

Cyclic vomiting syndrome: Light emerging from the black box

Distilled to its clinical essence, cyclic vomiting syndrome is characterized by a unique pattern of short-lived but intense episodes of rapid-fire vomiting, which punctuate periods of normal health.¹ Although this disorder remains a "black box" of unknown pathogenesis, there has been a recent resurgence in clinical interest.² Including its first description over a century ago, only 24 papers related to CVS appeared before 1990; in the last decade, 62 relevant papers have been published. Pediatric gastroenterologists in cooperation with the Cyclic Vomiting Syndrome Association, a professional-parent partnership founded in 1993, have organized 2 international symposia in 1994 and 1998 and published 33 manuscripts in the proceedings.^{3,4}

The article by Tóth et al⁵ signals a new era by its use of physiologic measures to investigate the pathogenesis of CVS. From the neurologic findings, they postulated that the sympathetic (vs parasympathetic) tone might be altered, similar to changes found in migraine headaches.⁶ The authors examined the autonomic nervous system function in 14 children with CVS and compared

them with healthy control subjects. A power spectral analysis (a standardized computerized algorithm) of a 20-minute electrocardiographic recording was used to analyze heart rate (R-R interval) variability. Based on previous validation, the areas under the low- and high-frequency peaks correspond to sympathetic (adrenergic) and parasympathetic (cholinergic) tone, respectively. The authors found a significantly higher ratio of low-to-high frequency areas in children with CVS, indicating a prevailing sympathetic balance.

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The findings of Tóth et al⁵ are consistent with recent observations on CVS and migraine. Many "autonomic" symptoms (eg, pallor and lethargy) are common to both CVS and migraine headaches. Episodic vomiting also occurs in familial dysautonomia, a disorder affecting the autonomic nervous system. Rashed et al⁷ recently observed that both children with CVS and adults with migraines manifest higher sympathetic responses as measured by cardiovascular reactivity to postural changes. The evidence supports the concept that the baseline (ie, between episodes) sympathetic tone in children with CVS differs from that of control subjects in a

pattern similar to that found in patients with migraine headaches. Further strengthening the tie between CVS and migraine, Good⁸ reported similar visually evoked responses in children affected with each disorder.

CVS Cyclic vomiting syndrome

These physiologic findings raise additional questions. Do other measures of autonomic function (eg, cold pressor response, tilt-table tests, postural adjustment ratio, heart rate variations during deep breathing and Valsalva's maneuver) provide a reproducible and consistent picture of altered sympathetic and parasympathetic balance in CVS? Do these baseline aberrations persist during the vomiting episodes? Do these tests demonstrate similar changes in children with migraine headaches in support of the notion that CVS and migraine are varied manifestations of the same disorder? Do the levels of autonomic mediators, from central adrenocorticotropin hormone to peripheral cortisols and catecholamines, reflect these changes?

What role could autonomic instability play in CVS? Although the observed autonomic imbalance could be an unrelated association with CVS, it is more likely part of the pathophysio-

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logic picture. For example, the altered balance could mediate some of the autonomic symptoms of CVS and account for the observation that β -adrenergic blockade effectively prevents episodes. With additional confirmatory studies, studies of autonomic function may eventually confirm the clinical overlap between CVS and migraines. In a recent study 82% of children with CVS could be classified clinically as having migraine-associated variant (ie, abdominal migraine), on the basis of a positive family history of migraine or subsequent development of migraine headaches. Because 11 of 14 subjects in the study by To et al⁵ met the criteria for migraine-related CVS, their findings suggest that CVS and migraines may share autonomic dysfunction as part of a common pathogenesis.⁹

What other etiologic possibilities are tenable? The hypothalamic-pituitary-adrenal axis appears to be altered in CVS. Sato et al¹⁰ described a group of children with cyclic vomiting, profound lethargy, and hypertension with a profile of elevated corticotropin, cortisols, vasopressin, prostaglandin E₂, and catecholamines. They postulated that this could represent a hypothalamic surge from impaired dopaminergic inhibition.¹⁰ Taché¹¹ has recently postulated that CVS could be a brain-gut disorder on the basis of extensive animal studies in which corticotropin-releasing factor causes gastric stasis and/or vomiting by vagal mediation. This neuroendocrine model could account for the frequent association between a proximate stressor, usually infectious or psychologic, and episodes of CVS. Whether the hyperreactivity resides in the endocrine or neural portion of the stress cascade remains to be seen. In our clinical series those children who fit the description of Sato et al¹⁰ had far more prolonged (92 vs 43 hours) and severe episodes (144 vs 24 emeses per episode) than usual and may represent a subgroup of patients who have a variant of CVS with its own unique mechanisms.

Two other etiologic possibilities should be noted, one involving mitochondrial energetics and the other involving transmembrane ion gradients. Mitochondrial disorders of fatty acid oxidation (eg, medium-chain acyl-coenzyme A dehydrogenase deficiency), respiratory chain defects (eg, mitochondrial encephalopathy, lactic acidosis, and stroke-like syndrome), and mitochondrial DNA deletion are associated with episodic metabolic crises and vomiting, often precipitated by viral illness or prolonged fasting.¹² Ptáček¹³ has proposed that abnormalities of ion channels could account for episodic phenomenon; recently, a defective calcium channel was identified in hemiplegic migraine.¹³ To link these 2 concepts, one could conjecture that either borderline mitochondrial adenosine triphosphate production or defective ion channels could result in episodic neuronal depolarization and initiation of the cascade.

Although cyclic vomiting remains a syndrome, the perturbation in autonomic function described by To et al⁵ provides an empiric glimpse into the complex pathophysiologic matrix. There are now several specific lines of investigation into the mechanisms of CVS. There may well be heterogeneity in the pathogenesis of CVS, just as several clinical subgroups can now be discerned: migraine-associated CVS, Sato's subgroup, and suspected mitochondrialriopathy (growth failure, developmental delay, and increased lactate). Classifying children with CVS into various subgroups may enable investigators to determine whether there are parallel pathways involved, interrelated mechanisms, or a single pathophysiologic continuum. With exciting inquiry on several pathophysiologic facets, light is indeed emerging from this century-old pediatric black box.

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