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Motility (H Parkman and R Schey, Section Editors)

Migraine, Cyclic Vomiting Syndrome, and Other Gastrointestinal Disorders

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Abstract

Purpose of review Cyclic vomiting syndrome (CVS) is a chronic functional gastrointestinal disorder characterized by episodic nausea and vomiting and is diagnosed using Rome IV criteria. CVS is being recognized more frequently in adults with a prevalence of 2%. It is associated with several functional disorders like autonomic dysfunction, anxiety, and depression, but the strongest association is with migraine.
Purpose of review To elucidate the close relationship between migraine and CVS and briefly discuss its association with other gastrointestinal disorders.
Recent findings We highlight similarities in pathophysiology, clinical presentation, and response to medications between CVS and migraine (tricyclic antidepressants, triptans, antiepileptics). We also discuss novel therapies like CGRP inhibitors which are effective in migraine and have potential for adaptation in patients with CVS.
Summary Using migraine as a template should enable investigators to elucidate the mechanisms underlying this disorder, develop novel therapies, and direct future research in CVS.

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Introduction

Cyclic vomiting syndrome (CVS) is a chronic functional gastrointestinal disorder (FGID) associated with episodic nausea, vomiting, and abdominal pain. It was thought to affect mostly children who outgrew their symptoms but developed migraine headaches as adults. It is now known that CVS also affects adults. The most descriptive report of CVS is by Fleischer et al., where the symptoms and four phases of CVS are characterized [1••]. Migraines were a frequent comorbidity in this cohort, with 70% of adults being affected. Given this relationship and the notion that CVS in adults is rare, it was referred to as "abdominal migraine." The relationship between CVS and migraine is complex and incompletely understood. Experts have speculated that these conditions have a common pathophysiology, based on the similarities in clinical presentation and response to similar medications.

We conducted a comprehensive literature search of relevant articles of adult cyclic vomiting syndrome and migraine disorders using PubMed. Database search was done using keywords "cyclic vomiting syndrome," "adult," "migraine," "treatment," "dysautonomia," and "pathophysiology." We utilized relevant articles to review the epidemiology, comorbidities, pathophysiology, and treatment modalities in CVS as it pertains to migraine headaches and also briefly discuss migraine in other gastrointestinal (GI) disorders. This review will also discuss novel therapies such as calcitonin gene-related peptide (CGRP) that are effective in migraine and offer opportunities for use in CVS.

Epidemiology

There are limited data on the prevalence of CVS in adults. A recent study in a tertiary outpatient gastroenterology clinic in the UK revealed a prevalence of 10.8%, which is comparable to other FGIDs such as irritable bowel syndrome (IBS) and chronic constipation [2, 3]. However, only 39.4% of these patients were asked about vomiting symptoms on initial visit and only 4.0% of physicians entertained the diagnosis of CVS [4•]. These findings highlight the lack of knowledge about CVS in the medical community and the significant delay in diagnosis and treatment. A recent population-based study showed that the prevalence of CVS was 2% in adults in the USA, similar to that in children [5]. Among children, the prevalence of CVS was ~2% in Scotland, Western Australia, and Turkey [6–8]. In general, CVS affects females more than males [1••, 9]. A summary of the studies in adult CVS reporting demographics, clinical characteristics, and association with migraine is shown in Table 1. Most adults with CVS are white and female with ages ranging from 29 to 41 years. A personal history of migraine headaches was seen in 6–70% with family history of migraines in first- and second-degree relatives of 7–64%. The low prevalence of concurrent migraines in one of the studies may reflect inadequacies in data collection rather than the true prevalence.

The prevalence of migraine is well documented; it affects 18% of women and 6% of men in the USA [10•]. It usually affects adults aged 30–39 years in both sexes and is rarely seen in adults >60 years [10•]. Frequency of attacks ranges from 1 to 4 headaches per month and half the patients reported pain severe enough to affect their daily routines.

