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Original Article

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ABSTRACT

Cyclic vomiting syndrome, which is characterized by severe discrete episodes of nausea, vomiting, and lethargy, is a fairly common, disabling, predominately childhood condition. Approximately 25% of cases have coexisting neuromuscular disease manifestations (cyclic vomiting syndrome plus). To determine whether patients with cyclic vomiting syndrome and neuromuscular disease represent a distinct subentity within cyclic vomiting syndrome, a clinical interview was conducted regarding 80 randomly ascertained sufferers of cyclic vomiting syndrome from a disease association database. Cyclic vomiting syndrome plus and "cyclic vomiting syndrome minus," herein defined as the presence of at least two and zero neuromuscular disease manifestations, were present in 23 and 44 subjects, respectively. Neuromuscular disease manifestations, including cognitive disorders, skeletal myopathy, cranial nerve dysfunction, and seizure disorders, were found to statistically cluster together among the same subjects. In addition, subjects with cyclic vomiting syndrome with neuromuscular disease had an earlier age at onset for vomiting episodes and a three- to eightfold statistically increased prevalence for certain dysautonomia-related (migraine, chronic fatigue, neurovascular dystrophy) and constitutional (growth retardation and birth defects) disorders. However, subjects with cyclic vomiting syndrome with and without neuromuscular disease were equally likely to have a sibling affected with neuromuscular disease manifestations. We conclude that cyclic vomiting syndrome plus, although likely not genetically distinct from cyclic vomiting syndrome minus, represents a distinct phenotypic entity that predicts an earlier onset of disease and increased comorbidity with a distinct list of medical conditions, possibly owing to a higher degree of mitochondrial dysfunction. (*J Child Neurol* 2006;21:182–188; DOI 10.2310/7010.2006.00040).

Cyclic vomiting syndrome is a disabling condition characterized by recurrent, distinct episodes of nausea, vomiting, and lethargy separated by asymptomatic intervals in the absence of a specific causal etiology, such as malrotation or a urea cycle defect.[1–3] Although the duration and other characteristics of episodes vary among patients with cyclic vomiting syndrome, most suffer from recurrent episodes that are stereotypical in that individual. Episodes usually are severe and can result in frequent hospitalizations for dehydration and multiple school absences.[1,2] Cases most commonly present in the preschool to early school-aged years, although the disorder can start at any time from infancy to adulthood.

Cyclic vomiting syndrome is widely thought to be a (predominantly) childhood manifestation of a migraine-like condition.[4] At least a third of cases evolve to migraine headaches,[4] whereas a family history of migraine headaches is present in 80% of families[4] and in 56% of first-degree relatives.[5] Abnormal autonomic regulation has also been documented in cyclic vomiting syndrome, as manifested by a low postural adjustment ratio of upper extremity capillary flow as measured by infrared photoplethysmography[6] and an increased low frequency to high frequency ratio on power spectral analysis of heart R-R rate variability.[7]

Although most children with cyclic vomiting syndrome are otherwise healthy and of normal intelligence, a significant subset have coexisting neuromuscular disorders, including cognitive delay, myopathy, and/or seizure disorders.[2,8] In this subset, neuromuscular disease manifestations exist between episodes, yet nausea, vomiting, and lethargy are confined to episodes. Among the 268 sufferers of cyclic vomiting syndrome listed on the International CVSA Research Registry maintained by the Cyclic Vomiting Syndrome Association USA/Canada, 24% have at least one neuro-

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Table 1. Neuromuscular Disease Manifestations That Define Our Cyclic Vomiting Syndrome Plus Population*

Neuromuscular Disease Manifestation	*Number (%) Reported Among All 80 Cases*	*Number (%) Reported Among 23 CVS+ Cases*
Skeletal myopathy†	16 (20)	14 (61)
Mental retardation‡[a]	13 (16)	13 (57)
Attention-deficit hyperactivity disorder[a]	12 (15)	7 (30)
Strabismus[b]	10 (12)	9 (39)
Seizure disorders (excluding simple febrile)	10 (12)	7 (30)
Hearing loss[b]	6 (8)	5 (22)
Microcephaly[a]	5 (6)	5 (22)
Ataxia	5 (6)	5 (22)
Cardiomyopathy	4 (5)	3 (13)
Autistic spectrum disorder (autism or PDD)[a]	4 (5)	4 (17)
Ptosis[b]	3 (4)	3 (13)
Olfactory deficit[b]	1 (1)	1 (4)
Any cognitive abnormality§	25 (31)	20 (87)
Any cranial nerve abnormality‖	14 (18)	11 (48)
Two or more neuromuscular disease manifestations (CVS+)	23 (29)	23 (100)¶

