Advanced Insights on Treating Seizures and Mitochondrial Issues in ASD

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DISCLAIMER

While Dr. Rossignol has attempted to make the information in this presentation as accurate as possible, the information is provided without any expressed or implied warranty. The purpose of this lecture is to provide information about different conditions or treatments that may affect individuals with autism and other conditions. Please be advised that Dr. Rossignol is not giving medical advice and that circumstances may dictate different treatments. All of the reviewed treatments in this lecture are considered off-label and not FDA-approved. Before beginning any treatment, please consult with your or your child’s physician.

The use of every treatment in autism is “off-label” except for Risperidone and Aripiprazole for the treatment of irritability.
* Important Concept *

- Several **metabolic abnormalities** have been reported to contribute to or cause a **potentially reversible form of autism**
  - e.g., Cerebral Folate Deficiency
- The goal is to **rapidly screen for these abnormalities**, identify them, and start treating them
- Testing can be done by measuring certain **biomarkers** (laboratory tests that may identify abnormalities)
- **ASD has a clear biological basis with features of known medical disorders** (e.g., in my opinion, it is **not just a psychiatric disorder**)

Meet the RMC Team
Brief review of normal brain functions
Brain Electrical Activity

- The nervous system is a network of brain cells called neurons which communicate by sending tiny electric signals to each other.
- The brain has around 100 billion neurons, and each communicates with thousands of others.
- The more signals that are sent, the more electricity the brain will produce. An EEG can measure the pattern of this electrical activity.
- Active areas of the brain also use more energy than less active parts - this is the basis of PET, SPECT and fMRI scanning.

Synapses and Neurotransmitters

- The brain makes up 2% of the body weight but uses 20% of the body oxygen
- The electrical signals (nerve impulses) carried by neurons are passed on to other neurons at junctions called synapses.
- The signal may be directly transferred at electrical synapses or, if there is no physical link between adjacent neurons, the signal is carried across the gap by chemicals called neurotransmitters.
Potential causes of regression in autism:

- **Mitochondrial dysfunction**
- **Deficiencies**
  - Folate related (Cerebral folate deficiency)
  - B12 related
- **Seizures and epileptiform activity**

Seizures and epileptiform activity in autism
Seizures: Definition

• Seizures are episodes of disturbed brain function that cause changes in attention or behavior
• Caused by abnormally excited electrical signals that disrupt the smooth-running pattern of electrical activity in the brain causing overload
• Epilepsy: recurrent seizures (at least 2 seizures)
Seizures: Symptoms

- Subclinical (silent)
- **Staring spells**
- Rapid blinking, holding of the hands to the ears, unprovoked crying episodes
- Loss of consciousness
- Violent convulsions
- Aura: strange sensation (such as tingling, emotional change, or smell of odor not there)
Seizures and epileptiform activity in autism

- Found in 1-2% of the general population
- Prevalence of seizures in autism ranges from 8-42%, with most estimates at 25-30%
- Up to 2/3 of children with autism have an abnormal EEG
  - 1/3 with normal EEG
  - 1/3 with epilepsy
  - 1/3 with subclinical discharges but no apparent or obvious clinical seizures (although there may be staring spells)
  - Some will have EEG slowing

Potential causes of seizures

- Brain malformations: onset at birth, developmental delay, tend to have microcephaly (small head size)
- Mitochondrial disorders (MD): children with autism and MD more likely to have seizures
- Cerebral folate deficiency
- Inflammatory processes
- Metabolic disorders: Adenylosuccinate lyase deficiency; Succinic Semialdehyde Dehydrogenase (SSADH) Deficiency
- Genetic disorders: Tuberous sclerosis; Fragile X; Rett syndrome
Scalp EEG Data Acquisition

Seizures in autism

- Two age peaks of seizures: Age 4-6 years old and after age 10 years old
- Prevalence of EEG epileptiform (seizure-like) activity 60% or more  
- Children over 10 years old 2.4 times more likely to have epilepsy  
  [Viscidi, et al., 2013 PLoS ONE 8(7):e67797]
- Children with seizure-like activity more likely to have stereotypes and aggressive behaviors  
- ASD children with epilepsy are more irritable and hyperactive  
  [Viscidi, et al., 2014 Autism 18(8):996-1006]
Seizures in autism