Table 1. Demographics, clinical characteristics, and prevalence of migraine in adults with CVS

Characteristic	Venkatesan et al. 2014 [36]	Hejazi et al. 2010 [23]	Kumar et al. 2012 [56]	Hejazi et al. 2010 [49••]	Fleisher et al. 2005 [1••]	Namin et al. 2007 [9]	Prakash et al. 1999 [102]	Shearer et al. 2018 [103]
Total N (%)	216	132	101	41	41	31	17	17
Male	69 (32%)	72 (55%)	35 (35%)	22 (54%)	24 (59%)	18 (58%)	8 (47%)	4 (24%)
Female	147 (68%)	60 (45%)	66 (65%)	19 (46%)	17 (41.5%)	13 (42%)	9 (53%)	13 (76.5%)
Race				N/A	N/A	N/A	N/A	N/A
Caucasian	187 (95%)	117 (89%)	79 (79%)					
African-American	2 (1%)	13 (10%)	17 (17%)					
Hispanic	6 (3%)	2 (2%)	3 (3%)					
Other	3 (1.5%)	0	1 (1%)					
Age (yrs.)	34 (25–46) median (range)	34 ± 4 (20–68)*	27 ± 12.3 (mean ± STD	35 (18–63) mean (range)	34 (20–64) mean (range)	29 (18–62) mean (range)	41 ± 4	29.8 ± 14.8 (19–75)
Age of onset (yrs.)	N/A	22 ± 2*	13.4 ± 12.5 (pediatric onset) 32.3 ± 12.3 (adult onset)	26 (10–52)	21 (2–49)	30 (14–53)	35 ± 4	N/A
History of migraine headache	84 (39%)	30 (23%)	46 (48%)	12 (29%)	28 (70%)	4 (13%)	4 (23.5%)	1 (6%)
Family history of migraine headache	78 (43%)	N/A	57 (64%)	3 (7%)	23 (57%)	14 (45%)	N/A	5 (29%)
Anxiety	N/A	10 (8%)	45 (47%)	N/A	N/A	26 (84%)	4 (23%)**	N/A
Depression	N/A	8 (6%)	42 (44%)	N/A	N/A	24 (77%)	4 (23%)**	N/A

N/A not available
*Responder data reported, non-responder data omitted; report of total cohort N/A
**Unspecified current psychiatric disorder (anxiety state or affective disorder)

Clinical features

CVS is episodic and unpredictable similar to migraine headache. The diagnosis of CVS rests on recognizing the typical clinical presentation. CVS is comprised of four major phases: prodrome, emesis, recovery, and the inter-episodic well phase (Fig. 1). Prodromal symptoms include pallor, diaphoresis, malaise, nausea, and autonomic responses like sweating and salivation [1••]. This can vary in duration from minutes to several hours and is important to recognize as abortive medications can be administered to prevent progression to emesis.

During the emetic phase, patients have frequent and violent bouts of vomiting or retching. They may report a peculiar "drinking and guzzling water" phenomenon, which they describe as soothing. Another curious phenomenon is the "compulsive hot-water bathing" pattern, where patients will have a hot shower or bath (up to 20 times a day) to obtain temporary symptomatic relief [11]. This bathing pattern is highly associated with cannabis use in CVS and is thought to be a hallmark of a related condition called cannabinoid hyperemesis syndrome (CHS). Patients with CHS have presentations similar to CVS, except for the history of chronic cannabis use that precedes symptom onset. A detailed review of CHS is beyond the scope of this article. This "compulsive hot-water bathing" pattern has not been reported in the literature in migraines except for a small subset of case reports involving hot baths that actually trigger a benign, self-limiting bath-related headache [12]. Specifically, a "hair-wash headache" has been documented in Indian women that present with acute thunderclap headache lasting < 4 h that is precipitated by hot water [13].

During the recovery phase of CVS, vomiting decreases in intensity and patients return to baseline and have from few to no symptoms. However, a subset of patients have increasing frequency of episodes resulting in a progressive decrease in the duration of the well phase leading to vomiting episodes that are nearly continuous [1••]. This is referred to as coalescent CVS and can cause delays in diagnosis as the typical periodicity is lost. The key to establishing a diagnosis is to obtain a thorough history to elicit the earlier episodic pattern of symptoms.

