How are cyclic vomiting syndrome, depression, autism, migraine, chronic pain and more related to mitochondrial function?

MitoAction 3-December, 2010

Richard G. Boles, M.D.
Medical Genetics
Childrens Hospital Los Angeles
Associate Professor of Pediatrics
Keck School of Medicine at USC
Potential Conflict of Interest

- CHLA and Dr. Boles have filed a PCT (international patent application) on molecular diagnostics of the mtDNA polymorphisms that will be presented.
Case Report - Zachary
Zachary – Clinical

- Autism – early infancy, dx at age 2 years
  - Lost early language skills acquired at 18 mos.
- Diagnosed with “autism” at age 2 yrs
- Cyclic vomiting syndrome – age 6 yrs
  - episodes of nausea, vomiting and lethargy lasting from a few days to a week or more
- Rhabdomyolysis – age 11 years
  - Hospitalized twice, max CK = 100K; precipitated by anesthesia (dental) and influenza B
- Complex regional pain syndrome – age 12 yrs
  - episodes in which right foot becomes cold, purple, tender, allodynia, unable to bear wt, wheelchair bound for months
- Other chronic intermittent symptoms
  - headache, muscle pain, constipation, photophobia, ptosis, tics, hours-long episodes of hiccups.
- Tanner I at age 15 years
- Severe exercise intolerance
- Nijmegen criteria: 10 pts c/w definite mitochondrial disorder
Complex Regional Pain Syndrome-I: allodynia, painful, edematous, cold, purple, unable to stand or walk
Zachary - Medications

- Methadone 15 mg q four to six hours
- MiraLax one capful twice a day
- Amitriptyline 75 mg per day
- Propranolol 10 mg BID
- Co-enzyme Q10 gel capsules 200 mg TID
- L-carnitor 3 tablets (330 mg each) BID
- B100 once per day
- Vitamin C 500 mg once per day

On mito-cocktail:

- no vomiting episodes, or rhabdomyolysis
- able to walk, including moderate distances
- improved expressive speech
- fewer temper tantrums
Somatic Complaints:
pain, cramping, itching, tingling, urgency, fatigue
*It’s What’s Bothering You*

- Are the leading cause of outpatient medical visits.
- Are the leading cause why patients with common mental disorders such as depression initially present to primary care.
- Are medically unexplained in at least one-third of patients.
“Functional” Disorders List:

- Anxiety disorder
- Autistic spectrum disorders
- Chronic fatigue syndrome
- Complex regional pain syndrome
- Cyclic vomiting syndrome
- Major depressive disorder
- Fibromyalgia
- Functional abdominal pain
- Ketotic hypoglycemia
- Interstitial cystitis
- Irritable bowel syndrome
- Migraine
- Post-traumatic stress disorder
- Restless legs syndrome
- Tinnitus

A population prevalence of 10-15% has been reported.
High Levels of Co-morbidity Among the Functional Disorders

- Migraine and Depression
  - Migraine: 5.8–fold higher risk for depression
  - Depression: 3.4–fold higher risk for migraine

- Migraine and Restless Leg Syndrome
  - 82% of restless legs syndrome patients have migraine.

- Migraine and Chronic Fatigue Syndrome
  - 67% of chronic migraine patients fulfilled the 1994 CDC criteria for CFS.

- Chronic Fatigue Syndrome and Fibromyalgia
  - Most patients have chronic pain, and several sources consider CFS and fibromyalgia to be the same condition.

- Irritable Bowel Syndrome and Fibromyalgia
  - 30% to 70% of fibromyalgia patients have IBS.
Functional Disorders

- Genetic components
- High degree of co-morbidity in individuals
- High degree of co-morbidity in families
- Respond to the same medications
Functional Disorders

- Genetic components
- High degree of co-morbidity in individuals
- High degree of co-morbidity in families
- Respond to the same medications

Could some of the genetic component for these conditions be shared?
The functional symptoms elephant

depression
migraine
fibromyalgia
restless legs syndrome
interstitial cystitis
irritable bowel syndrome
functional abdominal pain
cyclic vomiting
complex regional pain syndrome
tinnitus
depression
migraine
fibromyalgia
restless legs syndrome
interstitial cystitis
irritable bowel syndrome
functional abdominal pain
cyclic vomiting
complex regional pain syndrome
tinnitus

The elephant is lying down due to chronic fatigue
Maternal Inheritance of Functional Disorders

