Abdominal migraine and cyclical vomiting syndrome

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Abstract

Abdominal migraine and cyclical vomiting syndrome (CVS) are characteristic syndromes which have overlapping characteristics with migraine but lack the cardinal symptom of headache. Both abdominal migraine and CVS are characterised by recurrent attacks of nausea, vomiting and/or abdominal pain lasting hours to a few days, with symptom freedom between attacks. Both abdominal migraine and CVS typically occur in children and adolescents, who often go on to develop more typical migraine headaches when older, but may also present for the first time in adults. Due to their shared characteristics and association with migraine headaches, abdominal migraine and CVS are sometimes called "migraine equivalents" and their pathophysiology is assumed to overlap with migraine headache. This chapter describes what is known about the clinical characteristics, epidemiology, pathophysiology, and prognosis of abdominal migraine and CVS, and explores their relationship to migraine. We also review the existing evidence for the non-pharmacological management, acute treatment of attacks, and preventive treatments for both abdominal migraine and CVS.

Key words:

Abdominal migraine, cyclical vomiting, episodic syndromes, migraine equivalents, childhood migraine

Introduction

Abdominal migraine and cyclical vomiting syndrome (CVS) are syndromes characterised by recurrent attacks of nausea, vomiting and/or abdominal pain lasting hours to a few days, with symptom freedom between attacks, and not caused by any underlying identifiable physical pathology. Due to their shared characteristics and association with migraine headaches, abdominal migraine and CVS are sometimes called “migraine equivalents” and their pathophysiology is assumed to overlap with migraine headache. Other benign episodic childhood syndromes, which also may be associated with migraine, include infantile colic, benign paroxysmal torticollis, and benign paroxysmal vertigo (Abu-Arafeh and Gelfand, 2021).

Abdominal migraine

Clinical characteristics

Abdominal migraine is characterised by recurrent episodes of central or poorly localised abdominal pain with no identifiable secondary cause. The abdominal pain is often associated with lethargy, anorexia, pallor and nausea, sometimes with vomiting. Episodes have a similar duration to those of migraine (2-72 hours) and can occur between two to 100 times per year (Abu-Arafeh and Russell, 1995b). Episodes can be triggered by similar triggers to migraine such as stress and fatigue, and usually relieved by rest and sleep (Hyams *et al*., 2016).

Abdominal migraine is predominantly a childhood disorder but can occasionally present for the first-time during adulthood (d'Onofrio *et al*., 2006; Roberts and deShazo, 2012). People who suffer with abdominal migraine in childhood frequently go on to develop migraine headaches from adolescence or young adulthood onwards. A family history of migraine in a first-degree relative is twice as common in children with abdominal migraine compared to controls (Abu-Arafeh and Russell, 1995b) with a parental history of migraine as high as 69% in one study (Mortimer *et al*., 1993).

Current diagnostic criteria for abdominal migraine are included within the International Classification of Headache Disorders 3rd edition (ICHD-3) (Table 1) and the Rome IV Classification of functional gastroenterological disorders (Table 2) (Headache Classification Committee of the International Headache Society, 2018; Hyams *et al*., 2016).

Table 1. The International Classification of Headache Disorders, 3rd edition criteria for abdominal migraine (2018)

A	At least five attacks of abdominal pain, fulfilling criteria B–D
B	Pain has at least two of the following three characteristics: 1. midline location, periumbilical or poorly localized 2. dull or "just sore" quality 3. moderate or severe intensity
C	At least two of the following four associated symptoms or signs: 1. anorexia 2. nausea 3. vomiting 4. pallor
D	Attacks last 2-72 hours when untreated or unsuccessfully treated
E	Complete freedom from symptoms between attacks
F	Not attributed to another disorder