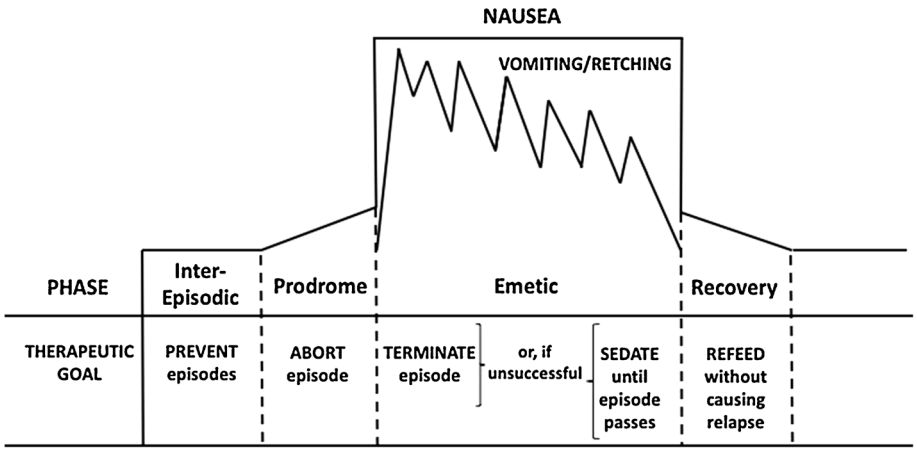

Fig. 1. Phases of cyclic vomiting syndrome. Referenced from Fleisher et al. [1••]

Episodes of CVS are triggered by both psychological and physiological stress in many patients. Both positive (happy and exciting events) and negative (unpleasant and sad events) emotional stress can trigger symptoms [1••]. Acute upper respiratory infection, lack of sleep, and physical exhaustion can also be triggers. Catamenial CVS is a subset of CVS that occurs in relation to the menstrual period [14]. Though less common, dietary triggers—chocolate, cheese, and monosodium glutamate—have also been correlated with episodes. Likewise, migraines can also be triggered by stress, fatigue, physical exhaustion, menses, sleep disturbances, various odors, hunger, and weather changes [15]. Lifestyle modifications such as sleep hygiene, avoiding fasting, and addressing stress through cognitive behavioral therapy/psychological consultation is recommended in both disorders.

Diagnosis

Diagnosing CVS is fraught with difficulties due to the absence of biomarkers and lack of awareness about CVS. Specific diagnostic criteria for CVS were first established in 2006 by the Rome foundation and revised in 2016 [16••]. They consist of:

- Stereotypical episodes of vomiting regarding onset (*acute*) and duration (*less than 1 week*)
  - Abrupt in onset
  - Lasting less than 1 week
  - occurring at least 1 week apart
- Three or more discrete episodes in the prior year
  - Two episodes in the past 6 months
- Absence of nausea and vomiting between episodes
  - But other milder symptoms can be present between episodes

There should not be any metabolic, gastrointestinal, central nervous system structural or biochemical disorders that explain these symptoms.

The differential diagnosis of CVS is extensive, and workup is indicated based on the clinical scenario. GI disorders such as intermittent small bowel obstruction can be excluded with appropriate imaging. Neurological signs or symptoms should be considered red flags and prompt evaluation with neurological referral and brain imaging. Other extra-gastrointestinal considerations such as nephrolithiasis or adrenal insufficiency can mimic CVS and relevant testing should clarify the diagnosis.

Migraines both with and without aura have been defined by the International Classification of Headaches (ICHD) society. Migraines without aura are classified as at least five recurrent headaches with attacks lasting between 4 and 72 h. The character of this pain is usually unilateral with pulsing intensity and is associated with photophobia, phonophobia, nausea, and vomiting. Migraines with aura are diagnosed when at least two recurrent headaches that have preceding auras involving visual, sensory, speech, motor, brainstem, and retinal

evocations. The auras themselves must have defining characteristics of unilaterality. Aphasia, visual scintillations, and paresthesia are some symptoms of an aura. Nausea and vomiting are frequently reported by patients with migraine and there should be a high degree of clinical suspicion to consider the possibility of CVS [17].

Comorbidities

Both CVS and migraine headaches are associated with several comorbidities (Table 2). Among hospitalized patients with CVS, the most common comorbidities were migraine, IBS, gastroparesis, and dysautonomia, with dysautonomia having the highest odds of being associated with CVS [18•]. The prevalence of dysautonomia in other studies has varied from 43 to 90% [19, 20]. Notable manifestations of dysautonomia in CVS are significant sudomotor dysfunction and postural orthostatic tachycardia in adult CVS [19]. Adults with migraine had similar findings of low postural adjustment ratio suggesting a relationship between these two entities [21]. During an acute attack, patients with migraine and CVS have a multitude of autonomic symptoms such as nausea, vomiting, hyperhidrosis, flushing, pallor, palpitations, diaphoresis, lightheadedness, constipation, and diarrhea [22].