Cancer

Colitis

Seizures, CVS, Migraine, Bipolar, Anxiety

GERD, Migraine, Depression, Seizures, Hearing loss

Bipolar, Migraine

Dyslexia

CVS, Migraine

Seizures

Migraine

Muscle weakness

Hypoglycemia

Abdominal migraine

Ptosis

Reyes syndrome

Failure to thrive

GERD, Migraine, Depression, Seizures, Hypoglycemia
Maternal Inheritance of Functional Disorders

- Migraine
- Dysmotility
- Optic retinopathy
- Hypothyroidism
- Chronic fatigue
- Muscle weakness
- Bipolar
- Hypoglycemia
- Seizure
- Hypothermia
- Chronic fatigue
- Body tremors
- Cold hands
- CRPS
- Migraine
- Lethargy
- Profuse sweating
- Double vision
- Dysmotility
- Seizure
- Hyperventilation
- Depression
- Cognitive delay
- Delayed Gastric emptying
- Respiratory problems
- Migraine
- Glaucoma
- SAB
- Depression
Maternal Inheritance of Functional Disorders

- Migraine
- Asthma
- CRPS
- CVS
- Dysmotility
- Near SIDS
- Frequent fevers
- Migraine
- Asthma
- CVS
- CRPS
- Dysmotility
- Apnea
- Decreased tearing
- Muscle cramps
- Vital sign changes
- Lethargy
- Developmental delay
- Abdominal pain
- SIDS
- SIDS
- ADHD
- Abdominal pain
Maternal Inheritance of Functional Disorders

- Migraine
- Partial paralysis
- Retinal disease
- Speech articulation deficits
- Psychosis
- Thyroid disease
- Seizures
- Colitis
- Malignancy
- CRPS
- Muscle cramps
- Migraine
- Syncope/Dizziness
- Temperature instability
- Depression
- Panic attacks
- Fatigue/Exercise Intolerance
- Nausea/vomiting
- Hypotonia
- Speech articulation deficits
Maternal Inheritance of Functional Disorders

AUTISM
Migraine
Cyclic vomiting S.
Complex regional pain syndrome
Rhabdomyolysis
Photophobia
Chronic fatigue S.

Learning disability
Sensory integration
Calf tumor

GI disease
Renal Failure
Diabetes

Migraine
Myalgia
Chronic fatigue S.
Vomiting
GERD
Exercise intolerance
Fasting intolerance
Insomnia

Behavior issues
Migraine
Fasting intolerance

Migraine
Depression
Chronic pain
Muscle weakness
Chronic diarrhea

Seizures
Migraine
Depression
Exercise intolerance

Mental retardation
Sensory integration
Seizure (fatal)

Mitral valve prolapse

Panic disorder
Depression
Anxiety disorder
GI disorder
Chronic pain
Exercise intolerance
Fasting intolerance

Bloating
Prematurity

Bloating
Prematurity

Migraine
Depression
Irritable bowel

Seizures
Mitral valve prolapse

Chronic fatigue S.

Vomiting
GERD
Exercise intolerance

Fasting intolerance

Insomnia

ADD
Depression
Anxiety disorder

Learning disability

Syndrome with Developmental delay, and Seizures
Quantitative Pedigree Analysis for Maternal Inheritance

Matrilineage: 21 neurological/endocrine conditions in 7 first and second degree relatives = 3 conditions/relative
Control: 3 neurological/endocrine conditions in 9 first and second degree relatives = 0.33 conditions/relative
3/0.33 = a *Maternal Inheritance Ratio of 9.0*
Quantitative Pedigree Analysis
Positive and Negative Controls
Quantitative Pedigree Analysis
Cyclic Vomiting Syndrome
**Functional Disease**

Could maternally inherited mtDNA sequences be the shared genetic component? Lee et al., Submitted

<table>
<thead>
<tr>
<th></th>
<th>CFS</th>
<th>Migraine</th>
<th>IBS</th>
<th>Depression</th>
<th>CVS</th>
<th>CRPS-I</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>76%</td>
<td>72%</td>
<td>52%</td>
<td>48%</td>
<td>36%</td>
<td>60%</td>
</tr>
<tr>
<td>Control Group</td>
<td>2/102</td>
<td>15/103</td>
<td>9/101</td>
<td>13/101</td>
<td>2/103</td>
<td>7/101</td>
</tr>
<tr>
<td></td>
<td>2%</td>
<td>15%</td>
<td>9%</td>
<td>13%</td>
<td>2%</td>
<td>7%</td>
</tr>
<tr>
<td>Odds Ratio (95% C.I.)</td>
<td>120</td>
<td>14</td>
<td>11</td>
<td>6.1</td>
<td>23</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>23-640</td>
<td>5-40</td>
<td>4-30</td>
<td>2.3-16</td>
<td>5-120</td>
<td>6-36</td>
</tr>
</tbody>
</table>

