

Cyclic Vomiting Syndrome Association USA/Canada

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Cyclic Vomiting in Mitochondrial Disease

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Gastrointestinal (GI) symptoms are commonly encountered in patients with mitochondrial disease. Most often, symptoms are episodic in that they come and go, and are related to 'functional' problems of the bowel. In particular, vomiting is common among sufferers of many different mitochondrial disorders, and among these individuals, vomiting itself has many different causes. An occasional bout of vomiting is common, especially in infants, and is often found to be caused by gastroesophageal reflux.

This article discusses one particular type of vomiting disorder, called 'cyclic vomiting'. Cyclic vomiting is not new as it was first described in the eighteenth century, although even today very few physicians or other clinical care providers have heard of it. Cyclic vomiting refers to discrete and severe episodes of vomiting, nausea and lethargy (severe tiredness). Episodes are discrete in that the sufferer is free of nausea and vomiting between episodes. Episodes are severe in that the sufferer almost always feels quite ill, preferring to lie down in a dark and/or quiet place, and not interested in any of the activities of life. Vomiting and loss of appetite can be severe enough to necessitate hospitalization for intravenous (IV) fluids with each episode. In other cases, nausea and lethargy may be much more troublesome than vomiting. Episodes can occur on a routine schedule (such as once a week or once a month), be triggered by physical or psychological stress, or appear to come at random. Each episode can last for hours to cases, nausea and lethargy may be much more troublesome than vomiting. Episodes can occur on a routine schedule (such as once a week or once a month), be triggered by physical or psychological stress, or appear to come at random. Each episode can last for hours to many days, but usually there is a characteristic duration in each individual patient. In some cases, an episode may be stopped if the child sleeps. Some sufferers have additional symptoms during episodes such as loose stools, drooling or headache. There may or may not be an 'aura', or symptoms which occur before vomiting begins. In most cases, cyclic vomiting starts in children ranging from age 3 to 8 years, although the disorder can start at any age including in infants and adults. Cyclic vomiting can run its course and resolve, continue indefinitely, or change into migraine headaches. Most sufferers have normal intelligence and are generally healthy between episodes, however, many of them have various degrees of developmental delay and/or additional problems such as epilepsy.

Cyclic vomiting has many known causes, including intestinal blockage, brain disorders, kidney disease, and several different metabolic disorders. Many of these causes are treatable, and a careful diagnostic work-up is important. However, in the vast majority of cases, none of the above causes can be found, and these individuals are given the diagnosis of 'cyclic vomiting syndrome' or 'CVS'. Migraine headaches and episodic severe abdominal pain (abdominal migraine) are very common in CVS sufferers and their family members alike (usually in the maternal relatives!). At present, migraine headaches, abdominal migraine and CVS are considered to be related, and possibly are different manifestations of the same disorder.

Cyclic vomiting has been reported in individuals with the A3243G 'MELAS' mutation in the mitochondrial DNA (mtDNA). In addition, one child with CVS, developmental delay, seizures, growth delay and additional problems was reported to have a large mtDNA deletion and duplication. However, in my experience as a metabolic geneticist, CVS with or without additional problems is not rare in children with mitochondrial disorders, and among this group, 'routine' mtDNA analysis fails to identify previously known mtDNA mutations in most of them.

To date, I have personally evaluated about 15 children with CVS and suspected mitochondrial disease. These and an additional 50 cases worldwide with CVS and additional neuromuscular problems (a group at risk for possible mitochondrial disease) have been entered into an ongoing research study. Many of these children have a specific pattern of additional clinical and laboratory findings including GI dysmotility (reflux, delayed gastric emptying, constipation), dysautonomia (unexplained fevers, high heart rate, etc.), muscle weakness, chronic fatigue, seizures and pain (head,

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abdomen and/or extremities). The latter is occasionally associated with swelling and skin discoloration in a manner suggestive of neurovascular dystrophy. No single child suffers from all of these problems, and when present in a given child the symptoms tend to be episodic and variable. In some of these children, cyclic vomiting itself is a minor part of the child's problems, and may disappear or never have been present. Intelligence ranges from gifted to severe mental retardation.