Other comorbidities such as fibromyalgia, IBS, complex regional pain syndrome, and fibromyalgia are seen in both CVS and migraineurs. Psychiatric disorders such as anxiety (8–84%) and depression (6%–78%) are also common in CVS and can affect outcomes [9, 23]. Similarly, there is a higher likelihood of major depressive disorder and generalized anxiety disorder in the migraine population [24]. The impact of CVS, both directly as well as due to underlying comorbidities, is significant with a third being disabled and many suffering job loss, delays in higher education, and even divorce [1••, 18•].

Migraineurs often report fatigue, lack of sleep, and difficulties in social functioning [25]. Studies have found that patients with migraine were more likely to be of lower socioeconomic status, had increased anxiety and suicidality along with higher utilization of mental health resources [26, 27•]. Comorbidities in both CVS and migraine warrant concurrent treatment.

Pathophysiology

Similarities in clinical presentation, comorbid conditions, and response to treatment in CVS and migraine suggest a common pathophysiology. Mitochondrial dysfunction, dysautonomia, and involvement of neuroendocrine signaling are areas first explored in migraine that have enhanced our understanding of CVS as a brain-gut disorder.

CVS and migraine as brain disorders

CVS is considered a brain-gut disorder with alterations in central neural circuits that regulate autonomic function, emesis, and cognitive function. Functional neuroimaging studies have been performed in both CVS and migraine evaluating the salience (SLN) and sensorimotor (SMN) intrinsic connectivity networks in the insula cortex. The SMN processing network is responsible for

Table 2. Comparison of characteristics of adult CVS and episodic migraine

	Adult cyclic vomiting syndrome [18•, 19, 104]	Episodic migraine [27•, 105]
Symptoms	Nausea, vomiting, retching, abdominal pain (epigastric focus with diffuse radiation), inter-episodic well phase	Pulsating headache pain, usually unilateral, associated with nausea, vomiting, photophobia, and phonophobia
Prodrome	Pallor, diaphoresis, malaise, nausea, and autonomic responses of intense sweating and salivation	Tiredness, difficulty concentrating, neck stiffness, photophobia, phonophobia, and irritability
Number	20,952	11,249
Age	36.6 yrs. (18–55) SE = 0.24	46 ± 13.8 yrs.
Gender	Female 13,252 (63%) Male 7700 (37%)	Female 8469 (75.3%) Male 2780 (24.7%)
Race	Caucasian 13,167 (63%) African-American 3857 (18%) Hispanic 1341 (6%) Asian/Pacific Islander 223 (1%) Native Americans 99 (1%) Other 2265 (11%)	Caucasian 9263 (87.3%) African-American 759 (7.2%) Other 587 (5.5%)
Common comorbidities	• Migraine • Anxiety • Complex regional pain syndrome (CPRS) • Depression • Dysautonomia • Fibromyalgia • Gastroparesis • Irritable bowel syndrome • Cannabis use	• Nausea/vomiting • Anxiety • Complex regional pain syndrome (CPRS) • Depression • Dysautonomia • Fibromyalgia • Irritable bowel syndrome
Prophylaxis	• Tricyclic antidepressants • Antiepileptics • Co-enzyme Q-10 • NK-1 antagonists	• Tricyclic antidepressants • Antiepileptics • Co-enzyme Q-10 • CGRP inhibitors
Abortive therapies	• Triptans • Ondansetron • Promethazine • Chlorpromazine • Benzodiazepines • Diphenhydramine	• NSAIDs • Triptans • Ergot alkaloids • Ondansetron • Chlorpromazine • Benzodiazepines • Diphenhydramine

delivering the "bottom-up" conscious perception of touch, pressure pain, temperature, position, movement, and vibration stimuli to the CNS while the SLN pathway has been hypothesized as responsible for triaging the importance of these internal and sensory stimuli [28]. Whole brain analysis revealed a decrease in SMN connectivity in both CVS and migraine groups compared to the controls. In addition, a significant increase of SLN connectivity in CVS patients was found in comparison to both control and migraine groups. This SLN increase was not evident in the migraine subjects in comparison to the controls [29]. These findings highlight similarities and differences in neuronal connectivity in CVS and migraine and need to be explored further.