Mitochondrial Group: 18 mothers and 7 maternal aunts of children with maternally inherited mitochondrial disorders.
Control Group: 5 paternal aunts and 5 aunts-in-law of the same children above, 18 mothers of children with autosomal recessive metabolic disorders, and 75 mothers of high school students.
Cyclic Vomiting Syndrome (CVS)

Definition:

- 1. Recurrent, identical episodes of nausea, vomiting and lethargy
- 2. Absence of these symptoms between episodes
- 3. Lack of a causal diagnosis following a work-up (except migraine)
Chromatograms from 16 3.21.07
Sequencer(tm) "3.21.07.SPF"

- 77-16.trimmed Fragment base #16,519. Base 100 of 139 -

- 66-16.trimmed Fragment base #16,519. Base 100 of 139 -

- 70-16.trimmed Fragment base #16,519. Base 98 of 136 -

- 73-16.trimmed Fragment base #16,519. Base 98 of 137 -

Thursday, September 13, 2007
Functional Disorder-Associated mtDNA Polymorphisms

16519 C>T
mtDNA control region

3010 G>A
16S-ribosomal RNA gene
## Cyclic Vomiting, Migraine & Chronic Fatigue

**Prevalence of Two mtDNA Common Polymorphisms in Haplogroup H Individuals With Functional Disorders**

<table>
<thead>
<tr>
<th></th>
<th>Cyclic Vomit Syndr.</th>
<th>Odds Ratio (95% C.I.)</th>
<th>Migraine w/o Aura</th>
<th>Odds Ratio (95% C.I.)</th>
<th>Chronic Fatigue Syndr.</th>
<th>Odds Ratio (95% C.I.)</th>
<th>Ctrl</th>
</tr>
</thead>
<tbody>
<tr>
<td>16519T</td>
<td>21/30</td>
<td>6.2 (2.7-14)</td>
<td>58/112</td>
<td>3.6 (2.2-5.9)</td>
<td>22/58</td>
<td>2.0 (1.1-3.7)</td>
<td>63/231</td>
</tr>
<tr>
<td></td>
<td>70%</td>
<td></td>
<td>52%</td>
<td></td>
<td>38%</td>
<td></td>
<td>27%</td>
</tr>
<tr>
<td>3010A</td>
<td>9/30</td>
<td>N/A</td>
<td>37/112</td>
<td>N/A</td>
<td>Pending</td>
<td>Pending</td>
<td>143/444</td>
</tr>
<tr>
<td></td>
<td>30%</td>
<td></td>
<td>33%</td>
<td></td>
<td></td>
<td></td>
<td>32%</td>
</tr>
<tr>
<td>3010A among pts with 16519T</td>
<td>6/24</td>
<td>17 (2-156)</td>
<td>15/58</td>
<td>15 (1.9-117)</td>
<td>Pending</td>
<td>Pending</td>
<td>1/63</td>
</tr>
<tr>
<td></td>
<td>29%</td>
<td></td>
<td>26%</td>
<td></td>
<td></td>
<td></td>
<td>1.6%</td>
</tr>
</tbody>
</table>
### Chronic Fatigue Syndrome

The 3010A mtDNA polymorphism predicts a several-fold increase in somatic symptoms.