Table 2. Rome IV criteria for abdominal migraine in children and adolescents

Must include all of the following occurring at least twice:	
1	Paroxysmal episodes of intense, acute periumbilical, midline or diffuse abdominal pain lasting 1 hour or more (should be the most severe and distressing symptom)
2	Episodes are separated by weeks to months.
3	The pain is incapacitating and interferes with normal activities
4	Stereotypical pattern and symptoms in the individual patient
5	The pain is associated with 2 or more of the following: a. Anorexia b. Nausea c. Vomiting d. Headache e. Photophobia f. Pallor
6	After appropriate evaluation, the symptoms cannot be fully explained by another medical condition.
Criteria must be fulfilled for at least 6 months before diagnosis	

Differential diagnosis

Abdominal pain is a common presenting complaint in children and adults, and has a huge variety of causes. The differential diagnosis of recurrent paroxysmal episodes of abdominal pain is smaller and includes functional and organic causes. Other "functional" causes of abdominal pain include adolescent rumination syndrome, cyclic vomiting syndrome, aerophagia, functional dyspepsia, irritable bowel syndrome, childhood functional abdominal pain syndrome, and functional constipation. These are all diagnosed by the clinical history and consensus criteria (Hyams *et al*., 2016). It is recognised that there is overlap in diagnostic criteria and patients can meet criteria for more than one disorder, and it is not known whether these criteria represent discrete disorders or different manifestations of shared underlying pathophysiology (Helgeland *et al*., 2009).

"Organic" causes (i.e., secondary to an identifiable organ pathology which can be treated directly) of recurrent abdominal pain include food intolerance, coeliac disease, gastro-oesophageal reflux, dysmenorrhea, urinary tract disease, inflammatory bowel disease, peptic ulcer disease, pancreatitis, biliary tract disease, familial Mediterranean fever, porphyria, and neoplastic disease (Bufler *et al*., 2011; Hyams *et al*., 2016).

On the one hand, "functional" causes of recurrent abdominal pain are common, and it is important for them to be recognised to avoid unnecessary testing or treatments, including invasive operations such as appendicectomy (Farquhar, 1956). On the other hand, it is important not to miss treatable organic pathology, which may otherwise lead to morbidity. There is little evidence to suggest that features of the abdominal pain itself can differentiate an "organic" from a "functional" cause of abdominal pain, however red flag features for secondary cause which have been suggested are family history of inflammatory bowel disease, persistent right upper quadrant or right lower quadrant pain, dysphagia, odynophagia, persistent vomiting, gastrointestinal blood loss, nocturnal diarrhoea, arthritis, perirectal disease, involuntary weight loss, deceleration of grown, delayed puberty and unexplained fever (Hyams *et al*., 2016). The presence of anxiety, depression, or behavioural problems is not thought to be a good differentiator between "functional" and "organic" abdominal pain as psychological problems have been found to be present at similar rates in both groups (Raymer *et al*., 1984).

Epidemiology

Recurrent abdominal pain is a common symptom in the paediatric population. Mortimer *et al.* found the prevalence of recurrent abdominal pain to be 8.4% in all children registered with a GP practice, and a prevalence of abdominal migraine of 2.4% (Mortimer *et al*., 1993). Other studies have estimated the prevalence of abdominal migraine in school-age children to be 1% (Saps *et al*., 2014) and 4.1% (Abu-Arafeh and Russell, 1995b). A more recent study using Rome III criteria (which are less strict) has estimated the prevalence of functional gastroenterological disorders overall as affecting 23.1% of children and adolescents, with prevalence of abdominal migraine of 9.2% (Lewis *et al*., 2016). The female:male ratio is estimated to be 1.6:1, and the mean age of onset is 7 years (Abu-Arafeh and Russell, 1995b).

Pathophysiology and relationship to migraine

Initially most authors considered abdominal migraine and other forms of recurrent functional abdominal pain to be a primarily psychologically driven condition, associated with mood disturbance and stressful life events. However, a case control study comparing 30 children with recurrent abdominal pain did not show any difference in psychological factors compared to pain free children (McGrath *et al*., 1983). Another study including a group of patients with "organic" abdominal pain (inflammatory bowel disease) with those with "non-organic" abdominal pain showed that psychological problems were present at similar rates in both groups (Raymer *et al*., 1984).

