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Expert Opinions

Cyclic Vomiting Syndrome and Abdominal Migraine in Adults and Children

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The first pediatric descriptions of cyclic vomiting syndrome were provided in the French literature by Heberden in 1806 and in the English literature by Gee in 1882.[1,2] An association of cyclic vomiting with migraine headaches was reported by Whitney in 1898.[3] Described by Liveing in 1873 and Buchanan in 1921, Brams introduced the term "abdominal migraine" in 1922.[4-6] We present 2 cases of cyclic vomiting syndrome and 3 cases of abdominal migraine in adults and provide a review.

CLINICAL HISTORIES

Case 1.—This is a 50-year-old male who presented with a 10-year history of episodes occurring about once every 6 months. The episodes typically awakened him about 5 am. He would first belch and then had recurring nausea and vomiting associated with diarrhea without abdominal pain for about 1.5-2 days almost always followed by a generalized aching headache with an intensity of 6/10 with light and noise sensitivity but no visual symptoms lasting about 12 hours. Acetaminophen did not help.

He had a history of headaches since the age of 6 that occurred anywhere from twice a week to once every 3 months. He described an aching pain behind the eyes and bifrontal with an intensity of 7-8/10 associated with light and noise sensitivity and occasional nausea but no vomiting or aura. He took oral sumatriptan with relief in 30 minutes. Changes in weather were a trigger.

He had been evaluated by 4 gastroenterologists. Extensive testing including upper and lower endoscopy, motility studies, and capsule endoscopy was negative. He was tried on trimethoprim/sulfamethoxazole and fluconazole without benefit.

He had 2 episodes in the prior week but no other episodes since his internist started him on amitriptyline 25 mg at bedtime 2 months previously. He was tried on sumatriptan nasal spray and oral ondansetron that helped once to greatly shorten an episode of nausea and vomiting but then the symptoms recurred the next day. He tried the combination again and the symptoms were relieved but recurred. On a third occasion, the combination relieved the nausea and vomiting when taken earlier without other symptoms and without recurrence. There was no headache associated with this briefer attack.

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Past medical history was negative. Family history was positive for his mother with a history of bad headaches. Neurological examination was normal.

Case 2.—A 36-year-old male was seen for spells. At the age of 14, he had 5-6 episodes over 2 weeks of intense, dull epigastric pain associated with nausea but no vomiting lasting several hours each.

Since the age of 19, he had about 1-2 episodes per year of nausea, vomiting, and diarrhea lasting up to 12 hours without abdominal pain or headache. With one episode, he saw zigzags with patterns in both eyes for about 20 minutes.

For the prior 7 years, he had a history of migraine with visual aura occurring about twice a month relieved by over-the-counter medication. Triggers included too much sleep, stress, chocolate, and red wine. He also reported a few-year history of a persistent migraine visual aura where he reported that it seemed that he was always looking through water with a visual distortion on each side.

Evaluation by a gastroenterologist was negative including upper and lower endoscopy, abdominal ultrasound, and testing for celiac disease.

There was a past medical history of anxiety and depression improved on venlafaxine 150 mg extended release daily started about 5 years previously but without a change in frequency of the headaches or spells. Neurological and neuro-ophthalmological examinations were normal. A magnetic resonance imaging (MRI) of the brain was normal.

Case 3.—This is a 52-year-old male who presented with an almost 3-year history of "spells." He had right shoulder blade pain with an intensity of 10/10 almost immediately followed by an "empty hunger" epigastric pain with an intensity of 6-8/10 associated with clear drainage from both nares, tearing from both eyes, and nausea and vomiting but no headache or diarrhea lasting 12-13 hours. The episodes were initially once a day.

He saw his primary care physician and then a gastroenterologist. He had an upper and lower endoscopy showing gastritis and a benign colon polyp. A computed tomography (CT) scan of the abdomen and pelvis, gallbladder ultrasound, and a gastric emptying study were normal. An MRI scan of the brain was normal. He saw a second gastroenterologist who diagnosed abdominal migraine (AM) and placed him on topiramate 50 mg daily without side effects and nortriptyline titrated up to 100 mg at bedtime. The spells decreased to about once a month. Oral promethazine, ondansetron, and metoclopramide did not help the symptoms.