<table>
<thead>
<tr>
<th></th>
<th>Headache</th>
<th>Fainting or Dizziness</th>
<th>Muscle Pain</th>
<th>Muscle Weakness</th>
<th>Sleep Problems</th>
<th>Numbness or Tingling</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>3010A</strong></td>
<td>14/21</td>
<td>11/21</td>
<td>19/21</td>
<td>17/21</td>
<td>19/22</td>
<td>12/21</td>
</tr>
<tr>
<td></td>
<td>67%</td>
<td>52%</td>
<td>90%</td>
<td>81%</td>
<td>86%</td>
<td>57%</td>
</tr>
<tr>
<td><strong>3010G</strong></td>
<td>8/25</td>
<td>5/28</td>
<td>16/28</td>
<td>17/28</td>
<td>13/27</td>
<td>6/24</td>
</tr>
<tr>
<td></td>
<td>32%</td>
<td>18%</td>
<td>57%</td>
<td>61%</td>
<td>48%</td>
<td>25%</td>
</tr>
<tr>
<td><strong>Chi Square</strong></td>
<td>P = 0.04</td>
<td>P = 0.02</td>
<td>P = 0.03</td>
<td>P = 0.22</td>
<td>P = 0.01</td>
<td>P = 0.06</td>
</tr>
<tr>
<td><strong>Odds Ratio (95% C.I.)</strong></td>
<td>4.0 (1.1-18)</td>
<td>4.7 (1.2-23)</td>
<td>5.9 (1.2-54)</td>
<td>NA</td>
<td>6.0 (1.4-38)</td>
<td>3.7 (0.95-18)</td>
</tr>
<tr>
<td><strong>T-test</strong></td>
<td>P = 0.004</td>
<td>P = 0.06</td>
<td>P = 0.005</td>
<td>P = 0.03</td>
<td>P = 0.046</td>
<td>P = 0.03</td>
</tr>
</tbody>
</table>
Functional GI Disorders
700 adult patients evaluated at Mayo, in collaboration with Dr. Camilleri

- 7028C (defines haplogroup H)
  - IBS-C: OR 0.6 (0.4-0.9), P = 0.006
  - IBS-alt: P = 0.035
  - Satiation: higher max tol volume, P = 0.037
  - Gas sensation: lower, P = 0.031, 0.032

- 3010A (defines sub-haplogroup H1)
  - Chronic abd pain: OR 3.2 (1.2-8.0), P = 0.02
  - Any FGID: OR 1.6 (1.0-2.8), P = 0.06
  - IBS-D: OR 1.7 (0.9-3.2), P = 0.09
  - Gastric emptying: faster P = 0.043
Hypoglycemia is common among matrilineal relatives in these families. Could nocturnal hypoglycemia in infants be the mechanism of SIDS?
Sudden Infant Death Syndrome

Glucose measurement in autopsied liver by GC/MS suggests heterogeneity, in which 20% of SIDS is associated with substrate depletion.

HAPLOTYPES
Glucose-depleted versus glucose-normal
P = 0.002; odds ratio (GT v. AC) = 40
95% confidence interval = 2.1 – 738
Glucose depleted v. controls: P = 0.06
Glucose normal v. controls: P = 0.0001

3010A
Glucose-normal versus controls:
P = 0.007
odds ratio 3.5, 95% C.I. 1.3-9.1
Is Autism Related To These Other Functional Disorders?

- Autism
- Migraine
- Cyclic vomiting S.
- Complex regional pain syndrome
- Rhabdomyolysis
- Photophobia
- Chronic fatigue S.

- GI disease
  - Renal Failure
  - Diabetes

- Panic disorder
  - Depression
  - Anxiety disorder
  - GI disorder
  - Chronic pain
  - Exercise intolerance
  - Fasting intolerance

- GI disease
  - Renal Failure
  - Diabetes

- Syndrome with Developmental delay, and
  - Calf tumor

- Learning disability
  - Sensory integration

- ADD
  - Depression
  - Anxiety disorder

- Migraine
  - Myalgia
  - Chronic fatigue S.
  - Vomiting
  - GERD
  - Exercise intolerance
  - Fasting intolerance
  - Insomnia

- Behavior issues

- Bloating
  - Prematurity

- Mitral valve prolapse
  - Renal failure
  - Chronic diarrhea
  - Muscle weakness

- Chronic pain
  - Exercise intolerance
<table>
<thead>
<tr>
<th>DSM-IV-TR Diagnosis</th>
<th>16519T</th>
<th>3010A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autistic Disorder (AD)</td>
<td>18/81</td>
<td>27/81</td>
</tr>
<tr>
<td>“Infantile Autism”</td>
<td>(22%)</td>
<td>(33%)</td>
</tr>
<tr>
<td>Pervasive Developmental Disorder NOS (PDD-NOS)</td>
<td>24/49</td>
<td>6/49</td>
</tr>
<tr>
<td>“Atypical Autism”</td>
<td>(49%)</td>
<td>(12%)</td>
</tr>
<tr>
<td>All Other Autistic Disorders</td>
<td>9/30</td>
<td>10/30</td>
</tr>
<tr>
<td>(30%)</td>
<td></td>
<td>(33%)</td>
</tr>
<tr>
<td>Non PDD-NOS ASD Cases (AD + Others)</td>
<td>27/111</td>
<td>37/111</td>
</tr>
<tr>
<td>(24%)</td>
<td></td>
<td>(33%)</td>
</tr>
<tr>
<td></td>
<td>$P = 0.002$</td>
<td>$P = 0.006$</td>
</tr>
<tr>
<td></td>
<td>O.R. 3.0 (1.5-6.0)</td>
<td>O.R. 0.30 (0.1-0.8)</td>
</tr>
<tr>
<td>Population Controls From USA, UK, Italy and Finland</td>
<td>63/231</td>
<td>143/444</td>
</tr>
<tr>
<td>(Prevalence rates are the same in these four nations)</td>
<td>(27%)</td>
<td>(32%)</td>
</tr>
<tr>
<td></td>
<td>$P = 0.003$</td>
<td>$P = 0.04$</td>
</tr>
<tr>
<td></td>
<td>O.R. 2.5 (1.4-4.8)</td>
<td>O.R. 0.31 (0.1-0.8)</td>
</tr>
</tbody>
</table>
Do Maternally Inherited mtDNA polymorphisms constitute a “Unified Theory” of Functional Disease?