CVS+ = cyclic vomiting syndrome plus; PDD = pervasive developmental disorder.
*By definition, all of the manifestations listed in this table were absent in all 44 cyclic vomiting syndrome minus cases.
†Skeletal myopathy was defined as hypotonia, weakness, or gross motor delay.
‡Mental retardation was recorded in children with a tested IQ < 70 or in children not tested if both motor and language function based on the interview were clearly less than a developmental level of 70.
§Includes above manifestations labeled with the letter "a."
‖Includes above manifestations labeled with the letter "b."
¶By definition.

muscular disease manifestation. It has been our clinical observation that neuromuscular disease manifestations are not evenly or randomly distributed across the cyclic vomiting syndrome population but are clustered into a significant minority of cases. In the same way that Kearns-Sayre syndrome with additional abnormalities is designated as "Kearns-Sayre syndrome plus," we had previously coined the term "cyclic vomiting syndrome plus" to indicate cases with cyclic vomiting syndrome and additional neuromuscular disease manifestations.[8] Thus, cases without neuromuscular disease are labeled as "cyclic vomiting syndrome minus."[9]

Patients with cyclic vomiting syndrome plus have many of the same neuromuscular conditions frequently reported in individuals with mitochondrial disease, and many are evaluated for the possibility of a mitochondrial disorder. Most cases of cyclic vomiting syndrome plus also demonstrate lactic acidosis, energy-deficient patterns on urine organic acid analysis, and pedigrees suggestive of maternal inheritance, suggesting that cyclic vomiting syndrome plus is a phenotype related to mitochondrial dysfunction secondary to predisposing mitochondrial DNA sequence variants.[8,10,11] Maternal inheritance is suggestive of mitochondrial DNA involvement because mitochondrial DNA is asexually inherited from the ova only, without recombination. Recently, we reported in a series of 80 subjects with cyclic vomiting syndrome randomly ascertained from a disease association database that maternal inheritance is equally prevalent in cases with and without neuromuscular disease, suggesting that cyclic vomiting syndrome in general is related to the mitochondrial DNA sequence and, hence, to energy metabolism.[9] This raises the following question: Is cyclic vomiting syndrome plus a distinct entity either clinically or genetically, or is neuromuscular disease simply another potential phenotype secondary to the mitochondrial dysfunction that is related to cyclic vomiting syndrome? To address this question, we performed further analysis on the clinical data from the 80 subjects with cyclic vomiting syndrome in the earlier study.[9]

METHODS

All subjects were recruited randomly based on the last two numbers of the US ZIP code or Canadian postal code from the database of the Cyclic Vomiting Syndrome Association USA/Canada, a parent-led organization dedicated toward family support, education, and research on cyclic vomiting syndrome. The clinical questionnaire was administered, in general, to both parents or directly to cognitively normal adult subjects.[9] Inheritance patterns in the study data were published separately,[9] and further details on subject ascertainment can be found therein.

Subjects were labeled as having cyclic vomiting syndrome with neuromuscular disease (cyclic vomiting syndrome plus) if at least two of the following list of "hard" neuromuscular disease manifestations were present: skeletal myopathy, cranial nerve abnormality, ataxia, seizure disorder, cardiomyopathy, mental retardation, attention-deficit hyperactivity disorder (ADHD), microcephaly, autism, or pervasive developmental disorder (Table 1) (some terms are defined in Boles et al[8]). Individuals with none of these neuromuscular disease manifestations were labeled as having cyclic vomiting syndrome without neuromuscular disease ("cyclic vomiting syndrome minus"). Subjects in which exactly one neuromuscular disease manifestation is present were not grouped but were pooled with the cyclic vomiting syndrome plus and cyclic vomiting syndrome minus groups for statistics involving all subjects. Learning disabilities, Asperger syndrome, affective and anxiety disorders, and dysautonomia-related conditions were not included in our "hard" neuromuscular disease manifestation list because of the uncertainty of obtaining and verifying the proper diagnosis in the context of our methods and the established association between cyclic vomiting syndrome and dysautonomia. Peripheral neuropathy and cardiac arrhythmia were removed from the list because it appeared on careful evaluation that, in many cases, the symptoms attributed toward these conditions were, in fact, likely secondary to an undiagnosed dysautonomia.