He had a history of headaches since the age of 16 occurring about 3-4 times per year for many years. He described throbbing and pressure above the right eye with an intensity of 5-6/10 with light and noise sensitivity but no nausea or aura. The headaches lasted 3-4 hours with ibuprofen or aspirin. He had no triggers.

There was a history of a second type of headache that last occurred a few years ago described as a bifrontal throbbing with a maximum intensity of 10/10 associated with nausea and vomiting lasting 8-10 hours without triggers. Oral sumatriptan helped. He has had 1-2 typical visual auras perhaps 10 years ago.

There is a past medical history of hypertension and diabetes mellitus type 2. A recent cardiac stress test was negative. Other medications include simvastatin, omeprazole, benazepril, and insulin.

General physical and neurological examination was normal. He was placed on prochlorperazine 25 mg suppository and eletriptan 40 mg to be taken at the onset of the spells. On follow-up 8 months later, he had 3 further episodes of abdominal spells. He took eletriptan and the symptoms resolved within one hour.

Case 4.—A 56-year-old man was evaluated for a 16-month history of paroxysmal abdominal pain and headaches. He reported episodes of left lower quadrant, occasional right lower quadrant, and occasional diffuse lower abdominal pain described as a stabbing feeling with an intensity of 7-10/10 with nausea but no vomiting, anorexia, constipation, or diarrhea lasting 5 minutes to 4 hours, with an average duration of 30 minutes occurring 5-6 times per day. About 50% of the time, he had an accompanying headache described as a left- or right-sided aching or bifrontal throbbing with light and noise sensitivity but no nausea or aura lasting 10-30 minutes. Attacks could be triggered by driving or being a passenger in a car for more than 5-6 miles or eating a Hershey's chocolate bar.

He had a history of headaches since childhood occurring about once every 2 months described as a

bifrontal aching with an intensity of 5-6/10 associated with light and noise sensitivities but no nausea or aura relieved by aspirin or acetaminophen in about 30 minutes. He had occasional generalized throbbing headaches with an intensity of 10/10 with nausea, light and noise sensitivity but no vomiting or aura relieved in 1 hour with a hydrocodone-acetaminophen combination.

He was initially treated for possible diverticulitis with antibiotics and subsequent surgery without improvement. Three CT scans of the abdomen, 2 colonoscopies, an abdominal arteriogram, testing for acute intermittent porphyria, and an erythrocyte sedimentation rate were negative. He was seen by 2 gastroenterologists, 2 colon and rectal surgeons, and a urologist, and the cause of the chronic pain was not determined. He was referred to a chronic pain specialist who started daily oral hydromorphone, hydrocodone bitartrate, and acetaminophen prn. He declined an MRI scan of the brain.

There was a past medical history of hypertension, hyperlipidemia, and kidney stones twice. Neurological examination was normal.

We discussed the risk of medication rebound and habituation with use of opiates more than twice a week, but he declined to taper off the opiates. He was placed on propranolol 40 mg twice a day that could not be increased due to dizziness and fatigue. Venlafaxine titrated to 150 mg daily was added without improvement. His medications were then changed to nebivolol 5 mg daily and amitriptyline 25 mg at bedtime that were titrated up to nebivolol 20 mg daily and amitriptyline 75 mg at bedtime without side effects over 3 months. He then reported daily episodes of right or left lower quadrant pain lasting 15-30 seconds about 20 times a day. He was not given triptans because of the frequency of the episodes.

Case 5.—This is a 27-year-old female with a 3-year history of bimonthly episodes that increased to once every week for the prior 2 months. She reported a "cold burn" in her chest, then an epigastric sharp throbbing pain with an intensity of 8-10/10 associated with nausea and retching lasting 1-5 days with an average of 2-3 days. Hydrocodone-acetaminophen combination (about 12 per month) and lorazepam may have helped.

She had seen 3 gastroenterologists and had 4 upper endoscopies, 2 computed axial tomograms, and a computed tomographic angiogram with negative findings. She had numerous emergency department visits and hospital admissions. She was placed on cyproheptadine and coenzyme Q10 without benefit.

She had a 3-year history of headaches occurring about twice a week described as an aching pain in the bitemporal and mandibular regions with an intensity of 4/10 associated with light and noise sensitivity but no nausea or aura. She took no medication, and the headaches lasted from 3 to 12 hours. She had no triggers. Past medical history was otherwise negative. Her father had migraines. Neurological examination was normal.

