chance of terminating a vomiting attack. Some children can be managed at home, but many will require a period of hospitalisation.

The first phase of acute management focuses on attempting to abort an established attack. Sumatriptan is occasionally beneficial in this situation and is worth a trial either by injection or sublingual administration.[17] Sublingual ondansetron wafers are also successful for some patients.

The administration of an intravenous fluid containing glucose may be effective in terminating attacks in up to 42% of cases and intravenous ondansetron has been shown to decrease the duration of an episode by more than 50%.[20] Standard antiemetic agents are seldom effective, and have the associated risk of extrapyramidal side effects.

Unfortunately in the majority of children it will not prove possible to abort the episodes of vomiting. The goal of treatment then becomes symptom minimisation and prevention of the complications of prolonged vomiting.[16] Hospital admission is necessary at this point. Symptom minimisation involves attention to psychological distress, severity of vomiting and dehydration.

Management includes care in a quiet, single room with subdued lighting. Intravenous fluids, usually with added glucose up to 10% to

limit ketosis are important, taking care not to overhydrate. Sedation and anxiolysis with agents such as chlorpromazine or lorazepam is important as sleep decreases vomiting frequency.

Success with alpha blockade using dexmedetomidine[21] and clonidine[22] has been reported for small numbers of patients. Proton pump inhibitors or H2 receptor antagonists should be considered for children who have prolonged or frequent episodes of vomiting.

Both the child and their family require support during this phase of illness. Many children will spit out large volumes of saliva.[3] This is thought to be a response to the intense nausea invoked by swallowing. The distracted preoccupation that children develop may make them appear uncooperative. These behaviours often frustrate clinicians who may feel that the child is 'putting it on'. Parents in turn may feel that their child is being judged and not taken seriously, or worse, punished because of their problem. Consequently they may lose trust in their health practitioner and seek multiple opinions in order to find a sympathetic doctor.

Many families and primary care providers find it useful to undertake review by a paediatrician and jointly work out a management plan. Initial review is best undertaken between vomiting episodes, and not at the time of acute illness when the child will find it difficult to cooperate and parents are distressed and distracted.

In general, as soon as the episode is over (and a child can usually tell us when this point is reached) discharge should be effected and the child returned to school and usual routines. Some children may end up requiring more than 20 admissions to hospital each year, and prolonging convalescence contributes to school loss. In the interval between attacks it is appropriate to check on school performance and look for evidence of acid damage to teeth.

Natural history and outcomes

The natural history of CVS is variable. Some children outgrow symptoms during adolescence, some trade cyclic vomiting for migraine headache and others continue to have episodes into adulthood.[6] Younger age at onset may be associated with a longer course of illness.[3,11] Up to 70% of adults with CVS have comorbid psychiatric diagnoses such as mood disorders, anxiety disorders and substance abuse.[23]

Cyclic vomiting syndrome is a chronic disabling disorder which presents in childhood, but occurs across the age spectrum. Treatment needs to be individualised with attention to prevention as well as acute therapy. A close relationship between the family and the GP is essential for optimal management.

Summary of important points

- CVS occurs in approximately 2% of the paediatric population.
- Diagnosis is on the basis of recurrent, stereotypic episodes of nausea and vomiting with episodes of wellbeing in the intervals between attacks.
- Vomiting is higher intensity, but bouts occur less frequently than for other chronic vomiting disorders.
- Management focuses on the phases of the illness: prevention of attacks, termination of vomiting, sedation and prevention of complications.
- There is a high risk of long term comorbid psychiatric disorders.

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