Migraine headaches and colonic dysmotility were recorded as previous reported.[8,9] A neurovascular dystrophy–like condition (herein called "neurovascular disease") was recorded for repetitive episodes of focal, tran-

Table 2. Parameters of Vomiting Episodes

Episode Parameter	*All Cases*	*CVS+ Group*	*CVS– Group*	*P CVS+ vs CVS–*
Median age at onset of cyclic vomiting episodes*	5 yr	4 yr	7 yr	.003
Median interval between start of sequential episodes†	1 mo	1 mo	1 mo	NS
Median duration of episodes‡	2–3 d	2–3 d	2–3 d	NS

CVS+ = cyclic vomiting syndrome plus; CVS– = cyclic vomiting syndrome minus; NS = not significant (where unspecified, $P > .1$).
*Chronic vomiting, often attributed by the family to gastroesophageal reflux, preceded the onset of cyclic episodes of vomiting in 25 subjects (31%), with a median interval of 2 years (range 0.5–15 years).
†The time interval between the start of sequential episodes was between 2 weeks and 2 months in 74% of cases, with no group differences.
‡The duration of episodes varied substantially among subjects, with 70% of subjects having their episodes usually lasting between 12 hours and 1 week, with equal proportions on either extreme. No group differences were found.

sient, and (generally) asymmetric findings of pain, cramping, color change, apparent temperature change, swelling, and/or functional disability, generally in the distal extremities. Gastroesophageal reflux disease was recorded only if treated by a physician for at least several months.

Among the 80 subjects, female subjects outnumbered male subjects by 53 to 27 (2:1). All subjects report being Caucasian, with one being of Hispanic ethnicity. Children (age < 18 years) comprised 62% of the subjects at the time of the interview, although 80% of the subjects were children at the onset of cyclic episodes of vomiting.

This study was approved by the Childrens Hospital Los Angeles Institutional Review Board, and written informed consent was obtained from all subjects or parents. Statistics were performed by *WinSTAT Statistics for Windows* (Kalmia Co. Inc., Cambridge, MA) using independent Student's *t*-test, chi-square, or Fisher exact test, as appropriate. Statistical significance was set at $P < .05$, and a Bonferroni adjustment for multiple tests was performed when appropriate.

RESULTS

Cyclic Vomiting Syndrome Plus Versus Cyclic Vomiting Syndrome Minus Assignment

Twenty-three subjects (29%) reported at least two neuromuscular disease manifestations and thus were labeled as "cyclic vomiting syndrome plus." Forty-four subjects (55%) reported no neuromuscular disease manifestations and thus were labeled as "cyclic vomiting syndrome minus." The 13 subjects with exactly one neuromuscular disease manifestation, most of whom reported ADHD (5 cases), seizure disorders, or skeletal myopathy (3 cases each), were not subgrouped.

Cyclic Vomiting Syndrome Parameters and Treatment in Our Subjects

The interval between episodes and the duration of episodes did not significantly vary between the cyclic vomiting syndrome plus and cyclic vomiting syndrome minus groups (Table 2). However, the median age at onset of cyclic vomiting episodes was significantly earlier in the cyclic vomiting syndrome plus than in the cyclic vomiting syndrome minus group (4 vs 7 years; see Table 2). Consistent with this observation, subjects with cyclic vomiting syndrome with neuromuscular disease were far less likely than subjects with cyclic vomiting syndrome without neuromuscular disease to have the adult onset (≥ 18 years) of cyclic vomiting (4% vs 29%; $P = .02$). In the converse, subjects with adult-onset cyclic vomiting were far less likely than subjects with childhood-onset cyclic vomiting to be labeled as cyclic vomiting syndrome plus (1 of 17 = 6% vs 20 of 55 cases = 36%; $P = .01$).

