# Cyclic vomiting syndrome in multisystem mitochondrial disorder

## Syndrome des vomissements cycliques dans les maladies mitochondriales multisystémiques

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**RÉSUMÉ**

**Prérequis :** Le syndrome des vomissements cycliques (SVC) est caractérisé par des épisodes répétitifs handicapant de nausées et vomissements accompagnés de douleur abdominale, entrecoupés par des périodes sans symptômes durant quelques semaines voire quelques mois.

**But:** Démontrer qu'une maladie mitochondriale peut présenter des symptômes typiques d'un SVC.

**Observation :** Une patiente âgée de 31 ans avec le diagnostic de SCV depuis la naissance, présente une petite taille, une surdité, un syndrome du côlon irritable, une cardiomyopathie hypertrophique en l'absence d'hypertension artérielle, une hépatopathie, une myopathie et des polyarthroses. Son histoire familiale a révélé un diabète et une migraine avec un mode de transmission maternel. La fréquence des épisodes de vomissements s'est réduite mais les autres manifestations se sont aggravées avec le temps. Devant l'atteinte multisystémique et les antécédents familiaux une maladie mitochondriale a été suspectée.

**Conclusion:** Le SVC souvent s'améliore à l'âge adulte. L'association d'un SVC à des atteintes multisystémiques devrait faire suspecter une maladie mitochondriale.

**Mots-clés**
mtDNA, mitochondrial, syndrome du côlon irritable, myopathie, maladie métabolique

**SUMMARY**

**Background:** Cyclic vomiting syndrome (CVS) is characterized by recurrent episodes of incapacitating nausea or vomiting accompanied by abdominal pain, interspersed with relatively symptom-free intervals that might last from a few weeks to months. There are a number of indications that CVS could be a manifestation of a mitochondrial disorder (MID).

**Aim:** To illustrate how a MID may present with symptoms typical of CVS.

**Case:** A 31 year old female diagnosed as having CVS since birth had additional features of short stature, deafness, irritable bowel syndrome, cardiomyopathy with myocardial thickening in the absence of arterial hypertension, hepatopathy with steatosis hepatis, myopathy, and polyarthrosis. Her family history was positive for diabetes, short stature, and migraine with a maternal mode of inheritance, frequently found in patients with MIDs. Frequency of CVS episodes decreased with age but other manifestations of the MID became worse over time. Due to the multisystem nature of the disease and the positive family history, a MID was assumed.

**Conclusions:** Early-onset CVS often improves in adulthood. CVS may be associated with multisystem disease, suggesting the presence of a MID. CVS should be regarded as a manifestation of a MID if typical clinical manifestations of a MID, which cannot be explained by other causes, are present.

**Key-words**
mtDNA, mitochondrial, irritable bowel syndrome, myopathy, metabolic disease

Cyclic vomiting syndrome (CVS) is an unusual debilitating syndrome, characterized by recurrent, stereotypic episodes of intense nausea, intractable vomiting, and abdominal pain lasting hours or days [1,2]. Range and severity of symptoms vary greatly in different patients. Diagnosis is frequently delayed, especially when symptoms first occur in adulthood. The etiology of CVS is unknown but there are indications that in many patients it could be a phenotypic manifestation of a mitochondrial disorder (MID) or of a fatty acid oxidation disorder [1,3]. Here we describe an adult diagnosed as having CVS since birth in whom other features, worsening in later life suggested a MID as underlying cause of the CVS.

## CASE REPORT

The patient is now a 31 year old Caucasian female, height 160cm, weight 105kg, with a previous history of recurrent episodes of vomiting and abdominal cramping since birth, which occurred 4-6 times/y until age 20y, becoming less in frequency since. During these episodes she vomited every 10 minutes and she was unable to retain food. Episodes lasted for 5-7d and were induced by overactivity or sleep deprivation. The episodes were so frequent that she was bedridden for up to half a year before age of 20y. The CVS episodes were never associated with headache or visual disturbances. At birth a paraesophageal hiatus hernia was diagnosed, for which she was operated at age 6 months with success. At age 5y she underwent surgery for duodenal ulcer. Since age 10y she developed severe rectal tenesms and an increasing stool frequency with 5-6 defecations/d. Defecations were preceded by abdominal pain each time and were not associated with CVS episodes. Since age 25y she also noted myalgia, which increased after exercise, and has now become permanent. At the same time she noted marked increase in preexisting easy fatigability, exhaustion upon minimal exercise, and a markedly increased need of sleep. Since age 28y she noted muscle cramping of the calves 2-3 times per year, which could be triggered by physical activity. There was no history of seizures or 'stroke-like episodes. Since adaptation of the therapeutic regimen two years ago, the frequency of CVS had decreased to one episode per year. The family history was positive for nausea and motion sickness (brother), migraine (brother, mother, grandmother from the mother's side), diabetes (mother, grandmother from the mother's side), colon carcinoma (grandmother from the mother's side), and obesity, arterial hypertension, and short stature (mother).