Abdominal migraine is now classed in ICHD-3 under "episodic syndromes that may be associated with migraine" (Headache Classification Committee of the International Headache Society, 2018). The relationship to migraine headache has been presumed on the basis of similar triggers (stress, fatigue, travel), similar associated symptoms (nausea, vomiting, anorexia, dizziness, photophobia, phonophobia) and similar alleviating factors (rest, sleep, analgesia). These factors suggest that, like migraine headaches, abdominal migraine has a neurological basis (Abu-Arafeh and Gelfand, 2021). The pathophysiology of migraine headaches, whilst there is no unified model, is becoming better understood. The susceptibility to migraine is currently thought of as a predominantly inherited polygenic disorder (except for rare familial hemiplegic migraine) which runs in families, and involves activation of the trigeminovascular system, neuropeptides such as calcitonin gene-related peptide, and sensitisation of several brain and brainstem regions (Goadsby *et al*., 2017).

Treatment

Treatments which have been described are symptomatic treatments of pain or nausea, or medications typically used for migraine headache. It is important to note that as attacks of abdominal migraine usually resolve spontaneously within a few hours, descriptions of acute treatment without a placebo control may not represent a real treatment effect. In migraine, reduction of attack frequency with placebo taken instead of a preventive treatment is also common. This is demonstrated by a large randomised controlled trial of amitriptyline and topiramate for paediatric migraine, where there was no improvement greater than placebo with either treatment (Powers *et al*., 2017).

Non-pharmacological measures

The diagnosis should be explained to the patient, and the parent (who is also likely to suffer from migraine) if the patient is a child. Lifestyle measures which are usually recommended for migraine may be helpful in preventing attacks, including hydration, not skipping meals, exercising, and good sleep hygiene. If there are reliable triggers for attacks, then these should be avoided where possible to prevent attacks from occurring.

During acute attacks, rest and sleep help relieve symptoms in the majority of children with abdominal migraine (Abu-Arafeh and Russell, 1995b), and it is sensible to pursue non-pharmacological measures in the first instance and use preventive medications if the pain is severe or not resolving spontaneously.

A cognitive-behavioural family intervention has been shown to help greater than standard care in children with recurrent functional abdominal pain (not specifically abdominal migraine).

Acute treatment

A variety of treatments can be used for the acute treatment of abdominal migraine attacks with the aim of relieving or aborting the symptoms, including analgesics, antiemetics, and triptans. Ibuprofen and paracetamol are reported to be effective, and intranasal sumatriptan has been reported to relieve pain in two cases (Kakisaka *et al*., 2010), but no treatment has been assessed in controlled studies.

Intravenous sodium valproate and intravenous dihydroergotamine have been effective as second line treatments in small series of patients with otherwise refractory episodes (Tan *et al*., 2006; Raina *et al*., 2013).

Preventive treatment

Preventive treatments are those which are taken daily with the aim of preventing attacks beginning. Trials of treatments for abdominal migraine which have included at least 10 patients are summarised in Table 3. The only placebo-controlled trial evidence in abdominal migraine is for pizotifen, which in a small study of 14 children aged 5-13 showed a significant improvement in abdominal pain compared to placebo (Symon and Russell, 1995).

Other preventive treatments are sometimes used in abdominal migraine, their use extrapolated from those used for migraine headaches, but evidence for efficacy is limited to case reports for topiramate, amitriptyline, sodium valproate and onabotulinumtoxinA injections (Woodruff *et al*., 2013; Hermanowicz, 2021).

In the largest case series of adults, most patients responded to one of the following medications: calcium channel blockers, anticonvulsants, pizotifen, and/or beta blockers (Roberts and deShazo, 2012).