We defined episodes by the presence of vomiting. Preictal (prodromic) and intraictal symptoms recorded did not vary signif-

Table 3. Prodromic and Intraictal Symptoms Noted Among Our Cases

Symptom	*Number (%) in All 80 Cases*	*Number (%) in 23 CVS+ Cases*	*Number (%) in 44 CVS– Cases*
Prodromic			
Altered mentation: lethargy, irritability	24 (30)	8 (35)	13 (30)
Gastrointestinal: abdominal pain, diarrhea	24 (30)	4 (17)	14 (32)
Altered secretions: tearing, drooling	13 (16)	5 (22)	5 (11)
Headache*	12 (15)	4 (17)	4 (9)
Pallor	4 (5)	3 (13)	1 (2)
Any prodromic sign/symptom	57 (71)	18 (78)	31 (70)
Intraictal			
Vomiting	80 (100)	23 (100)	44 (100)
Nausea*	76 (95)	22 (95)	41 (93)
Lethargy	76 (95)	23 (100)	40 (91)
Photophobia†	66 (82)	15 (65)	38 (86)
Abdominal pain	54 (68)	18 (78)	29 (66)
Irritability	45 (56)	15 (65)	23 (52)
Headache*	38 (48)	12 (52)	20 (45)
Altered secretion	38 (48)	12 (52)	22 (50)
Pallor	23 (29)	5 (22)	13 (30)
Diarrhea	17 (21)	4 (18)	10 (23)

CVS+ = cyclic vomiting syndrome plus; CVS– = cyclic vomiting syndrome minus.
*Likely underrecognized in mentally retarded individuals.
†$P = .046$ yet not significant with a Bonferroni adjustment for multiple tests.
Otherwise, $P > .1$ for all cyclic vomiting syndrome plus versus cyclic vomiting plus syndrome minus group comparisons.

Table 4. Treatments Most Frequently Attempted in Our Subjects

Treatment	*All Subjects,* n *(%)*	*CVS+ Group,* n *(%)*	*CVS– Group,* n *(%)*
Prophylactic			
Amitriptyline (Elavil)	16/15/5 (52)	5/2/2 (71)	9/9/3 (50)
Cyproheptadine (Periactin)	11/7/3 (61)	5/1/2 (83)	2/5/1 (29)
Propranolol (Inderal)	5/10/0 (33)	1/3/0 (25)	4/5/0 (44)
Abortive or symptomatic (intraictal)			
Intravenous dextrose–containing fluids	21/3/0 (88)	7/0/0 (100)	11/1/0 (92)
Ondansetron (Zofran)	42/10/2 (81)	12/4/0 (75)	23/4/2 (85)
Lorazepam (Ativan)	23/7/2 (77)	5/3/2 (62)	14/2/0 (88)
Promethazine hydrochloride (Phenergan)	13/10/0 (57)	5/4/0 (56)	6/6/0 (50)
Sumatriptan succinate (Imitrex)	8/0/1 (100)	2/0/0 (100)	3/0/1 (100)

CVS+ = cyclic vomiting syndrome plus; CVS– = cyclic vomiting syndrome minus.
Data recorded as x/y/z (%) where x = the number of subjects treated reported to have significant benefit, y = the number of subjects treated with insignificant or no benefit, and z = the number of subjects whose side effects were considered troublesome by the family and/or physician; % is the percentage of subjects tried on the medication reporting a significant benefit (excluding cases discontinued early because of side effects, in which efficacy data is not known). Both response data (positive or negative) and a side effect were reported in some subjects. Specific side effects reported were (in a single subject each unless otherwise specified) as follows: amitriptyline: lethargy (2 subjects), mood swings, abdominal cramping, and syncope; cyproheptadine: weight gain (2), behavioral change, and hallucinations; ondansetron: palpitations and allergy; lorazepam: "untoward reaction" (2); and sumatriptan succinate: hallucinations. $P > .1$ (not significant) for all subject group comparisons, except for cyproheptadine, whereas $P = .048$ for cyclic vomiting syndrome plus versus cyclic vomiting syndrome minus yet was not significant with a Bonferroni adjustment for multiple tests.

icantly between the groups (Table 3), except that photophobia was mildly less common in the cyclic vomiting syndrome plus than in the cyclic vomiting syndrome minus group. Treatment attempts with 61 different chemical agents were recorded, 54 of which were considered to be efficacious by at least one family. Table 4 lists the most frequent agents recorded. The numbers of subjects in each of the subgroups reported on each medication are small, and no significant intergroup differences were noted, except for cyproheptadine, which is possibly more efficacious in the cyclic vomiting syndrome plus group than the cyclic vomiting syndrome minus group (see Table 4).

