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Cyclic Vomiting Syndrome versus Inborn Errors of Metabolism: A Review With Clinical Recommendations

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Structured Abstract

Background—Inborn errors of metabolism are on the differential for patients presenting with a cyclic vomiting syndrome phenotype. Classes of disorders to consider include: mitochondrial disorders, fatty acid oxidation disorders, urea cycle defects, organic acidurias and acute intermittent porphyria.

Aim—This article reviews the metabolic differential diagnosis and approach to screening for inborn errors in children and adults presenting with a cyclic or recurrent vomiting phenotype.

Conclusion—Cyclic vomiting syndrome is thought to be an episodic syndrome that may be associated with migraine. It is a diagnosis of exclusion. Inborn errors of metabolism should be considered in the patient presenting with a recurrent vomiting phenotype. Mitochondrial dysfunction may play a role in cyclic vomiting syndrome, and true mitochondrial disorders can present with a true cyclic vomiting phenotype.

Keywords

Cyclic vomiting syndrome; inborn error of metabolism; abdominal migraine; mitochondriopathy

Introduction

Pediatric neurologists are often asked to determine whether a child having spells has a “migraine variant” or a “childhood periodic syndrome”. These migrainous disorders include things like benign paroxysmal torticollis, benign paroxysmal vertigo, abdominal migraine, and cyclic vomiting syndrome (CVS) and are now referred to in the International Classification of Headache Disorders III edition (beta version) as “Episodic syndromes that may be associated with migraine”[1]. The clinical phenotypes of these childhood periodic syndromes are reviewed in this issue of *Headache Currents* by Drs. Rothner and Parikh.

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Conflict of Interest Statement:

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Dr. Gallagher: Has been a local site-principal investigator for a clinical trial of a medication for urea cycle disorders, has been a consultant for Horizon Pharma, and formerly for Hyperion Therapeutics, and has received personal compensation for medical-legal consulting.

The purpose of this manuscript is to review the main metabolic disorders, such as inborn errors of metabolism, than can mimic cyclic vomiting syndrome in order to provide the clinician with an overview of the metabolic differential and a practical guide to initial screening tests for these. Cyclic vomiting syndrome is the main migrainous periodic syndrome phenotype that might mimic presentation of a metabolic disorder. Because of some overlap in clinical symptomatology, abdominal migraine might also be thought of similarly. Both of these disorders are now under the same subheading in ICHD-III beta, *1.6.1 Recurrent gastrointestinal disturbance*.

The other periodic syndromes are unlikely to raise significant suspicion for a metabolic disorder. Benign paroxysmal vertigo attacks are most commonly less than five minutes in duration, thus generally too brief to be a manifestation of a metabolic disturbance[1–3]. In infants with benign paroxysmal torticollis, the differential is generally focused on seizure, reflux, structural brain lesion, or dystonia[1]. Glutaric aciduria has reportedly been considered in the differential in infants with benign paroxysmal torticollis, but to our knowledge no case has been reported[4].

Children with cyclic vomiting syndrome manifest with periodic attacks of nausea with frequent vomiting. Attacks can last from hours to days. Typically attacks have a certain periodicity and are stereotyped within an individual[1]. Onset is most commonly around age five years[5, 6]. A personal or family history of migraine is common[7] and this relationship has been recognized since the 1800's[8]. Abdominal migraine typically has its onset in school-aged children around age seven[9]. Attacks are characterized by abdominal pain that is dull or "just sore" in quality and peri-umbilical or poorly localized. Children may have associated nausea, vomiting, pallor and anorexia with attacks[1]. In the child who has prominent abdominal pain and very frequent vomiting during their attacks, the abdominal migraine and cyclic vomiting phenotypes may overlap. From here forward we will just refer to the cyclic vomiting phenotype, but the metabolic evaluation decision-making could be applied in either.