Laboratory analysis in children with CVS and mitochondrial disease demonstrates elevated lactic acid and abnormal urine organic acids (ketones, Krebs cycle intermediates, and/or ethylmalonate) early in vomiting episodes, but biochemical tests are rarely abnormal at other times. A few children have received muscle biopsies which revealed findings suggestive of mitochondrial dysfunction, including increased variation in fiber size, mitochondrial proliferation, and/or complex 1 deficiency. In my opinion, the most striking finding is maternal inheritance of the same episodic problems often seen in the affected children themselves, but usually to a lesser degree, including migraine, cyclic vomiting, GI dysmotility, dysautonomia, muscle weakness or pain, chronic fatigue, and/or seizures. At the time of this writing, at least 5 unrelated cases were found to have heteroplasmic (two different mtDNA sequences present in the same individual) nucleotide changes in the HV1 area of the mtDNA control region. These molecular variants are maternally inherited (present in mother and siblings, even if they themselves are without symptoms) and were not found in over 100 children without mitochondrial disease. The same control region variants were found in children with mitochondrial disease but without CVS, and the significance of our recent findings are not yet clear and are the subject of ongoing investigation. However, our data does demonstrate that mitochondrial disease with cyclic vomiting is often maternally inherited.

Unlike most published cases with mitochondrial disorders, disease progression appears to be rare in these children. One exception to the general benign disease course is that a few families have had infants under age 2 years who suddenly died and were labeled as "SIDS". Most children, and especially their affected relatives, attend normal schools or have jobs/careers, and their lives are fairly normal between disease episodes. In many school-aged affected children, severe fatigue and muscle weakness has necessitated the occasional usage of wheelchairs and/or half day or home schooling. All too often, clinic care providers and/or school personnel have down-played the disease process, even to the extent of labeling the child/family as exaggerating symptoms, being psycho-logically disturbed, or having caused the illness (Munchausen By Proxy).

The good news is that treatments are available for cyclic vomiting in individuals with mitochondrial disease. In mitochondrial disease, symptoms are believed to occur when energy supply cannot meet energy demand. Since often little can be done to increase energy supply, decreasing energy demand is a major part of therapy. In practical terms, this means the reduction of stress, including the avoidance of fasting, limiting exposure to environmental temperature extremes, and the prompt treatment of infections and dehydration. Cyclic vomiting and other symptoms often improve with frequent feedings of complex carbohydrate, including between meals and at bedtime. Other children improve if awakened during sleep for a snack and/or placed on a low fat diet. In addition to physical stress, the reduction of psychological stress is important: not because this is the cause of the disease, but because stress increases energy demand and can trigger an episode. In cases in which the response to these simple measures is not adequate, anti-migraine medication including amitriptyline-line (Elavil), cyproheptadine (Periactin) or propranolol (Inderal) taken daily or more often can reduce the number of vomiting episodes in most cases, sometimes dramatically. When they do occur, vomiting episodes are treated with IV fluids (10% dextrose with standard electrolytes at a rate of 1.5 to 2 times maintenance) in a dark and quiet room in order to facilitate sleep. In some cases, ondansetron (Zofran) and/or medications to induce sleep (i.e. lorazepam/Ativan) are helpful.

Diagnostic work-up (testing) must be tailor-fit to each individual child. Of course, confirming the diagnosis of mitochondrial disease and ruling out other treatable metabolic disorders (urea cycle disorders, organic acidemias) should be pursued. I suggest that a minimum work-up should include serum electrolytes, routine urinalysis, plasma lactate, quantitative plasma amino acids and quantitative urine organic acids (including full quantification of Krebs cycle intermediates and other potential 'mitochondrial markers'), with samples obtained early in a severe or typical vomiting episode. Mitochondrial DNA analysis should include at a minimum PCR for A3243G and Southern blotting. Unless the diagnosis of mitochondrial disease is firm and CVS symptoms respond to treatment, work-up for other potential causes of cyclic vomiting should be performed, possibly including but not necessarily limited to: upper GI series, abdominal

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ultrasound, brain CT scan, and testing for sinusitis, prophyria and pregnancy. Probably no single individual requires, or should receive, all of the studies listed, and it is important to discuss the work-up with your child's physician.

This is a very new and rapidly evolving field, and not even half of the answers are known yet. Much of our understanding of, and hopefully our ability to treat, this disorder will improve over the next several months to years. I am writing this article at this early stage with the hope that some children will be steered towards treatments now which may be somewhat helpful to them. For more information, CVSA and the United Mitochondrial Disease Foundation, may be helpful. I suggest browsing their websites at www.cvsaonline.org or www.umdf.org In addition, information on any available studies in CVS (with or without mitochondrial disease) and their entrance criteria and procedures are listed there.

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Cyclic Vomiting Syndrome Association-USA/Canada, founded in 1993 actively pursues the following mission:

"CVSA USA/Canada will raise awareness, provide education and support to those affected by CVS and advocate for research about nausea and vomiting."