Neuromuscular Disease Manifestations in Our Cyclic Vomiting Syndrome Plus Subjects

The specific neuromuscular disease manifestations reported among our subjects with cyclic vomiting syndrome with neuromuscular disease are listed in Table 1. The four main neuromuscular disease manifestation categories, cognitive disorders, skeletal myopathies, cranial nerve abnormalities, and seizure disorders, were found to cluster together among the subjects, as shown in Table 5.

Nonvomiting Clinical Manifestations in Our Subjects

The clinical manifestations (both neuromuscular disease and otherwise) reported most often (in ≥ 15 subjects) among all 80 subjects were, in descending order, gastroesophageal reflux disease, colonic dysmotility, migraine, chronic fatigue, skeletal myopathy, and neurovascular disease (Tables 1 and 6). Except for skeletal myopathy, each of these conditions is compatible with a dysautonomia (see Discussion). Additional dysautonomic symptoms seen in less than 15 subjects include palpitations or tachycardia and abnormal temperature regulation (see Table 6). Altogether, 57 subjects (71%) reported at least one of these "dysautonomia-related" manifestations. When broken down by subject group, colonic dysmotility, migraine, chronic fatigue, and neurovascular disease were individually nearly two- to eightfold more common in the cyclic vomiting syndrome plus versus the cyclic vomiting syndrome minus group ($P \leq .01$, except for colonic dysmotility; see Table 6). Gastroesophageal reflux disease was reported in about equal proportions between the groups, whereas for palpitations or tachycardia and abnormal temperature regulation, the numbers were too small for meaningful comparison.

Other conditions found in between 2 and 15 subjects include learning disabilities, affective or anxiety disorders, growth retardation, birth defects, and endocrine disorders (see Table 6). Except for the latter, the incidence for each was found to be at least twofold higher in the cyclic vomiting syndrome plus group versus the cyclic vomiting syndrome minus group, although the numbers are small and statistical significance was achieved only with growth retardation and birth defects (see Table 6).

Segregation of Neuromuscular Disease Within Families

As reported elsewhere regarding this same subject population,[9] despite the high degree of maternal inheritance for dysautonomic manifestations reported in both the cyclic vomiting syndrome plus and cyclic vomiting syndrome minus subject groups, neuromuscular disease manifestations were almost never recorded among the adult relatives of subjects, yet they are common among the (predominantly pediatric) siblings of subjects. Interestingly, our subjects with cyclic vomiting syndrome with neuromuscular disease were no more likely than subjects with cyclic vomiting syndrome without neuromuscular disease to have siblings affected by one or more neuromuscular disease manifestations (5 of 23 = 22% vs 7 of 42 = 17%; P = not significant) or two or more neuromuscular disease manifestations (9% vs 10%; P = not significant).

DISCUSSION

Our data demonstrate that multiple neuromuscular disease manifestations cluster together in our subject population, including cognitive disorders, skeletal myopathy, cranial nerve abnormalities, and seizure disorders (see Tables 1 and 5). This association appears to be strongest for cognitive disorders versus our other three major categories. Given that the vast majority (87%) of our cyclic vomiting syndrome plus cases versus only 9% of all other cases have a cognitive disorder, perhaps the cyclic vomiting syndrome population can be divided into subgroups based on the presence or absence of this parameter alone.

As we have previously discussed,[8] the most common conditions reported among our subjects and their affected matrilineal relatives are clinical conditions compatible with abnormal autonomic nervous system function (dysautonomia).[9] These same conditions are often found in patients with familial dysautonomia (Riley-Day syndrome)[12] and include gastroesophageal reflux disease, colonic dysmotility, migraine, chronic fatigue, neurovascular disease, palpitations or tachycardia, and abnormal temperature regulation. Our present data demonstrate that many of these conditions also cluster together in the cyclic vomiting syndrome plus group, achieving statistical significance for migraine headaches, chronic fatigue, and neurovascular disease (see Table 6). Seventy-one percent of our subjects have a dysautonomia-related clinical manifestation based on the presence of one or more of these conditions. However, this figure is likely an underestimate because, in the clinical practice of the first author, several patients previously labeled with "seizure disorders" and "hypoglycemia" on further investigation had a normal ictal electroencephalogram and glucose values and appear to have dysautonomic attacks similar to those seen in familial dysautonomia. Furthermore, many patients previously labeled with "peripheral neuropathy" actually meet our criteria for neurovascular disease, and many patients labeled with "panic" or "anxiety" disorders prove to have supraventricular or other tachycardias. If cyclic vomiting syndrome is included in this list, because it is also a "dysautonomia-associated condition,"[6, 7] of course, all of our subjects suffer from dysautonomia.