For a patient presenting with a cyclic vomiting phenotype, there is a broad differential to consider beyond migraine associated cyclic vomiting syndrome. In addition to inborn errors of metabolism, other potential causes include gastrointestinal, renal[10] and epileptic disorders (such as Panayiotopoulus syndrome in a young child[11]), and in the adolescent or adult patient cannabinoid hyperemesis syndrome would be a possibility[12]. Another important diagnostic consideration would be migraine itself[1]. In some children, the vomiting component of attacks may be most prominent and therefore the chief complaint, but careful history taking will reveal that they also have headache and sensitivity features during attacks and meet ICHD criteria for migraine, albeit with a notable periodicity to attacks.

It is problematic that the term "cyclic vomiting" may sometimes be used erroneously in the literature to refer to a child or adult whose vomiting pattern is simply recurrent, severe, or frequent. This makes it difficult to determine how often migrainous cyclic vomiting syndrome, in which there is a true periodicity to attacks which are stereotyped in an individual and independent of acute intercurrent illnesses, truly phenotypically overlaps with presentations of recurrent emesis due to inborn errors of metabolism. The concern for

metabolic disorders is really about ensuring we do not miss a disorder that could come to cause serious morbidity or mortality down the line in an adult or child who presents with a cyclic or recurrent vomiting phenotype.

A key feature of migrainous periodic syndromes is that the children are *completely well* between attacks. Children with developmental delay, developmental regression, seizures, poor growth, an abnormal neurologic examination, or a progressive clinical course do not fit this phenotype and presence of these features in a child with a cyclic vomiting phenotype should prompt further evaluation for inborn errors and other etiologies.

Inborn errors of metabolism in childhood that may mimic cyclic vomiting syndrome

The main classes of metabolic disorders to consider in children with recurrent vomiting that may mimic cyclic vomiting are: fatty acid oxidation disorders, urea cycle defects, and organic acidurias [6, 13–15].

Mitochondrial disorders are another diagnostic consideration, and, in contrast to the disorders above, may present with a true cyclic vomiting phenotype. The known pathogenic mitochondrial DNA mutation, 3243 A>G, has been described in a family with cyclic vomiting[16].

Affected family members included a 5-year old boy, his mother, his maternal grandmother, and his maternal aunt. All three adult relatives reportedly experienced Cyclical Vomiting Syndrome (CVS) in childhood followed by migraine in adulthood. The boy's attacks came every 15–20 days and lasted "many hours". The mother had lactic acidemia and an elevated lactate/pyruvate ratio at all times, and the grandmother and aunt had slightly elevated lactate levels. At least during attacks, the boy had an elevated lactate and lactate/pyruvate ratio as well as a metabolic acidosis. The mutation was present in 70% of the boy's blood, and 35%, 25% and 30% of the mother's, maternal grandmother's, and aunt's, respectively. The boy's case was implied to be the most severe of the four, although phenotype of mitochondrial disorders does not always correlate with degree of heteroplasmy.

This mutation is the most commonly found mutation in MELAS (mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes), and is within the gene that encodes the mitochondrial transfer RNA for leucine[17]. The mutation results in impaired synthesis of the electron transport chain subunits encoded by the mitochondrial DNA. There was no mention in this family's report of encephalopathy, muscle pain, weakness, dementia, seizures, or stroke-like episodes which can occur in MELAS [16]. It is possible that they had not yet developed these other clinical features, or that their degree of clinical severity was milder as the spectrum of severity with this mutation reportedly includes asymptomatic carriers, likely due to heteroplasmy[17]. Perhaps a phenotype that clinically manifests only as CVS in childhood followed by migraine headaches in adulthood is possible in some MELAS families. Recurrent or cyclic vomiting has been reported to be the most frequently seen gastrointestinal symptom in MELAS syndrome[17].

Two mitochondrial DNA variants, 16519 C>T and 3010 G>A, have been associated with CVS as well as migraine in children[18], although how or if these affect mitochondrial function is unknown. The 16519 C>T and 3010 G>A mitochondrial DNA variants have not been found to be more common in adults with CVS. Adult CVS patients are reported to be more likely to have a maternal inheritance pattern, and mitochondrial DNA is maternally inherited[19]. However, as migraine is threefold more likely to be expressed in women[20], likely due at least in part to estrogen effects modulating expression of underlying migraine genes, inheritance patterns in migraine related phenomena may appear to have a maternal inheritance pattern, even if in actuality migraine genes are being passed to offspring equally from both parents.