- 16519T is statistically associated with:
  - Migraine headache (odds ratio 4)
  - Cyclic vomiting syndrome (odds ratio 6)
  - Chronic fatigue syndrome (odds ratio 2)
  - Complex regional pain syndrome (odds ratio 2)
  - Atypical autism (odds ratio 2.5)
  - SIDS subset with low hepatic glucose

- 3010A is statistically associated with:
  - Migraine headache in patients with 16519T (odds ratio 15)
  - Cyclic vomiting syndrome in patients with 16519T (odds ratio 17)
  - Constipation-type irritable bowel syndrome
  - Non-specific abdominal pain (odds ratio 3)
  - Functional co-morbidity in chronic fatigue syndrome (OR 4-6)
  - SIDS (common glucose-normal type) (odds ratio 3)

- 3010G is statistically associated with:
  - Atypical autism (odds ratio 3)
  - GI co-morbidity in major depressive disorder
  - Total functional symptomatology in high school students
Potential Applications:
Clinical Diagnostics: Urine Organic Acids

- Must be quantitative and collected during physiological stress:
  - At the beginning of an “episode”
  - With intercurrent illness causing fever or vomiting

- Elevations in:
  - Ketones
  - Krebs cycle intermediates (fumarate, malate, aconitate)
  - Dicarboxylic acids (including ethylmalonate and glutarate derivatives)
  - Lactate (occasional)
Potential Applications:
Therapy: General Principles

- Combine mitochondrial-directed treatment together with symptom-directed treatment.

- Mitochondrial-directed treatment is to:
  - Decrease energy demand
  - Increase energy supply
Potential Applications:

Therapy: Agents

- Fasting avoidance
  - “3+3 diet”
  - Special caution during viral illnesses, may need IVF
  - D10 with lytes at 1.5 times maintenance
- Exercise
- Co-enzyme Q10 (10 mg/kg/day; adult dose 300 mg/day; divided BID)
- L-carnitine (100 mg/kg/day; adult dose 2-3 grams/day; divided BID)
- Riboflavin 100-400 mg/day (or “B100”)
- Amitriptyline (0.5 to 1 mg/kg/day; all qhs)
**Co-enzyme Q10 Versus Amitriptyline in Cyclic Vomiting Syndrome Prophylaxis**

<table>
<thead>
<tr>
<th></th>
<th>Amitriptyline</th>
<th>Co-enzyme Q10</th>
<th>P Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Episode Improvement</strong></td>
<td>127/177</td>
<td>17/25</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>72%</td>
<td>68%</td>
<td></td>
</tr>
<tr>
<td><strong>Side Effects Reported</strong></td>
<td>102/202</td>
<td>0/28</td>
<td>0.00000005</td>
</tr>
<tr>
<td></td>
<td>50%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td><strong>Stopped Therapy Due to Side Effects</strong></td>
<td>42/198</td>
<td>0/28</td>
<td>0.007</td>
</tr>
<tr>
<td></td>
<td>21%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td><strong>Subjects’ Statement Risks V. Benefits</strong></td>
<td>63/134</td>
<td>17/22</td>
<td>0.009</td>
</tr>
<tr>
<td></td>
<td>47%</td>
<td>77%</td>
<td>3.6 (1.2-10)</td>
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### Cyclic Vomiting Syndrome (CVS) Practice Review - Demographics