Two predominant theories have been proposed to explain the genesis of migraine: the vascular and neuronal theory [30]. The vascular theory proposed that cerebral and meningeal vasoconstriction followed by vasodilation, induces release of proinflammatory neuropeptides such as substance P, neurokinin A, and CGRP inciting pain and discomfort. The neuronal theory is now favored and involves activation of the trigeminal nerve system and pain from diffuse cortical spreading depression. The resulting depolarization of neuronal and glial cells is followed by sustained suppression of neuronal activity. The rate of neuronal inhibition was found to correlate with localized changes in blood flow at similar rates [31]. These changes have been observed through neuroimaging and linked to causing the visual scintillations presenting during migraine auras [32]. On the other hand, CVS is thought to result from abnormalities in the neural circuitry that is responsible for allostatic regulation of the sympathetic nervous system. Thus, an episode of CVS may be triggered when a certain threshold is exceeded by an allostatic load.

Mitochondrial dysfunction

A strong maternal inheritance has been observed in the pediatric CVS population [33]. Further, two single nucleotide polymorphisms (SNPs) in mtDNA, namely, 16519T and 3010A, were associated with pediatric CVS. However, these polymorphisms were not associated with adult-onset CVS and may reflect a selection bias in the pediatric cohort [34–36].

Mitochondrial dysfunction has also been implicated in the pathogenesis of migraine. This is supported by the effectiveness of supplements such as coenzyme Q-10 and riboflavin, known to be involved in energy metabolism. A lack of ATP production resulting from mitochondrial dysfunction can increase the likelihood of cortical spreading depression and induce migraines. However, recent analysis of mtDNA mutations with known mitochondrial disorders such as MELAS and MERRF has found no significant association with the migraine population [37]. Advancements in genome-wide analysis have identified 44 independent SNPs that were significantly associated with migraine risk. It was found that several of these genes are involved with known ion-channel regulation, ion homeostasis, oxidative stress, and nitric oxide signaling [38].

Neuroendocrine factors

The endocannabinoid system (ECS) has been investigated in both CVS and migraines. The endocannabinoids, N-arachidonylethanolamine (AEA) and 2-arachidonoylglycerol (2-AG), act on cannabinoid receptors type 1 and 2 (CB1R and CB2R) and are important regulators of nausea, vomiting, and GI motility.

Endocannabinoid-related lipids, N-oleoylethanolamine (OEA) and palmitoylethanolamide (PEA), were increased during an episode of CVS in comparison to controls [39]. Examination of the endocannabinoid receptor genes showed that the G allele of CB1R rs806380 was associated with an increased risk of CVS whereas the CC genotype of CB1R rs806368 was associated with a decreased risk of CVS. Further, AG and GG genotypes of OPRM1 r1799971 were linked to an increased propensity for migraine headaches and the CT and CC genotype of CB1R rs806368 with a family history of migraines [40].

Cannabis acts on CB1R though its major psychoactive ingredient, tetrahydrocannabinol (THC), has been used to treat migraine historically [41]. In addition to their analgesic properties, endocannabinoids interact with serotonin transmission, CGRP release, and nitric oxide production leading to modulation of cerebrovascular tone. CB1Rs have been localized in the periaqueductal gray, rostral ventromedial medulla, and nucleus trigeminalis caudis, which are areas associated with migraine propagation [42]. From these findings it has been speculated that a chronic endocannabinoid deficiency may contribute to migraine [43]. Small studies have shown significantly lower levels of PEA in the cerebrospinal fluid of patients with chronic migraines [44].

CGRP in migraine

CGRP is a 37-amino acid neuropeptide, produced by alternative RNA splicing of the calcitonin gene. CGRP is located in both neuronal and non-neuronal tissue and is one of the many proinflammatory signals that are released from trigeminal ganglion neurons during an active migraine attack [30, 45]. The trigeminal nerve fibers innervate meningeal blood vessels and the release of CGRP and other neuropeptides is thought to play a role in the genesis of migraine. Other studies demonstrate a significant increase in CGRP with an inverse relation to serotonin concentration in migraineurs with nitric oxide-mediated headache with nitroglycerin [46, 47]. A study of 15 patients demonstrated that injections of human α CGRP induced migraine without aura in all of their migraine cohort within 11 h [47]. Furthermore, inhibitors of CGRP reduce migraine headache in various studies [48•]. This has led to multiple trials of CGRP inhibitors in the treatment of migraine headache. There are no studies in the role of CGRP in CVS to date and warrants further investigation.