Perhaps up to a third of children with CVS have some degree of laboratory evidence of possible mitochondrial dysfunction[21]. In a retrospective study of 106 children seen for CVS at a single academic center, metabolic lab investigations were sent on 92% of children and 37 (38%) had findings suggestive of mitochondrial dysfunction in either a well state, in an ill state, or both. [22]. It is important to note that, to our knowledge, no study has examined prevalence of laboratory evidence of mitochondrial dysfunction in a population-based sample of children with CVS. Selection bias is possible, and the high frequency of abnormal laboratories suggesting mitochondrial dysfunction seen in an academic center sample may not be generalizable. Two children (2%) with CVS in that same study had findings suggestive of fatty acid oxidation dysfunction and/or inappropriate ketosis, which could in turn be related to mitochondrial dysfunction[21]. However, the authors note that the laboratory abnormalities seen in their study are of unclear clinical significance, and their results must be interpreted with caution.[21].

Laboratory features that would suggest a fatty acid oxidation disorder in a patient with recurrent vomiting episodes include hypoketotic hypoglycemia, metabolic acidosis, elevated AST and ALT, CK and lactate. Hypoglycemia develops secondary to being unable to fully utilize fatty acids to produce ketones to use for energy, an energy source that is critical to preventing hypoglycemia during times of illness when oral intake is poor and glycogen stores have been used up. The metabolic acidosis is due to accumulating lactate and fatty acids. There have been several cases reported of apparent cyclical vomiting in patients with multiple acyl-coenzyme A dehydrogenase deficiency (MADD), also known as glutaric aciduria type II[23, 24]. MADD is an autosomal recessive disorder that affects metabolism of fatty acids, amino acids, and choline. It is due to a defect in the electron transport flavoprotein (ETF) or in the ETF dehydrogenase. These interact with multiple dehydrogenases, and a defect in this complex disrupts multiple dehydrogenation reactions and affects transfer of electrons from these to the mitochondrial respiratory chain[23, 24]. Several of the dehydrogenases affected are involved in fatty acid oxidation, and others are involved in amino acid catabolism. There are at least six cases (including one pair of siblings) of MADD associated with “cyclic vomiting”, though it is not clear that the episodes were truly cyclic, versus merely recurrent or frequent, episodes of vomiting. All six were not diagnosed with MADD until their teens or twenties[23, 24]. Interestingly, all were female, and five had had episodes of encephalopathy (typically precipitated by an illness) and/or severe weakness prior to diagnosis. In one case of MADD that ultimately proved fatal, a 20 year-old young woman had been having episodes of “cyclic vomiting” from age

9. Clinical clues that her case was not CVS and that should have raised suspicion for an underlying inborn error included that she presented in infancy (age six months) with episodes of being limp and “lifeless”, and that she collapsed multiple times during adolescence.

Acute intermittent porphyria was discovered in one patient in a study of children and adolescents with cyclic vomiting. The patient was a teenager who presented with attacks of abdominal pain, vomiting, and ataxia that were precipitated by fasting and alcohol[6].

Urea cycle defects can also present with recurrent episodes of vomiting and encephalopathy. Avoidance of high-protein foods and/or vomiting following high-protein meals would suggest this as an etiology, but are by no means required features[25]. Growth failure and developmental delay can be seen in patients with urea cycle defects or organic acidurias, but again are not necessarily present.

Does every child with a cyclic vomiting syndrome phenotype need a metabolic evaluation?

Generally speaking, diagnostic yield of metabolic testing is highest if performed during an attack. Normal results, particularly if testing was performed interictally, do not definitively rule out a metabolic disorder[26]. For the child who requires intravenous rehydration with attacks, getting blood and urine tests is not terribly difficult, as they are already presenting to a clinical setting where these tests can be collected.