She was advised to taper off the opiates and started on topiramate titrated up to 100 mg per day for prevention and eletriptan 40 mg to be taken at the onset of episodes of abdominal pain or headaches (she declined sumatriptan subcutaneous or nasal spray). When seen 2 months later, she reporting having one episode a week but none in the prior 3 weeks. Eletriptan relieved the symptoms in about 15 minutes.

Questions.—What are the diagnosis, pathophysiology, and treatment for these cases? Are they related to migraine? Are adult cases similar to pediatric cases?

EXPERT OPINION

Cyclic Vomiting Syndrome.—*Epidemiology and Clinical Features.*—Cyclic vomiting syndrome (CVS) has been classified as a childhood periodic syndrome (CPS) or "migraine equivalent" that are commonly precursors of migraine in the International Classification of Headache Disorders-II (ICHD-II).[1,7] Even though cases have been reported in adults early in the 20th century, CVS still is described as a CPS.[8] CVS affects about 2% of children (a slight predominance of girls over boys), with a mean age of onset of 5.2 years and a mean age of 8.3 years.[8] Up to 87% of patients will go on to develop migraine, hence its inclusion in ICHD-II.[9] In a meta-analysis, the prevalence of headache/migraine was 40.5%, a family history of migraines of 27.8%, a history of anxiety or depression in 26.7%, and travel sickness in 28.3%.[8] The delay in diagnosis is 2.6-3.1 years.

The key feature of CVS in children is recurrent episodes of severe vomiting with interval wellness (Table 1).[9]

Table 1.—International Classification of Headache Disorders-II Criteria for Cyclic Vomiting Syndrome

A.	At least 5 attacks fulfilling criteria Band C
B.	Episodic attacks, stereotypical in the individual patient, of intense nausea, and vomiting lasting from 1 hour to 5 days
C.	Vomiting during attacks occurs at least 4 times/hour for at least 1 hour
D.	Symptom-free between attacks
E.	Not attributed to another disorder

Up to 80% may have triggers most commonly psychological stress (44%) and excitement and infections (31%; most commonly upper respiratory) but also motion sickness, physical exhaustion, excessive exercise, overeating, foods such as chocolate or cheese, menses, hot weather, and asthma.[10] There are 4 phases to episodes: a "well phase" without symptoms; a prodrome with pallor, intense sweating, and nausea; intense vomiting with up to 20-30 vomiting episodes of retching and dry heaving per day; and the recovery phase. Up to 80% may have associated abdominal pain.[11] The vomiting typically occurs in early morning or soon after awakening. There is a cyclical pattern of attacks with 0.8 mean episodes per month, with a mean duration of 3.4 days in a meta-analysis although most attacks last 24-48 hours.[8]

The prevalence of CVS among adults is not known, although the disorder is seen in up to 14% of patients in gastrointestinal motility clinics. In a meta-analysis, the mean age of onset was 25.4 years with a mean age of 34 years. The prevalence of headaches/migraines was 56%, a family history of headache/migraine in 56%, and coexistent anxiety/depression in 39.7%.[8] There is a slight male predominance.[12] The average delay in diagnosis is 7.9 years.[13]

The phases of the episodes may be similar to those in children. Up to 70% of episodes are associated with severe abdominal pain. Adults more than children may progress to "coalescent CVS," a pattern of subacute symptoms of nearly continuous nausea and frequent vomiting lasting weeks to months present in 39% of a cohort of 101 adults seen at a tertiary care clinic.[14] Adults may have similar triggers to children including menstruation, deeming this catamennial CVS.[15-17]

In a case series of 31 patients, 84% reported an anxiety disorder.[18] Panic attacks have been reported not only as a trigger of episodes, but they can occur interictally in adults, which is typically contrary with what children experience.[16,19] Depression may be present in the majority of adults with CVS.[18]

Pathophysiology.—CVS may have the same physiological mechanisms as migraine. Nausea, lethargy, and anorexia are shared between the 2 disorders as well as favorable responses to migraine medication in CVS (discussed later).[16] Approximately 39-87% of children go on to develop migraine, and 24-70% of adults with CVS have migraine as a comorbid disorder.[20]

Migraine is associated with dysfunction in the periaqueductal gray region that is also a site of vomiting attenuation and could be involved in the genesis of CVS.[21] Further functional neuroimaging studies on CVS would be needed for determination. Furthermore, there is strong evidence that autonomic dysfunction plays a role in many of the symptoms in CVS, as in migraine.