Current therapies

Both migraine and CVS are treated with similar medications. Prophylactic medications such as tricyclic antidepressants (TCAs) and antiepileptic drugs (AEDs) are used to prevent episodes when symptoms are severe. Abortive therapies such as triptans and antiemetics are administered during the prodromal phase to mitigate and avoid progression of an attack of both CVS and migraine.

Tricyclic antidepressants

Amitriptyline is considered first-line therapy for CVS, although lacking randomized controlled trials. Adults with CVS showed a reduction in the frequency of emergency department visits and hospitalizations with amitriptyline [49••].

On the contrary, the efficacy of TCAs in migraine headache is well documented: a meta-analysis of randomized clinical trials showed that TCAs as monotherapy were effective in reducing overall symptoms by at least 50%. TCAs also reduced analgesics taken for both tension and migraine headaches [50]. Reported side effects of TCAs included dry mouth, somnolence, chronic fatigue, constipation, and blurred vision; these can be barriers to use in both migraine and CVS populations [49••].

Coenzyme Q-10

Co-Q10 is an electron shuttle between complexes 1 or 2 and complex 3 of the mitochondrial respiration chains. In CVS, coenzyme Q-10 was as effective as amitriptyline in prophylaxis of CVS with similar improvement in episode frequency, duration, numbers of emesis, and severity of nausea [51].

In the migraine population, Co-Q10 supplementation was more effective than placebo in randomized controlled trials [52, 53].

Antiepileptics

Zonisamide and levetiracetam have been shown to be effective in the treatment of CVS. Studies using topiramate as a prophylactic agent are restricted to the pediatric population [54, 55]. However, in a comparison between pediatric- and adult-onset CVS cohorts, topiramate as a prophylaxis agent was equally effective in both groups [56]. Antiepileptics (AEDs) are also effective in migraine prophylaxis [57]. The newer generation of AEDs has a more tolerable side-effect profile expanding the treatment repertoire for migraine.

NK-1 inhibitors

NK-1 inhibitors such as aprepitant and lanepitant inhibit the substance P ligand and were effective in 81% of children with refractory CVS [58, 59]. Similar studies have not been done in adults with CVS [58, 59]. However, NK-1 inhibitors are not effective in the treatment of acute migraine and this serves as a distinction from CVS [60].

CGRP inhibitors

The first direct inhibitor olcegepant, a non-peptide CGRP receptor antagonist, marked the development of a new class of drugs called gepants. Olcegepant was the first gepant that was studied in migraine with a response rate of 66% compared to placebo [61]. The most significant adverse effect was paresthesia in this study. Unfortunately, one of the limitations of this drug was the need for an intravenous injection. Following this, oral medications such as telcagepant were studied and were superior to placebo in multiple trials [62]. However, these trials were terminated due to concerns with hepatoxicity [63]. Newer generation gepants without hepatic toxicity such as ubrogepant are underway that show potential with phase III trials in treating migraine attacks [64, 65].

Pharmacological research has also developed monoclonal antibodies that achieve CGRP blockade. Monoclonal antibodies have longer half lives up to 1 month and show promise for effective, longer-lasting preventive options [63]. Four anti-CGRP antibodies (eptinezumab, galcanezumab, fremanezumab, and

erenumab) have all been shown to significantly reduce the duration of migraine compared to placebo in phase II trials [48•]. Of these, erenumab, an antagonist of the CGRP receptor, was approved by the FDA for use in migraine and demonstrated ≥ 50% reduction in monthly migraine days than placebo [66•]. This was followed by approval of fremanezumab that demonstrated 3.6 fewer headaches per month versus 2.5 days with placebo [67•]. Currently, CGRP inhibitors have been proposed to serve as a secondary therapy for patients intolerant to triptans [68]. One of the main advantages of CGRP inhibitors is the lack of cardiovascular side effects that is seen with triptans due to the vasoconstriction that they can cause.

No large-scale studies have been conducted in the CVS population yet, though considering the long-shared history of migraine therapy effectiveness in the CVS population, investigation of CGRP inhibition is a promising new direction in CVS.

Abortive therapies

Use of abortive medications such as triptans and antiemetics can prevent progression of an episode of both migraine and CVS [69]. Case reports have documented the effectiveness of sumatriptan in adults with CVS [70, 71]. General clinical consensus has supported the role of triptans to abort the emetic phase [72, 73]. Patients with migraine were more likely to achieve successful pain-free relief from migraine episodes if triptan therapy was administered before the onset of allodynia [74]. Similar studies are yet to be performed in CVS.