Table 3. Studies of preventive treatments for abdominal migraine

Author and year	**Population**	**Intervention**	**Study type**	**Outcome**
(Symon and Russell, 1995)	14 children	Pizotifen	Double blind placebo-controlled crossover trial	Pizotifen statistically superior to placebo (pain frequency and severity)
(Worawattanakul *et al*., 1999)	36 children	Propranolol	Open-label case series	18/24 (75%) had a good response to treatment
		Cyproheptadine	Open-label case series	4/12 (33%) had a good response to treatment

(Kothare, 2005)	10 children	Flunarizine	Open-label case series	61% reduction in frequency of attacks
(Madani *et al*., 2016)	18 children	Cyproheptadine	Open-label case series	13/18 (72%) had a significant improvement

Prognosis

One study of 54 children has assessed the long-term prognosis of abdominal migraine. At follow-up of approximately six years, with a mean age at follow up of 17, abdominal migraine had resolved in 61% of cases (Dignan *et al*., 2001a). At follow up migraine headaches were present in 52% of patients, whereas in the baseline study only 24% of the children with abdominal migraine also had migraine headaches, suggesting that several patients transformed from abdominal migraine to more typical migraine headache.

Cyclical vomiting syndrome

Clinical characteristics

CVS is a disorder characterised by recurrent episodes of severe nausea and vomiting lasting from hours to days which cannot be attributed to any secondary disorder. Episodes are usually separated by weeks or months of symptom-freedom, and within each patient attacks tend to be stereotyped with predictable periodicity (Fleisher and Matar, 1993). Sometimes episodes can be triggered, for example by stress, excitement, certain foods, fatigue, and menstruation in adolescents/adults. The vomiting phase may be preceded by a prodrome characterised by lethargy, anorexia, nausea, or pallor. The vomiting episodes may be associated with abdominal pain, loose stools, pallor, low-grade fever, headache, and other migraine-like symptoms such as photophobia, phonophobia, or dizziness. Unlike in migraine, the vomiting does not usually help symptoms. Finally, there is a recovery phase, usually over a few hours.

Current diagnostic criteria for CVS are included within the ICHD3 (Table 4) and the Rome IV Classification of functional gastroenterological disorders (Table 5) (Headache Classification Committee of the International Headache Society, 2018; Hyams *et al*., 2016).

Table 4. International Classification of Headache Disorders, 3rd edition criteria for cyclical vomiting syndrome

A	At least five attacks of intense nausea and vomiting, fulfilling criteria B and C
B	Stereotypical in the individual patient and recurring with predictable periodicity
C	All of the following: 1. nausea and vomiting occur at least four times per hour 2. attacks last for at least one hour, up to ten days 3. attacks occur at least one week apart
D	Complete freedom from symptoms between attacks
E	Not attributed to another disorder

Table 5. Rome IV criteria for cyclic vomiting syndrome in children and adolescents

All of the following:	
1	The occurrence of 2 or more periods of intense, unremitting nausea and paroxysmal vomiting, lasting hours to days within a 6-month period.
2	Episodes are stereotypical in each patient.
3	Episodes are separated by weeks to months with return to baseline health between episodes.
4	After appropriate medical evaluation, the symptoms cannot be attributed to another condition.

CVS typically affects children, but can affect all age groups, and compared to abdominal migraine, CVS has been more extensively described in adults, and onset has been reported as late as 73 years old (Prakash and Clouse, 1999). Symptoms appear to be similar in children and adults (Prakash *et al*., 2001), although adults may be more likely to have interictal symptoms of milder nausea and vomiting (Abell *et al*., 2008).

Psychiatric symptoms, particularly anxiety, are common in those with CVS. Panic attack-like symptoms have been reported to be a trigger for episodes of CVS as well as present during attacks (Fleisher *et al*., 2005). 47% of children and adolescents and 84% of adults with CVS have been found to meet diagnostic criteria for an anxiety disorder (Tarbell and Li, 2008;

Namin *et al*., 2007). Depression may also be present in as many as 78% adults with CVS (Namin *et al*., 2007).