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>13</td>
<td>31%</td>
</tr>
<tr>
<td>Female</td>
<td>29</td>
<td>69%</td>
</tr>
<tr>
<td><strong>Race/Ethnicity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>28</td>
<td>67%</td>
</tr>
<tr>
<td>Hispanic</td>
<td>11</td>
<td>26%</td>
</tr>
<tr>
<td>African-American</td>
<td>2</td>
<td>5%</td>
</tr>
<tr>
<td>Native-American</td>
<td>1</td>
<td>2%</td>
</tr>
<tr>
<td><strong>Inheritance Pattern</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probable maternal</td>
<td>21</td>
<td>60%</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>4</td>
<td>11%</td>
</tr>
<tr>
<td>Probable non-maternal</td>
<td>10</td>
<td>29%</td>
</tr>
</tbody>
</table>
Cyclic Vomiting Syndrome (CVS)  
Practice Review - Protocol

- Dietary: “3+3 diet” and the avoidance of fasting.
- Co-Q: Ubiquinone in liquid or gel capsule form (from a variety of brands) at a starting dose of 10 mg/kg/day, or 200 mg, divided twice a day, whichever is smaller.
- L-carnitine: Starting dose of 100 mg/kg/day divided BID, or 2 grams twice a day, whichever is smaller. A small minority of families, all with untreated blood levels >30 μM, were not treated.
- Amitriptyline: Subjects < 5 years with continued vomiting episodes despite the above therapies were treated at a starting dose of 0.5 mg/kg/day given at night.
- Cyproheptadine: Subjects < age 5 years and over with continued vomiting episodes despite the above therapies were treated at a starting dose of 0.25 mg/kg/day divided twice a day.
- Topiramate: Two participants who were refractory to all of the above measures were started on 25 mg of topiramate twice a day.
Dosages were increased every one to a few months until one of the following occurred:

- Resolution of vomiting episodes
- Intolerable side effects that failed a reduction in dosage followed by a slow dosage increase
- The following maximum was reached (empirically-derived):
  - Co-Q: blood level > 3.0 mg/L
  - L-carnitine: free carnitine blood level > 40 μM
  - Amitriptyline*: amitriptyline + nortriptyline blood level > 150 ng/ml
  - Cyproheptadine: Dosage of 0.5 mg/kg/day
  - Topiramate: Dosage of 200 mg BID (adolescents and adults)

*Blood levels were not routinely monitored for dosages < 1 mg/kg/day as they were uniformly low in the authors’ prior experience.
Cyclic Vomiting Syndrome (CVS)
Practice Review - Treatment

- **Clinical Success**
  - Episodes essentially resolved on therapy: 23
  - Episodes greatly improved (>75% improvement): 2
  - Episodes improved (50-75%), then lost-to-follow-up: 2
  - Total: 27/30 (90%)

- **Clinical Failure**
  - Episodes unchanged on therapy: 1
  - Episodes resolved, but could not tolerate tx, then returned: 1
  - Episodes continue, not able to tolerate amitriptyline: 1
  - Total: 3/30 (10%)

- **Not Judged**
  - Lost to follow-up after 1 or 2 visits, results unknown: 9
  - Episodes self-resolved: 2
  - Episodes improved, still not therapeutic level of amitriptyline: 1
  - Total: 12/42 (29%)

- **Side Effects**
  - Amitriptyline: 6
  - Cyproheptadine: 1
  - Co-enzyme Q10: 1
  - Unclear (non-specific on high doses of multiple agents): 2
  - Total: 8/30 (27%)
Conclusions - 1

- 1. There is increasing evidence of a shared genetic predisposition towards multiple (possibly most) functional disorders.
- 2. Some families have mtDNA sequences that confer a several-fold increased risk for the development of at least some functional disorders.
- 3. 16519T and 3010A constitute a substantial proportion of the increased risk in these families, at least within haplogroup H.
Conclusions - 2

4. The data suggest that energy metabolism is involved in the etiology of at least some cases of migraine, depression, chronic fatigue syndrome, CRPS, IBS, abdominal pain, CVS, SIDS and possibly other functional disorders as well.

5. These cases can be screened for in a primary care setting by the application of a few questions, followed by referral for pedigree analysis and “stressed” urine organic acid determination.

6. Anecdotal clinical experience and some pilot data suggests that “mito-somatic disorders” are somewhat treatable.
Kathleen Adams
Erin Baldwin
Sawona Biswas
Michael Camilleri
Kingshuk Das
Martin Dichgans
Tobias Freilinger
Katie Heisner
Tomo Higashimoto
Jonathan Kerr
Thomas Klopstock
Piero Rinaldo
Lee Ung
Bai-Lin Wu
Essam Zaki
Haitao Zhu

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