Zaki and colleagues have reported that 2 common mitochondrial DNA polymorphisms, 16519C→T and 3010G→A, are highly associated with migraine and CVS in children and haplogroup H.[22] However, these polymorphisms are not associated with adult onset CVS suggesting that childhood and adult onset CVS are genetically distinct.[23]

A popular theory is that CVS is a "brain-gut disorder" mediated by the neuroendocrine system.[24] During acute episodes, elevated levels of ACTH, antidiuretic hormone, cortisol, and other endocrine substances have been found in the serum, as well as increased serum and urinary catecholamines.[25] These are released after stimulation from corticotropin-releasing factor (CRF) upon the endocrine system.

CRF is probably released from the hypothalamus as a reaction to stress that can cause nausea and delayed gastric emptying because of its inhibitory effects on the dorsal motor nucleus of the vagus nerve.[16,26-28] Tricyclic antidepressants, which inhibit the promoter activity of the CRF gene, are highly efficacious in treating CVS.[16,29]

Differential Diagnosis.—In adults, a single episode of vomiting from CVS needs to be distin-

guished from other acute illnesses, such as acute appendicitis, because a pattern of multiple episodes of vomiting must be seen before diagnosing CVS. In many clinical respects to migraine, CVS is essentially a diagnosis of exclusion because there are no reliable tests of confirmation.[30]

Treatment.—During episodes, supportive measures may be indicated especially intravenous hydration and management of electrolyte derangement.[31] Because stress is a trigger in acute episodes, a quiet, dark, and nonstimulating environment may be helpful. Supportive medicines include treatment of the nausea with 5-HT_3 antagonists, such as ondansetron (which has a 62% efficacy), attenuation of the anxiety in adults with the use of benzodiazepines, and induction of sleep with diphenhydramine.[31,32] Neuroleptics tend to have a poor response in CVS, suggesting that the dopamine axis does not play a role in the pathophysiology.[17]

Sumatriptan subcutaneous or nasal spray can be an effective treatment for children and adults taken at the onset of the episode.[33,34] There have been anecdotal reports of zolmitriptan and frovatriptan being effective as well.[16] Secondary abortive agents include non-steroidal anti-inflammatory drugs such as intravenous ketorolac and opioids.

As in migraine therapy, there has not been any molecule designed to prevent CVS, so prophylactic medicines have been utilized successfully from many classes of drugs typically used in other disorders. 79% of patients who respond to traditional antimigraine prophylactic agents used in CVS (as well as sumatriptan) have a family history of migraine.[35] The 3 primary medicines used in children with excellent success are cyproheptadine, propranolol, and amitriptyline. Amitriptyline results in improvement in more than 80% with continued efficacy on 2-year follow up.[12,36] Carbamazepine, phenobarbital, valproic acid, gabapentin, zonisamide, and levetiracetam have been used particularly for those patients with CVS and abnormal electroencephalograms (EEGs), the latter 2 drugs being tested in CVS without EEG testing.[37-40] Other preventatives include erythromycin, L-carnitine, and coenzyme Q10.[16,41,42]

In a retrospective review of 101 adults with CVS, 86% had either a complete or partial response to preventive treatment with tricyclic antidepressants (amitriptyline or notriptyline with a mean dose of 83.3 mg), topiramate, carnitine 1 g twice daily, coenzyme Q-10 200 mg twice daily, or riboflavin 100 mg once daily, which were given depending upon efficacy and tolerability.[14] Oral contraceptives might be beneficial for those with menstrual CVS.[16]

Interestingly, there is a high placebo rate in patients from just visiting with a physician and ruling out other pathology. As in migraine, many times just decreasing stress and reducing anxiety will decrease attacks.