One study has reported a high prevalence of myopathic, epileptic, and cognitive conditions in those affected by CVS, but this has not been reported by other studies (Boles *et al*., 2003).

Differential diagnosis

Vomiting in children is common and usually caused by gastroenteritis; other infections (respiratory, urinary, ear, meningitis); food allergy; gastro-oesophageal reflux; or structural gastroenterological pathology (appendicitis, intussusception, pyloric stenosis, inflammatory bowel disease). Secondary causes of *cyclical* vomiting in young children include adrenal insufficiency, inborn error of metabolism, malrotation with volvulus or intussusception or constipation; and in adolescents or adults also includes cannabis hyperemesis syndrome and eating disorder (Shields and Lightdale, 2018). Vomiting is common in typical migraine episodes, and rarely an ictal phenomenon in epilepsy. Rarely a structural neurological cause such as posterior fossa tumour (e.g., medulloblastoma or brainstem glioma) or Chiari malformation can present with recurrent vomiting. Red flag features for a secondary cause of vomiting are haematemesis, bilious emesis, focal neurological deficits, lack of nausea, vomiting waking from sleep, abdominal distension and dehydration (Shields and Lightdale, 2018). Abdominal migraine may also cause recurrent vomiting, but in abdominal migraine the pain is the predominant feature, rather than vomiting.

The diagnosis of CVS is often delayed, especially in adults (Abell *et al*., 2008; Prakash *et al*., 2001). It is often only reached after multiple hospital attendances and extensive investigation. One study showed that adults with CVS vomited in the emergency departments an average of seven times before diagnosis, and it was not recognised in the emergency department in 93% of cases, in many cases even in patients with an established diagnosis of CVS (Venkatesan *et al*., 2010b). A study of 41 adult patients who received an ultimate diagnosis of CVS found that most had undergone invasive or radiation-involving investigations, most commonly oesophago-gastro-duodenoscopy, barium studies, computed tomography (CT) scans, and colonoscopies. Fourteen (39%) of the patients had undergone surgeries, most commonly cholecystectomy, which did not result in improvement of their symptoms (Fleisher *et al*., 2005).

Epidemiology

Estimates of the prevalence of CVS in school-age children have ranged from 0.3% (Saps *et al*., 2014) to 2% (Abu-Arafeh and Russell, 1995a). The typical age of onset is between age five and seven and with an approximately equal male:female ratio (Abu-Arafeh and Russell, 1995a; Ertekin *et al*., 2006).

Although epidemiological studies in adults have not been performed, CVS is usually thought to be rare in adults. However, a study of patients seen in an adult outpatient gastroenterology clinic found that most patients who had negative investigations had symptoms compatible with CVS, and the overall prevalence of CVS in the clinic was 10.8% (Sagar *et al*., 2018).

Pathophysiology and relationship to migraine

Like abdominal migraine, the pathophysiology of CVS and distinction from other functional gastroenterological disorders is imperfectly understood. A family history of migraine has been reported in 170/214 (79%) children with CVS, a rate which is far higher than expected in the general population (Li *et al*., 1999). Like abdominal migraine, CVS is classed in the ICHD-3 under "episodic syndromes that may be associated with migraine" (Headache Classification Committee of the International Headache Society, 2018).

Autonomic dysfunction has been proposed by some authors as a cause of CVS given the (mostly parasympathetic) autonomic symptoms which often accompany attacks, such as salivation, gastroparesis, and orthostatic hypotension. Abnormalities which have been found on autonomic nervous system function testing in patients with CVS include changes in heart rate variability, postural tachycardia syndrome, or abnormal sudomotor function, compared to controls (To *et al*., 1999; Venkatesan *et al*., 2010a; Hejazi *et al*., 2011).