Abdominal pain is a significant component of the symptomatology in CVS and remains a challenge. Chronic opiate therapy is a risk factor for non-response in CVS and experts discourage the use of narcotics in CVS. The use of opiates in migraine can contribute to overuse headache and transformative migraine and has not demonstrated superiority to NSAIDs or triptans [75]. These along with the risks of opiates such as dependence, addiction, and even suicide make it imperative to test other treatment modalities for pain in both conditions. In summary, there is significant overlap in the management of CVS and migraine and a biopsychosocial model of care that incorporates lifestyle management, prophylactic treatment when episodes are severe or frequent along with abortive therapy is recommended [73].

Migraine and other GI disorders

Many other GI disorders are also linked to migraine though this association is less robust in comparison to CVS. A meta-analysis showed a significantly higher *H. pylori* infection rate in migraineurs vs controls [76]. Migraine and *H. pylori* infections demonstrate a chronic inflammatory response due to vasoactive and inflammatory mediators in the circulation [77]. Some studies suggest an improvement in migraine headaches with *H. pylori* eradication [78], though this remains to be confirmed.

The pathogenic mechanisms in migraine and IBS include neuroendocrine and immunological factors, the brain–gut axis, and the intestinal microbiota [79]. Certain studies show migraine-like headaches in 6–32% of IBS patients compared to only 2.2–18% in controls [80–82]. An IgG-

based food elimination diet symptomatically improved both conditions [83]. Delayed gastric emptying and increased pyloric tone in both the ictal and interictal periods have been linked to migraine [84, 85]. These are thought to be due to the increased sympathetic response during migraine attacks [86, 87]. Also, delayed emptying affects the absorption and therapeutic efficacy of medications, emphasizing the need for using non-oral migraine medications during an episode [87, 88]. Contrary to this, other studies did not find a delay in gastric emptying in the interictal period [89]. Gastric emptying patterns are variable in the inter-episodic phase of CVS and usually tend to be rapid [90]. Migraine headaches are frequently encountered in celiac disease (21%) though screening for celiac disease in migraine patients is not standard practice. Studies have shown both complete and partial relief of migraine headache in patients with celiac disease treated with gluten-free diet [91].

There is an association between migraine and hepatobiliary disorders, which is stronger in monozygotic twins suggesting a genetic influence [92, 93]. Other findings including the efficacy of a low-lipid diet in migraine treatment [94] and the considerable coexistence of right upper quadrant pain in migraine have been cited in support of the association between migraine and hepatobiliary disorders. Obesity and insulin resistance, determinants of NAFLD, are also associated with migraine [95, 96]. Regulation of these metabolic parameters and weight loss may improve migraine headaches [96].

Other FGIDs like constipation and diarrhea show a higher prevalence in people with primary headaches though the specific link to migraine is unclear [97]. Reflux symptoms are common in migraine patients but the concurrent use of NSAIDS in this population may explain this phenomenon [98]. Finally, gut microbiota influence brain function and pain behavior through modulation of the brain–gut axis [99]. The serotoninergic and CGRP mechanisms of migraine pathophysiology are differentially affected by the gut microbiota in multiple pathways [100•]. The therapeutic efficacy of probiotic supplements in patients with migraine reveals the role of dysbiosis in the migraine pathophysiology [101•]. There are no data on dysbiosis in CVS and it remains to be determined if a diet used to treat IBS that is low in FODMAPs (Fermentable Oligosaccharides, Disaccharides, Monosaccharides, And Polyols) or fecal transplantation improves symptoms of CVS.

Conclusions

CVS and migraine are distinct diagnostic entities but have significant overlap. Both conditions predominantly affect young adults, are episodic in nature, and are triggered by psychological or physiological stress. They also share comorbidities and response to therapies. These similarities in epidemiology, clinical presentation, comorbidities, and response to therapies suggest a common pathophysiology. This can help direct future research and advance our understanding of CVS. Additionally, the use of novel therapies in migraine such as CGRP inhibitors can be also effective in CVS and warrant further investigation. Using migraine as a template may serve to elucidate the pathophysiology of CVS and advance novel therapies.

Compliance with ethical standards

Conflict of interest
Elliot S. Yu, Yasodara Priyadharsini S.S., and Thangam Venkatesan declare no conflict of interest.

Human and animal rights and informed consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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