Prognosis.—CVS resolves in many children by their preteen or early teenage years. In a 13-year follow-up study of 41 out of 51 children, vomiting had resolved in 61%, 42% had regular headaches, and 37% had abdominal pain.[43] In an average of 4.1-year follow up of 37 out of 41 adults, 86% indicated that their symptoms were better.[19]

AM.—*Epidemiology and Clinical Features.*—Another CPS or "migraine equivalent," AM, is much less accepted as an adult disorder than CVS.[5] It is characterized by recurrent, episodic attacks of abdominal pain of at least moderate intensity with associated nausea, vomiting, and/or lethargy lasting as long as a typical migrainous attack (see Table 2). AM is regarded as a subtype of chronic recurrent abdominal pain (after other organic causes are excluded) and is recognized as a functional gastrointestinal disorder by the Rome III Child/Adolescent Committee.[44]

The mean age of onset in children is typically 7 years with a significant decrease in attacks as they

Table 2.—International Classification of Headache Disorders-II Criteria for Abdominal Migraine

A. At least 5 attacks fulfilling criteria B-D
B. Attacks of abdominal pain lasting 1-72 hours (untreated or unsuccessfully treated)
C. Abdominal pain has all of the following characteristics:
   1. Midline location, periumbilical or poorly localized
   2. Dull or "just sore" quality
   3. Moderate or severe intensity
D. During abdominal pain at least 2 of the following:
   1. Anorexia
   2. Nausea
   3. Vomiting
   4. Pallor
E. Not attributed to another disorder

get older. A survey of 2165 children ages 5-15 years found a 1-year prevalence of 4.1% for AM with a male : female ratio of 1:1.6.[45] The 1-year prevalence of migraine headache in children with AM (24%) was over 2 times higher compared with the prevalence of migraine headaches in this population (10.6%), and the prevalence rate of AM in children with migraine (9%) is just over twice the prevalence of AM in the general childhood population. The prevalence of migraine in first-degree relatives was twice as common in children with AM as in control healthy children. AM is underdiagnosed in the United States.[46]

The pain is usually periumbilical in location and must be distinguished from organic disorders. Nausea and vomiting occur in most, but it is not as severe as CVS. Even children with a personal or family history of migraine do not typically have a headache during an attack (thought it can be mild). The episodes can be separated by a period of weeks to months.[45] The mean frequency of episodes is 14 times per year, with a mean attack duration of 17 hours.[44] Triggers including stress, tiredness, travel, lack of sleep, certain foods, and missing a meal are similar to migraine triggers.[45]

AM has only rarely been reported in adults. The multiple case reports on adult-onset AM confirm that AM is not strictly a childhood disorder and may be underdiagnosed in adults.[47-50]

Roberts and deShazo analyzed 10 adult patients (9 females) ranging in age from 23 to 57 years, with an average age of 39.4 years with definite or probable AM (2 of their own and 8 from an extensive literature search) who met ICDH-2 criteria.[47] The average age of onset of symptoms was 30.6 ± 17 years, and 7 patients had onset on or after age 18 years. The abdominal pain was located in the epigastrium in 5, in the periumbilical area in one, poorly localized in one, and the location was not specified in 3. In the 5 who characterized their pain, it was either dull, crampy, or both. The average frequency of episodes was 1.97 per month with a range of 0.2-4.5 episodes per month, with an average duration of each episode of 41.63 ± 38 hours (3 had episodes lasting around 7 hours, and 5 had episodes lasting around 50 hours).

One-third had triggers including night-time, stress, food, and alcohol. Half had at least one premonitory symptom before the abdominal pain including dyspepsia in 2, headache in 2, nausea in 2, flushing in one, throat discomfort in one, and light and noise sensitivity in one. During attacks of abdominal pain, common symptoms included nausea (100%), vomiting (90%), vasomotor symptoms (60%), diarrhea (40%), and headache (40%). There is a single case report of a young adult with AM associated with Alice in Wonderland syndrome.[51]

Pathophysiology.—There has been controversy over the years as to whether AM even exists as a separate entity or is just really chronic recurrent abdominal pain.[52,53] This may be because abdominal pain is not a common feature of migraine across all ages and that approximately 10% of children have recurrent abdominal pain, but migraine only occurs in about 3% of children ages 7-9.[44,54,55] AM was not even part of the first edition of the ICHD, but many studies called for its inclusion.[44,56]

As the mechanisms of pathophysiology of AM are unknown, the association with migraine as an etiology is based on clinical and epidemiological characteristics. Besides Dignan et al's prognosis study, patients with AM have similar triggers, relieving factors, and associated symptoms during attacks as those with migraine.[45] Also, many of the treatments effective for AM are also effective for migraine (see later).