Mitochondrial dysfunction has also been proposed to play a role in the pathophysiology of some or all cases of CVS, due to a frequent maternal inheritance pattern. In one study, in whom many of the children with CVS also had myopathic features, there was a frequent elevation of blood ketones, blood lactate or other markers of metabolic disease (Boles *et al*., 2003). Another study found disease-associated mitochondrial variants were more common in CVS than controls (Wang *et al*., 2004).

Familial inheritance has also been reported in families who do not have features of mitochondrial disease e.g., (Haan *et al*., 2002), and other genetic factors have also been

linked. In a next-generation sequencing study of over 1100 genes the only gene that was statistically associated with CVS compared to controls was the RYR2 gene, which encodes a calcium channel (Lee *et al*., 2015). Another study found an association with variants in CNR1 and ORPM1 genes (Wasilewski *et al*., 2017). A variety of inherited metabolic diseases have been reported to cause a "cyclical vomiting syndrome" but they are not strictly CVS, which by definition is a primary/functional disorder.

It is possible that there are subgroups of CVS, which are caused by different pathophysiology (migraine-like, autonomic disorder, mitochondrial disorder). One study has found differences in the phenotype and treatments responses between children with CVS who have a personal or family history of migraine, and those who did not. "Migraine associated CVS" was more likely to be associated with abdominal pain, headache, photophobia, and motion sickness, and more responsive to anti-migraine therapy (Li *et al*., 1999).

Treatment

Treatments usually given for CVS are either general symptomatic measures e.g., analgesia or antiemetics, or treatments which have proven efficacy in migraine headache. Like abdominal migraine, attacks of CVS will resolve spontaneously after a few hours to few days, therefore descriptions may not represent a real treatment effect, and there is also a lack of placebo-controlled trials for preventive treatments. Guidelines for the management of CVS in adults have been published by the American Neurogastroenterology and Motility Society and the Cyclic Vomiting Syndrome Association (Venkatesan *et al*., 2019).

Non-pharmacological measures

The patient (and parent in an affected child) should be educated about the syndrome. As in migraine, if there are reliable triggers for attacks, then these should be avoided where possible. Lifestyle measures in the interictal period may reduce the frequency of episodes, including a good level of hydration, not skipping meals, exercising, and good sleep hygiene (Li, 2018).

Most attacks can be managed at home with rest, hydration, sleep, and oral antiemetics taken in the prodromal phase. If episodes are prolonged or there is severe vomiting leading to dehydration and inability to take oral medications, hospital admission may be required for intravenous hydration or antiemetics. In one study approximately 50% of children with CVS

who required hospital admission improved (defined as a 50% reduction in vomiting) with supportive therapy with intravenous hydration (Li *et al*., 1999).

Given the strong association with anxiety and depression, addressing psychological symptoms is important, although it is not known whether this will also improve the vomiting symptoms. Guidelines recommend to screen for and treat comorbidities such as anxiety, depression, migraine headache, autonomic dysfunction and sleep disorders (Venkatesan *et al*., 2019). In the same guideline, it is recommended that techniques such as meditation, relaxation and biofeedback may be offered as complementary therapy as they are unlikely to cause side effects and may have other benefits on well-being. Cognitive behavioural therapy and heart rate variability biofeedback has been reported as effective in a single case report (Slutsker *et al*., 2010).

Acute treatment

Although no placebo-controlled trials have been conducted for acute treatment of CVS, a variety of acute treatments (analgesics, antiemetics, and triptans) have been described as effective in open label trials or retrospective case series (Gui *et al*., 2019). Parenteral treatments may be more likely to be absorbed and therefore more successful than tablets when there is active vomiting. The most studied acute treatment is ondansetron. Studies which have reported acute treatment response and included at least 10 patients are summarised in Table 6. Guidelines recommend using ondansetron and/or triptans or aprepitant as acute treatments (Venkatesan *et al*., 2019).