Clinical neurologic examination revealed myopia, bilateral hearing loss, an elicitable masseter reflex and positive pyramidal signs confined to the right upper extremity. She had clinical evidence of a sicca-syndrome. Blood pressure measurements were normal. Blood chemical investigations revealed repeatedly elevated SGOT, SGPT, GGT, transferrin saturation, ferritin, and hyperlipidemia (table 1). Serum lactate was normal. Ultrasonography of the abdomen showed liver steatosis only. Echocardiography revealed concentric thickening of the left ventricular myocardium despite the absence of arterial hypertension. MRI of the cerebrum as well as visually-evoked potentials were non-informative. Gastroenterological investigations showed gastro-esophageal reflux with reflux esophagitis. For CVS episodes she was taking lorazepam 2mg/d, ondansetron 16mg/d, and zolmitriptan in case of abdominal cramping. Outside the CVS episodes she was taking extractum fructus silybi for hepatopathy, chondroitini natrii sulfans for polyarthrosis, and domperidone 20mg/d for stool problems. Her gynecologist had prescribed the pill to decrease gastrointestinal symptoms shortly before the period. L-carnitine and coenzyme-Q were proposed. Consent to muscle biopsy has not been obtained to date and mtDNA analysis has not been carried out on other tissues.

**Table 1:** Selected blood chemical values of the described patient

| Parameter | Reference limit | | 21/2/08 | 2/6/08 | 18/2/10 | 5/9/12 |
|---|---|---|---|---|---|---|
| Sodium | 130-152mmol/l | | 139 | nd | 137 | 141 |
| Potassium | 3.5-5.5mmol/l | | 5.4 | nd | 4.5 | 4.5 |
| GOT | <35U/l | | 52 | 41 | 15 | 89 |
| GPT | <35U/l | | 91 | 83 | 81 | 107 |
| GGT | <43U/l | | 126 | 95 | 147 | 173 |
| Cholesterol | <200mg/dl | | 210 | 286 | 277 | 289 |
| Triglycerides | <170mg/dl | | 213 | 197 | 150 | 415 |
| Transferrin saturation | | 16-45% | nd | nd | 47 | nd |
| | | 20-40% | nd | 29 | nd | nd |
| Ferritin | 13-150ng/ml | | 426 | 499.7 | 453.0 | nd |

Nd: not determined

## DISCUSSION

The presented patient is interesting for the association of CVS with a number of manifestations suggesting MID. Manifestations in addition to CVS were hypoacusis, sicca-syndrome, myocardial thickening in the absence of arterial hypertension, rectal tenesms and increased stool frequency (irritable bowel syndrome), hepatopathy with steatosis hepatis, short stature, muscle cramping, and polyarthrosis. Due to her multisystem disease and type of abnormalities, the clinical presentation was suggestive of a MID. Organs involved in the presented MID were the myocardium (myocardial thickening), the inner ear (hypoacusis), the autonomic nervous system (sicca-syndrome), the endocrine system (short stature), the liver (steatosis hepatis, hepatopathy), the gastrointestinal tract (CVS, irritable bowel syndrome), the muscle (cramping), and the cartilage (polyarthrosis). A further argument for a MID as the underlying cause of CVS is the family history, which suggests maternal transmission of manifestations frequently found in patients with MIDs, such as diabetes, short stature, or migraine.

Arguments for MID as the cause of CVS from the literature are the association of mitochondrial DNA single nucleotide polymorphisms (SNPs) m.16519C>T and m.3010G>A with migraine and childhood CVS [4,5], the frequent transmission of CVS via a maternal trait of inheritance [6,7], the increased frequency of migraine in patients with CVS [8,9], the frequent association of CVS with other typical clinical manifestations of a MID [5,10,11], the abnormal urine organic acid profile in some CVS patients [6], and the occasional beneficial response of CVS to compounds such as L-carnitine or coenzyme-Q [12], proposed as supportive measures in MIDs.

Additionally, seven of the eleven patients described in the first publication of the MELAS syndrome had episodic vomiting similar to that which occurs in CVS [13]. A further argument for a causative link between MID and CVS is the report of a patient with Kearns-Sayre syndrome and CVS [14]. In this particular patient a typical mtDNA

deletion and typical phenotypic features of Kearns-Sayre syndrome were reported in addition to CVS [14]. There are also reports about CVS patients in whom serum lactate was elevated [15].