Differential Diagnosis.—As in CVS, it is important to differentiate AM from other primary causes of abdominal pain such as bowel obstruction, Crohn's disease, pancreatitis, intracranial hypertension, and acute intermittent porphyria. Twenty percent of patients with chronic recurrent abdominal pain have structural issues.[57]

Treatment.—Russell and colleagues suggest that drug therapy be only one aspect of management of AM, with avoidance of triggers, dietary management, and explanation and reassurance being the primary factors in treatment.[58]

Symptomatic medications have included simple analgesics along with anti-emetics and intravenous fluid replacement. Sumatriptan nasal spray has been reported to be effective in case reports.[58,59] Known to be effective in migraine, intravenous valproic acid aborted an acute attack of AM.[60]

Of the preventative medications that have been tried in children, only pizotifen, a serotonin receptor antagonist not available in the United States, proved effective in a randomized, double-blind, placebo-controlled trial.[61] Another drug not available in the United States, flunarizine, was effective in a small trial to prevent AM and also effective in larger study of children with migraine and functional gastrointestinal disorder.[44,62,63] Propranolol and cyproheptadine show efficacy in retrospective trials.[64] These studies, however, have all been completed in children with AM.

In the analysis of 10 adults with AM, all but one responded to either preventive or abortive migraine medications including the following: calcium-channel blockers ($n = 5$), triptans ($n = 2$), anticonvulsants ($n = 2$), pizotifen ($n = 2$), and a beta-blocker ($n = 1$).[47] All but one treated patient reported no recurrence of symptoms on medication. Roberts and deShazo even suggest that response to triptans can be used as a diagnostic test for AM in adults.[47]

There is a case report of an adult who improved following tapering off overused opioids suggesting that medication overuse might occur in AM.[48] The patient also responded to topiramate daily for prevention and sumatriptan subcutaneous for symptomatic treatment.

Prognosis.—In a 7- to 10-year follow-up study of 54 children with AM, 61% had resolved.[65] Seventy percent with AM were either current (52%) or previous (18%) migraineurs compared with 20% of controls.

Discussion of Cases.—Case 1 is an adult migraineur with a 10-year history of CVS. Case 2 is a man with an unusual combination of a history of migraine with visual aura for 7 years, migraine with persistent visual aura for a few years, and CVS as a teen presenting with a recent history of AM. Case 3 is AM for almost 3 years in a migraineur who had an excellent response for prevention of AM with topiramate and nortriptyline. Case 4 is a case consistent with AM present for 16 months in a migraineur with the unusual feature of progressively briefer multiple attacks of abdominal pain. His triggers are similar to migraine triggers. Medication overuse of opiates (prescribed by his pain specialist that he declined to decrease) is a consideration.[48] Finally, case 5 is another case consistent with AM in a woman with a history of migraine without aura who may also have had medication overuse. She had an excellent response to topiramate for prevention, similar to one prior report,[48] and a triptan for acute treatment similar to 3 prior cases[47,48] and case 3. However, case 4 described his pain as stabbing, and case 5 described her pain as sharp throbbing that do not meet ICHD-II criteria of "dull or 'just sore' quality pain," which have not been applied to adult cases.

CONCLUSION

Even though it took many years for CVS and AM to be included in the migraine section of the ICHD, they are still under the heading of "Childhood Periodic Syndromes." This can be misleading as noted by the increasing evidence that adults can have these disorders not necessarily as a continuation from childhood but also de novo later in life. More cases need to be identified and examined utilizing functional MRI to determine if the mechanisms of migraine are seen in CVS and AM. Between the shared symptoms, comorbidities, triggers, and responses to treatment, it is becoming obvious that CVS and AM are probably not separate entities from adult migraine but a part of the same migraine spectrum. The CPS is currently included in the migraine section of the ICHD-2. The 2 entities should be placed in the same section with the CPS subheading removed in future revisions. The description of the quality of AM pain may need to be broadened as 2 of the cases exemplify to include adult cases.

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