Table 6. Studies of acute treatments for cyclical vomiting syndrome

Author and year	**Population**	**Intervention**	**Outcome**
(Li *et al*., 1999)	214 children (176 migraine-related[$] and 38 non-migraine-related CVS)	Promethazine	At least a partial response in 11/48 (23%) in migraine-associated [$] and 2/15 (13%) in non- migraine-associated CVS
		Cisapride	At least a partial response in 6/32 (19%) in migraine-associated [$]

			and 2/8 (25%) in non- migraine-associated CVS
		Ondansetron	At least a partial response in 28/36 (77%) in migraine-associated [$] and 5/7 (71%) in non-migraine-associated CVS
		Sumatriptan (subcutaneous)	At least a partial response in 24/35 (69%) in migraine-associated[$] and 1/3 (33%) non-migraine-associated CVS
(Boles *et al*., 2003)	62 children with CVS, most of whom had feature of neuromuscular or cognitive disorder	Ondansetron (intravenous)	Improvement[#] in 24/52 (46%) patients
		Carbohydrate (oral or intravenous)	Improvement[#] in 35/60 (58%) patients
(Hikita *et al*., 2011)	11 children, who experienced 35 attacks	Sumatriptan (subcutaneous or intranasal)	Complete response in 7 (20%) attacks, and partial response in 19 (54%) of attacks
(Moses *et al*., 2014)	85 children	Ondansetron (oral)	Improvement[#] in 6/85 (66%)
(Cristofori *et al*., 2014)	25 children	Aprepitant	Complete response in 3 (12%) and partial response in 16 (64%)

*Complete response defined as abortion of the attack, and partial response defined as 50-99% reduction in vomiting

[#]Not defined

[$]Migraine-associated CVS defined as a personal or family history of migraine headache

Preventive treatment

Preventive treatment is usually recommended if there are more than four episodes per year, episodes last more than two days, there is a long recovery from episodes, or if episodes require hospitalisation. Tricyclic antidepressants, especially amitriptyline, are the most commonly used preventive medications in CVS, although other anti-migraine drugs, antiemetics, and prokinetics may also be used. Current guidelines recommend amitriptyline as the first-line prophylactic treatment, with topiramate and aprepitant as second-line options (Venkatesan *et al*., 2019).

The majority of studies assessing preventive treatment of CVS are retrospective studies, and there are no placebo-controlled trials. Three prospective randomised comparison studies have been performed, one which compared amitriptyline and cyproheptadine (Badihian *et al*., 2018), one which compared a combination of erythromycin and propranolol to propranolol alone (Haghighat *et al*., 2015), and one compared amitriptyline to topiramate (Bagherian *et al*., 2019). Studies which have reported preventive treatment responses for individual treatments in at least 10 patients are summarised in Table 7. Other treatments trialled in small numbers of patients include flunarizine, riboflavin, zomisamide and levetiracetam (Kothare, 2005; Martinez-Esteve Melnikova *et al*., 2016; Clouse *et al*., 2007).

One study compared children who had a personal or family history of migraine headaches to those who did not and suggested that those patients with a migraine history may be more likely to respond to migraine treatment (Li *et al*., 1999). Another study investigated predictors of response to amitriptyline and found that non-responders were more likely to have co-existing migraine, more likely to have co-existing psychological disorders, and more likely to use marijuana and opioid analgesia (Hejazi *et al*., 2010).

Table 7. Studies of preventive treatments for cyclical vomiting syndrome

Author and year	**Population**	**Intervention**	**Outcome**
(Vanderhoof *et al*., 1993)	20 children	Erythromycin	Complete remission in 13 (65%)
(Andersen *et al*., 1997)	22 children	Amitriptyline	Complete remission in 16 (73%) and partial response in 4 (18%)