In addition to the clustering of neuromuscular disease and dysautonomia-related manifestations among the 29% of our subjects with cyclic vomiting syndrome labeled as cyclic vomiting syndrome plus, these same subjects demonstrate a fivefold higher prevalence of both birth defects and growth retardation versus subjects with cyclic vomiting syndrome without neuromuscular disease (see Table 6). All of these cyclic vomiting syndrome plus–associated disease manifestations have been reported in individuals with documented mitochondrial disorders. The consistent phenotype, along with the presence of lactic acidosis, energy-depleted patterns on urine organic acids, abnormal muscle biopsy data, and maternal inheritance in most cases of cyclic vomiting syndrome plus,[8,11] as well as mitochondrial DNA mutations in some,[10,13,14] strongly suggests that cyclic vomiting syndrome plus is a mitochondriopathy.

We initially hypothesized that only cyclic vomiting syndrome plus cases are mitochondrially related. However, on further study, we demonstrated that cyclic vomiting syndrome plus or cyclic vomiting syndrome minus status is associated neither with the proportion of cases that demonstrate maternal inheritance (both cyclic vomiting syndrome plus and cyclic vomiting syndrome minus demonstrated maternal inheritance in just over 50% of the cases[9]) nor with the prevalence of disease-associated mitochondrial DNA control region sequence variants (which were found equally among one third of our present subjects with and without cyclic vomiting syndrome[14]; and data not shown). We concluded that mitochondrial DNA sequence–related mitochondrial dysfunction is a risk factor for disease development in cyclic vomiting syndrome in general, whether or not neuromuscular disease manifestations are present.[9] Furthermore, it is evident that these mitochondrial DNA sequence variants are associated with far milder phenotypes than present in our subject population because pedigrees of children with cyclic vomiting syndrome with and without neuromuscular disease frequently demonstrate a very wide degree of phenotypic variability among the matrilineal relatives. This variability includes individuals with multiple disease manifestations of highly probable mitochondrial etiology, individuals

Table 5. Clustering of Neuromuscular Disease Manifestations Among Our 80 Subjects

	*Cognitive Disorder**	*Skeletal Myopathy**	*Cranial Nerve Abnormality**	*Seizure Disorders**
Cognitive disorder*	—	12/25 (48%) with, 4/55 (7%) without; $P = .00002$	9/25 (36%) with, 5/55 (9%) without; $P = .006$	7/25 (28%) with, 3/55 (5%) without; $P = .009$
Skeletal myopathy*	12/16 (75%) with, 13/64 (20%) without; $P = .00002$	—	7/16 (44%) with, 7/64 (11%) without; $P = .002$	5/16 (31%) with, 5/64 (8%) without; $P = .01$
Cranial nerve abnormality*	9/14 (64%) with, 16/66 (24%) without; $P = .006$	7/14 (50%) with, 9/66 (14%) without; $P = .002$	—	4/14 (29%) with, 6/66 (9%) without; $P = .045$
Seizure disorders*	7/10 (70%) with, 18/70 (26%) without; $P = .009$	5/10 (50%) with, 11/70 (16%) without; $P = .01$	4/10 (40%) with, 10/70 (14%) without; $P = .045$	—

*As defined in Table 1.
For example, in column 2, row 3, 12 of 16 subjects with a skeletal myopathy have a coexisting cognitive disorder versus 13 of 64 subjects without a skeletal myopathy.

Table 6. Non-Neuromuscular Disease Manifestations Seen in at Least Two of Our Subjects