A famous patient with CVS and presumed manifestations of a MID was Charles Darwin (CD) [16,17]. CVS in DC had an adult onset and remained a severely compromising condition throughout his life. CVS was most likely the cause why CD suffered from abnormal sea-sickness [18]. Gastrointestinal dysmotility in CD manifested also as flatulence, and bloating with abdominal pain [16]. Symptoms in addition to CVS attributable to a MID in CD were tiredness, exercise intolerance, easy fatigability, exhaustion, headache, dizziness, dyslexia, panic attacks, presyncope, hypesthesia and dysesthesia in a glove-type distribution suggesting polyneuropathy, palpitations and chest pain, muscle twitching, myalgias, occasional edema of face, and dermatological problems [16,17].

Some of his complaints were also present in the presented patient further emphasising the mitochondriopathic nature of her abnormalities.

This case shows that CVS may be associated with multisystem disease, suggesting the presence of a MID and that early-onset CVS may improve in adulthood. CVS patients should be investigated for evidence of a MID if additional clinical manifestations of a MID, not explained by other causes, are present.

## References


1. Fitzgerald M, Crushell E, Hickey C. Cyclic vomiting syndrome masking a fatal metabolic disease. Eur J Pediatr 2013;172:707-10
2. Keller K, Beule J, Scholz M, Pfnür M, Dippold W. Cyclic vomiting syndrome (CVS) in adults - frequently overlooked? Z Gastroenterol 2012;50:694-8.
3. Kumar N, Bashar Q, Reddy N, Sengupta J, Ananthakrishnan A, Schroeder A, Hogan WJ, Venkatesan T. Cyclic Vomiting Syndrome (CVS): is there a difference based on onset of symptoms--pediatric versus adult? BMC Gastroenterol 2012;12:52.
4. Camilleri M, Carlson P, Zinsmeister AR, McKinzie S, Busciglio I, Burton D, Zaki EA, Boles RG. Mitochondrial DNA and gastrointestinal motor and sensory functions in health and functional gastrointestinal disorders. Am J Physiol Gastrointest Liver Physiol 2009;296:G510-6.
5. Boles RG, Zaki EA, Lavenbarg T, Hejazi R, Foran P, Freeborn J, Trilokekar S, McCallum R. Are pediatric and adult-onset cyclic vomiting syndrome (CVS) biologically different conditions? Relationship of adult-onset CVS with the migraine and pediatric CVS-associated common mtDNA polymorphisms 16519T and 3010A. Neurogastroenterol Motil 2009;21:936-e72.
6. Boles RG, Adams K, Li BU. Maternal inheritance in cyclic vomiting syndrome. Am J Med Genet A 2005;133A:71-7.
7. Venkatesan T, Zaki EA, Kumar N, Sengupta J, Ali M, Malik B, Szabo A, van Tilburg MA, Boles RG. Quantitative pedigree analysis and mitochondrial DNA sequence variants in adults with cyclic vomiting syndrome. BMC Gastroenterol 2014;14:181.
8. Lin YP, Ni YH, Weng WC, Lee WT. Cyclic vomiting syndrome and migraine in children. J Formos Med Assoc 2011;110:382-7.
9. Stickler GB. Relationship between cyclic vomiting syndrome and migraine. Clin Pediatr (Phila) 2005;44:505-8.
10. Boles RG, Adams K, Ito M, Li BU. Maternal inheritance in cyclic vomiting syndrome with neuromuscular disease. Am J Med Genet A 2003;120A:474-82.
11. Moses J, Keilman A, Worley S, Radhakrishnan K, Rothner AD, Parikh S. Approach to the diagnosis and treatment of cyclic vomiting syndrome: a large single-center experience with 106 patients. Pediatr Neurol 2014;50:569-73.
12. Boles RG. High degree of efficacy in the treatment of cyclic vomiting syndrome with combined co-enzyme Q10, L-carnitine and amitriptyline, a case series. BMC Neurol 2011;11:102.
13. Pavlakis SG, Phillips PC, DiMauro S, De Vivo DC, Rowland LP. Mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes: a distinctive clinical syndrome. Ann Neurol 1984;16:481-8.
14. Boles RG, Baldwin EE, Prezant TR. Combined cyclic vomiting and Kearns-Sayre syndromes. Pediatr Neurol 2007;36:135-6.
15. Boles RG, Williams JC. Mitochondrial disease and cyclic vomiting syndrome. Dig Dis Sci 1999;44(suppl 8):103S-107S.
16. Hayman JA. Darwin's illness revisited. BMJ 2009;339:b4968.
17. Hayman JA. Charles Darwin's impressions of New Zealand and Australia, and insights into his illness and his developing ideas on evolution. Med J Aust 2009;191:660-3.
18. Finsterer J, Hayman J. Mitochondrial disorder caused Charles Darwin's cyclic vomiting syndrome. Int J Gen Med 2014;7:59-70.