(Gokhale *et al*., 1997)	14 children	Phenobarbital	Complete remission in 11 (79%) and partial response in 3 (21%)
(Prakash and Clouse, 1999)	17 adults	Tricyclic antidepressants	Complete remission in 17.6%, and partial response in 58.8%
(Li *et al*., 1999)	214 children (176 migraine-related[$] and 38 non-migraine-related CVS)	Isometheptene	At least a partial response in 4/13 (31%) in migraine-associated [$] CVS
		Propranolol	At least a partial response in 37/52 (71%) in migraine-associated [$] and 3/8 (38%) in non-migraine-associated CVS
		Cyproheptadine	At least a partial response in 15/32 (47%) in migraine-associated [$] and 0/5 in non-migraine-associated CVS
		Amitriptyline	At least a partial response in 8/12 (75%) in migraine-associated [$] and 1/1 in non- migraine-associated CVS
(Boles *et al*., 2003)	62 children with CVS, most of whom had feature of neuromuscular or cognitive disorder	Amitriptyline	Improvement[#] in 17/22 (77%)
		Cyproheptadine	Improvement[#] in 8/14 (57%)
		Propranolol	Improvement[#] in 6/13 (46%)
(Hikita *et al*., 2009)	13 children	Sodium valproate	Complete remission in 2/13 (15%), and partial response in 9/13 (69%)

(Hejazi *et al*., 2010)	132 children	Amitriptyline	At least a 25% decrease in frequency or duration of episodes, emergency department visits or hospitalisations in 115/132 (87%)
(Boles *et al*., 2010)	30 children (13 of whom received this combination)	Combination of amitriptyline, co-enzyme Q10 and L-carnitine	Complete remission in 10/13 (77%) and partial response in 1/13 (8%)
(Moses *et al*., 2014)	85 children	Cyproheptadine	Improvement[#] in 30/61 (49%)
		Amitriptyline	Improvement[#] in 23/40 (58%)
(Cristofori *et al*., 2014)	16 children	Aprepitant	Complete remission in 3 (19%) and partial response in 10 (62%)
(Haghighat *et al*., 2015)	301 children	Combination of propranolol and erythromycin or propranolol alone	Symptom freedom for at least one month after treatment in 140/155 (90%) treated with combination and 113/146 (77%) treated with propranolol alone, significant difference between the two groups p=0.002
(Sezer and Sezer, 2016)	38 children	Propranolol	Complete remission in 13/22 (59%) and partial response in 5/22 (23%)
		Topiramate	Complete remission in 13/16 (81%) and partial response in 2/16 (13%)
(Badihian *et al*., 2018)	64 children	Amitriptyline	Complete remission in 21/32 (66%) and partial response in 8/32 (25%)
		Cyproheptadine	Complete remission in 16/32 (50%) and partial response in 8/32

			(25%), no significant difference to amitriptyline
(Bagherian *et al*., 2019)	72 children	Amitriptyline	Complete remission in 23/34 (68%)
		Topiramate	Complete remission in 14/36 (39%), significant difference between the two groups p=0.016

*Complete remission defined as 100% response, and partial response defined as 50-99% response

[#]Not defined

[$]Migraine-associated CVS defined as a personal or family history of migraine headache

Prognosis

In many cases, CVS resolves in adolescence, but a significant minority continue to experience attacks. In one follow-up study of 26 children with CVS, with mean age at follow up of 17 years, vomiting episodes had resolved in 69% of cases, although at follow up some of the adolescents whose vomiting episodes had resolved were now experiencing migraine headaches (Dignan *et al*., 2001b). In another follow-up study of 41 patients, vomiting had resolved in 61% of cases. In the 25 adolescents whose CVS had resolved, 40% had ongoing episodes of headache, again suggesting that they were transitioning into developing migraine (Fitzpatrick *et al*., 2007).

Conclusion

CVS and abdominal migraine are both associated with a personal and family history of migraine greater than expected by chance and have many shared clinical features. Both disorders predominantly affect children, but may also present in adults, especially CVS. There is a lack of randomised controlled trials for treatment of both abdominal migraine and CVS. Lifestyle measures may help, and acute management is typically supportive with antiemetics and analgesia. The greatest evidence exists for pizotifen in the preventive treatment of abdominal migraine, and amitriptyline in the prevent treatment of cyclical vomiting syndrome.

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