Condition	*All Subjects,* n *(%)*	*CVS+ Group,* n *(%)*	*CVS– Group,* n *(%)*	P *CVS+ vs CVS–*
Gastroesophageal reflux*	33 (41)	10 (43)	17 (39)	NS
Colonic dysmotility*†	21 (26)	9 (39)	9 (20)	NS
Migraine*	19 (24)	10 (43)	7 (16)	.01
Chronic fatigue*	16 (20)	11 (48)	4 (9)	< .001
Neurovascular disease*	15 (19)	9 (39)	2 (5)	< .001
Affective/anxiety disorders‡	14 (18)	6 (26)	5 (11)	NS
Learning disabilities	12 (15)	5 (22)	4 (9)	NS
Birth defects	12 (15)	8 (35)	3 (7)	.005
Endocrine disorder (any)	10 (12)	3 (13)	5 (11)	NS
Growth retardation (height or weight < 5th percentile)	10 (12)	6 (26)	2 (5)	.02
Palpitations/tachycardia*	8 (10)	3 (13)	2 (5)	NS
Abnormal temperature regulation*	6 (8)	2 (9)	3 (7)	NS
Any dysautonomia-associated condition§	57 (71)	22 (96)	26 (59)	.01

NS = not significant (for all cases in this table: $P > .1$).
†Most meet the criteria for irritable bowel syndrome.
‡Affective and anxiety disorders were difficult to distinguish using our methods and were lumped together, although the large majority of cases report depression, either unipolar or bipolar.
*A dysautonomic-associated condition.
§The presence of at least one condition marked with an asterisk (*).

with lesser degrees of clinical manifestations (eg, migraine, colonic dysmotility, chronic fatigue) that might be in part attributable to mitochondrial dysfunction, and individuals who are asymptomatic,[8,11] yet all of these individuals presumably carry the same mitochondrial DNA sequence. Although our data demonstrate that the mitochondrial DNA sequence confers an increased predisposition for the development of several different clinical conditions, including cyclic vomiting syndrome plus or cyclic vomiting syndrome minus,[9] some individuals carrying the same sequences are disease free; thus, other factors must also influence disease development.

Although it is tempting to assert that the factor responsible for these broad phenotypic differences is varying degrees of heteroplasmy (referring to a mixture of mutant and wild-type mitochondrial DNA in the same sample) for a mitochondrial DNA mutation, heteroplasmy was absent in all but one of our present cases on assaying 90% of the mitochondrial DNA by temporal temperature gradient gel electrophoresis.[14] However, we have not ruled out the possibility of mitochondrial DNA heteroplasmy in target tissues, such as autonomic or brainstem neurons, which is absent in the tissues that we assayed, blood and hair root. Marked phenotypic variability is also a common finding in families segregating homoplasmic (only one mitochondrial DNA sequence present) mitochondrial DNA mutations, such as those resulting in Leber hereditary optic neuropathy, whereas nuclear-modifying genes are postulated to operate.[15] Environmental conditions might also be at least partially responsible.

We conclude that although the mitochondrial DNA sequence is a major risk factor for mitochondrial dysfunction–related disease, including cyclic vomiting syndrome plus and cyclic vomiting syndrome minus,[9] additional factors operate to determine the degree of mitochondrial function and, hence, to affect the clinical phenotype in each individual. We propose that those individuals on the most severe end of the spectrum, labeled as cyclic vomiting syndrome plus, have the highest degree of mitochondrial dysfunction and thus are at higher risk of developing neuromuscular disease manifestations, dysautonomia, growth retardation, and birth defects, as well as to manifest an earlier age at onset for vomiting episodes. Although patients with cyclic vomiting syndrome with and without neuromuscular disease demonstrate mitochondrial dysfunction based on body fluid metabolite excretion analyses, our clinical observations indicate a potential difference in degree because patients with cyclic vomiting syndrome with neuromuscular disease generally demonstrate lactic acidosis, whereas patients with cyclic vomiting syndrome without neuromuscular disease generally demonstrate normal blood lactate values (unpublished data).[11] We are attempting to validate our hypothesis by demonstrating intermediate levels of mitochondrial dysfunction by functional assays in children with cyclic vomiting syndrome without neuromuscular disease compared with children with cyclic vomiting syndrome with neuromuscular disease and control children in continued studies.

Interestingly, our data demonstrate that the presence (cyclic vomiting syndrome plus) or absence (cyclic vomiting syndrome minus) of neuromuscular disease manifestations in the proband does not predict the presence or absence of neuromuscular disease manifestations in affected siblings. This suggests that cyclic vomiting syndrome plus and cyclic vomiting syndrome minus are not genetically distinct in terms of the primary genetic, mitochondrial DNA sequence–mediated factor. In addition, we have seen both cyclic vomiting syndrome plus and cyclic vomiting syndrome minus within the same matrilineages among families outside this study, which provides further support for this conclusion.