For the child who is able to weather the attacks at home, the decision of whether to put a copiously vomiting child into the car to bring them in for medical testing during an attack is a bit more complicated. Probably, there are some children in whom this testing can be avoided. The specifics of an individual child’s case should guide the clinician’s decision making, however below are some general suggestions for when metabolic testing should be pursued:

1. **There is *any* degree of abnormality between attacks**—As mentioned above, children with migrainous cyclic vomiting syndrome are completely normal between attacks. Children with interictal abnormalities—including poor growth and developmental delay--require more extensive investigation.
2. **Presence of encephalopathy with attacks**—While certainly a vomiting child might feel miserable and be less active than usual, true encephalopathy should prompt further evaluation for metabolic derangement. The spectrum of encephalopathy would include combative behavior, which can be seen in patients with hyperammonemia due to a urea cycle defect[27].
3. **Attacks are precipitated by illness, fasting, high fat, or high-protein meals**—Periods of illness or fasting provoke catabolism, in which individuals rely on body stores of fat and protein for energy, and these periods can unmask a partial deficiency of fat or protein metabolism that does not manifest when the person is well. Children with ICHD cyclic vomiting syndrome generally have a periodicity to their attacks[1], which should be independent of acute intercurrent illnesses.

Vomiting episodes triggered by high-protein meals would suggest a urea cycle disorder, particularly if accompanied by poor growth, developmental delay, food refusal or aversion to high-protein containing foods[25]. In a male with mild pyruvate dehydrogenase deficiency, a high-carbohydrate meal may lead to episodes of ataxia, and there may be associated vomiting and lactic acidosis[28]. On a related note, patients whose attacks are triggered by alcohol intake or certain medications, fasting, or menses in females, and accompanied by significant abdominal pain, would raise suspicion for acute intermittent porphyria[29].

How to screen for metabolic disorders in patients with a cyclic or recurrent vomiting phenotype

Laboratory testing on blood and urine is relatively non-invasive and can be used to screen for inborn errors of metabolism. As noted above, the diagnostic yield of these tests is highest if samples are drawn during an attack. Normal test results, particularly if performed interictally, do not rule out a metabolic disorder. Conversely, abnormal testing in an attack may reflect the clinical state, and not an underlying inborn error. Laboratories in both a compensated and a decompensated state may be needed for full interpretation, and additional testing may be required. Interpretation of some of the tests can be complex and involvement of a metabolic specialist is recommended. Ideally, samples would be collected before the child is given dextrose-containing intravenous fluids, as certain metabolic derangements can start to rapidly correct once glucose is given. However, dextrose should not be withheld in order to facilitate diagnosis. Consultation with the laboratory and the emergency room staff may be helpful to ensure samples are handled appropriately. For example, lactate generally needs to be obtained without a tourniquet and processed rapidly; ammonia must be placed on ice and processed immediately. Table 1 provides a list of serum and urine metabolic tests to consider in the evaluation of a child with a cyclic vomiting phenotype.

How to treat children with cyclic vomiting syndrome

Individuals recognized to have a fatty acid oxidation disorder, urea cycle defect, or organic aciduria do not have CVS. Their care is highly complex and subspecialized, and these patients should be referred to a metabolic geneticist. Individuals with a defined mitochondrial disorder should be followed both by a neurologist and by a geneticist.

For those patients with CVS, which is thought to be migrainous in etiology, to our knowledge there are no randomized placebo-controlled trials to guide treatment selection.

As episodes of frequent vomiting and poor oral intake may lead to some degree of secondary energy failure even in those children who have presumably normal mitochondrial function at baseline, therapies that help support mitochondrial function might be worth consideration even if metabolic testing is reassuring.

Children with CVS should probably avoid fasting and irregular sleep schedules. This is good advice for migraine sufferers in general[30–33]. Given that there is evidence for efficacy for riboflavin (400 mg daily)[34] and coenzyme Q10 (CoQ10)[35–38] in migraine prophylaxis, and

that the migraine benefit with these agents may be mediated through mitochondrial function even in the absence of a specific identified disorder[39], it would seem reasonable to offer these relatively benign treatments to children with CVS. CoQ10 supports electron transfer between complexes in the mitochondrial respiratory chain[40]. Riboflavin is a cofactor for complex I of the mitochondrial electron transport chain[41]. Given there is a limit to how much riboflavin the body can absorb at one time[41, 42], dividing it out to twice daily dosing may optimize absorption. Taking riboflavin with food also improves absorption[42, 43].