The greater degree of severity in terms of the age at onset of cyclic vomiting episodes and the frequency of comorbid conditions in cases with cyclic vomiting syndrome with neuromuscular disease versus cases without neuromuscular disease does not translate into a greater degree of severity in terms of the frequency, duration, or response to pharmacologic therapy for vomiting episodes. Among prophylactic therapies, the “antimigraine” medications amitriptyline, cyproheptadine, and propranolol were the most widely prescribed in our study and demonstrated fair to good efficacy (33–61%) overall. Cyproheptadine was statistically more efficacious in the cyclic vomiting syndrome plus subgroup, but this is likely related to the younger age of the subjects in that subgroup (the age at time of treatment was not recorded, but the median age at onset of vomiting episodes was 2.8 years in responders versus 9.6 years in nonresponders; $P = .15$), and empiric observation suggests that cyproheptadine might have a higher efficacy in cyclic vomiting syndrome among younger children. The most widely prescribed agents for intraictal symptomatic relief were

ondansetron, lorazepam (given for sedation), intravenous dextrose–containing fluids, and promethazine hydrochloride, all of which were reported to be highly efficacious (57–88%). Our anecdotal methods and the small numbers reported on each agent do not allow for a careful evaluation of the efficacy of various treatment modalities, especially any comparison between our subject groups or between therapeutic agents. However, in general, the present data and our own clinical experience support current recommendations on the treatment of cyclic vomiting syndrome,[16,17] whether or not neuromuscular disease manifestations are present. To these recommendations, based on the frequent occurrence of fasting intolerance in patients with mitochondrial disorders[18] and our clinical experience regarding the frequent occurrence of fasting intolerance in patients with cyclic vomiting syndrome with or without neuromuscular disease, we add frequent feedings as part of prophylaxis and the early use of 10% intravenous dextrose–containing fluids (instead of the standard 5%) at 1.5 times the maintenance rate during vomiting episodes requiring medical treatment. During vomiting episodes, our clinical experience has shown that the presence of ketosis as detectable by standard urine dipsticks and an elevation in the serum anion gap are both powerful tools for the determination of the presence of "metabolic decompensation" and the probable need for intravenous dextrose–containing fluids.

Although two population-based studies in Caucasians demonstrated remarkably similar incidences of cyclic vomiting syndrome of as high as 2% of all school-aged children,[19,20] many of the cases they report are milder than the typical child presenting for specialty care, as well as most of those who contact the Cyclic Vomiting Syndrome Association and are entered into their registry and, hence, recruited into the present study. Our present subject group is similar to the population of children with cyclic vomiting syndrome referred for specialty care. In particular, our cases with cyclic vomiting syndrome with neuromuscular disease, for the most part, represent the typical child with cyclic vomiting syndrome with neuromuscular disease seen in a neurology or genetics tertiary care setting in which an inborn error of metabolism or mitochondrial disorder is frequently suspected. In addition, our cyclic vomiting syndrome minus cases, for the most part, represent the typical child or adult with cyclic vomiting syndrome seen in a gastroenterology office setting: an otherwise healthy, intellectually normal individual in whom cyclic vomiting dominates the clinical presentation. Although 29% of our cyclic vomiting syndrome population is labeled as cyclic vomiting syndrome plus, we suspect that this proportion would be lower in a less biased, non–registry-based population. Our data do not address whether our findings can be generalized to the larger group of individuals with milder presentations of cyclic vomiting syndrome who either do not seek medical care or who are cared for exclusively by community practitioners.

In conclusion, our data support our clinical observations that the presence of neuromuscular or cognitive disease manifestations (cyclic vomiting syndrome plus) in a child with cyclic vomiting syndrome apparently represents a clinically distinct phenotype that is associated with both a younger age at onset of vomiting episodes and a high likelihood that the same individual also suffers, or will suffer at some point, from among a specific group of additional neuromuscular-cognitive, dysautonomic and constitutional ailments. This has clinical implications in terms of anticipatory guidance, medical surveillance, developmental testing, and genetic counseling for these children. Vomiting episodes respond in most cases to a combined antimigraine and antimitochondrial dysfunction treatment approach, without obvious differences between cyclic vomiting syndrome plus and cyclic vomiting syndrome minus cases. We hypothesize that cyclic vomiting syndrome plus represents those cyclic vomiting syndrome cases with relatively greater degrees of mitochondrial dysfunction.

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