L-carnitine supplementation has also been reportedly helpful in pediatric cyclic vomiting syndrome cases [44–46]. L-carnitine is required for transport of long chain fatty acids across the mitochondrial membranes. Supplementation may be therapeutic in CVS even when pre-treatment carnitine levels are normal[44, 45] and in the absence of a specific identified metabolic disorder[45]. In a retrospective uncontrolled chart review study, treatment with combined L-carnitine and CoQ10 supplementation appeared useful for children with CVS[46].

Treatment with standard migraine preventive medications such as amitriptyline, cyproheptadine, or propranolol may also be helpful for children with CVS. In a consensus statement by the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition, amitriptyline was recommended for children age five and up and cyproheptadine for those under five[47]. In an uncontrolled study, the neurokinin-1/substance P receptor antagonist aprepitant appeared efficacious both as an acute therapy and as a preventive therapy for CVS[48].

Table 2 provides dosing information for these medications and supplements.

Conclusions

The differential is broad in children presenting with a cyclic vomiting syndrome phenotype and includes metabolic disorders. Red flags that raise suspicion for a metabolic disorder include 1) any degree of interictal abnormality, 2) encephalopathy with attacks, and 3) attacks triggered by fasting, illness, or high-protein, carbohydrate or high-fat foods. Individuals with inborn errors of fat and protein metabolism do not have a cyclic vomiting syndrome, but a metabolic disorder that can mimic this. These patients should be evaluated and treated by a metabolic geneticist. Patients with mitochondrial disorders may present with cyclic vomiting, and mitochondrial dysfunction may play a role in cyclic vomiting in individuals without a clear mitochondrial disorder. In patients with migraine associated cyclic vomiting syndrome, treatment with migraine preventives, and/or mitochondrial supplements such as CoQ10, riboflavin and L-carnitine, may improve symptoms.

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Table 1

Metabolic Testing to Consider in Patients Presenting with a Cyclic Vomiting Syndrome Phenotype

Lab Test	**Type of disorder being tested:**
Blood tests:	
Quantitative plasma amino acid analysis	Urea cycle disorder, organic aciduria, mitochondrial dysfunction
Plasma acylcarnitine profile (fractionation of esterified carnitines)	Fatty acid oxidation disorder, organic aciduria, ketone utilization defect, mitochondrial dysfunction
Plasma total and free carnitine	Carnitine transport defect, fatty acid oxidation disorder, organic aciduria, mitochondrial dysfunction
Lactate	Mitochondrial dysfunction, fatty acid oxidation disorder, organic aciduria
Pyruvate	Mitochondrial dysfunction
Ammonia	Urea cycle defect *Check in an attack*
Glucose	Fatty acid oxidation disorder (may be low in prolonged fasting and/or illness)
Electrolytes (to calculate anion gap for metabolic acidosis)	Fatty acid oxidation disorder, organic aciduria
Urine tests:	
Urine Ketones	Fatty acid oxidation disorder (inappropriately low in most of these when glucose is low), ketone utilization defect (high in illness *and* in well state)
Urine organic acids	Organic aciduria, ketone utilization defect, fatty acid oxidation disorder, mitochondrial dysfunction
Quantitative orotic acid	Urea cycle defect, mitochondrial dysfunction
Urine acylglycines	Fatty acid oxidation disorder (sensitive test for MADD), some organic acidurias
Urine porphobilinogen	Acute porphyrias *Check in an attack*

Table 2

Preventive treatment Options to Consider in Cyclic Vomiting Syndrome

Treatment	Dosing
Coenzyme Q10	10 mg/kg/day (max 200 mg), divided twice daily
L-carnitine	50 –100 mg/kg/day (max 4 grams), divided twice daily
Riboflavin (vitamin B2)	400 mg daily or divided twice daily
Amitriptyline	1 mg/kg nightly
Cyproheptadine	0.25–0.5 mg/kg/day divided twice daily, or nightly
Aprepitant	2x/week <40 kg: 40 mg 40–60 kg: 80 mg >60 kg: 125 mg