- Seizure-like activity can impair attention [Kawatani, et al., 2012 Brain Dev 34(9):723-730]
- Tall children with autism more likely to have seizures [Valvo, et al., 2013 PLoS ONE 8(9):e75015]
- 92% of ASD children who have one seizure will have a second one within one year [Qadir, et al., 2017 J Child Neurol 32(10):876-879]

Subclinical discharges (seizure-like activity)

- Specific syndromes, such as Landau-Kleffner syndrome, are relatively rare
- Recent studies have reported that subclinical discharges (epileptiform or seizure-like activity) are common in children with autism
- Some reports have suggested that the location of focal discharges correlate with specific symptoms
- One study reported that frontal lobe discharges were significantly associated with later epilepsy development in children with ASD [Kanemura, et al., 2013 Eur J Paediatr Neurol 17(3):232-237]
Electroencephalogram discharges in atypical cognitive development

A RETROSPECTIVE STUDY

...We retrospectively reviewed the charts of 22 children with atypical cognitive development that did not respond to standard educational therapy and demonstrated discharges on EEG. Most children demonstrated no obvious symptoms of seizures...The majority of children demonstrated a language and attention disorder and autism symptomatology and had multifocal discharges on EEGs. Of the 20 patients treated with antiepileptic medications, 70% demonstrated definite improvement within 1 clinic visit. This study suggests that children with EEG discharges and developmental cognitive disorders demonstrate a unique pattern of symptomatology and discharges...

Frye, et al., 2010  J Child Neurol 25(5):556-566
AED treatment improves symptoms

A RETROSPECTIVE STUDY

Frye, et al., 2010 J Child Neurol 25(5):556-566

Levetiracetam is associated with decrease in subclinical epileptiform discharges and improved cognitive functions in pediatric patients with autism spectrum disorder

A CONTROLLED STUDY

Wang, et al., 2017 Neuropsychiatr Dis Treat 13:2321-2326

<table>
<thead>
<tr>
<th>Improvement within One Clinic Visit</th>
<th>70%</th>
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<tr>
<td>Improvement with Increasing AED Dose</td>
<td>10%</td>
</tr>
<tr>
<td>Limited Improvement</td>
<td>5%</td>
</tr>
<tr>
<td>No Improvement</td>
<td>15%</td>
</tr>
</tbody>
</table>

METHODS: A total of 70 children with ASD (4-6 years) and SEDs... were randomly divided into two equal groups to receive either levetiracetam and educational training (treatment group) or educational training only (control). RESULTS: ...At the 6-month follow-up, the PEP-3 scores of the treatment group were significantly higher than those of the control, whereas the CARS and ABC scores were significantly lower, and the rate of electroencephalographic normalization was significantly higher in the treatment group. CONCLUSION: Levetiracetam... was also associated with improved behavioral and cognitive functions.
Several lines of evidence point to valproate, lamotrigine, and levetiracetam as the most effective and tolerable AEDs for individuals with ASD. Limited evidence supports the use of traditional non-AED treatments, such as the ketogenic and modified Atkins diet, multiple subpial transections, immunomodulation, and neurofeedback treatments. Although specific treatments may be more appropriate for specific genetic and metabolic syndromes associated with ASD and seizures, there are few studies which have documented the effectiveness of treatments for seizures for specific syndromes. CONTINUED …

Frye, et al., 2013  Front Public Health 1:31

Limited evidence supports l-carnitine, multivitamins, and N-acetyl-l-cysteine in mitochondrial disease and dysfunction, folinic acid in cerebral folate abnormalities and early treatment with vigabatrin in tuberous sclerosis complex. Finally, there is limited evidence for… magnesium with pyridoxine, omega-3 fatty acids, the gluten-free casein-free diet, and low-frequency repetitive transcranial magnetic simulation. Zinc and l-carnosine are potential novel treatments supported by basic research but not clinical studies. This review demonstrates the wide variety of treatments used to treat seizures in individuals with ASD…

Frye, et al., 2013  Front Public Health 1:31
Seizure: Potential treatments

- Nutritional supplements
- Medications
- Steroids / IVIG
- Diet (ketogenic)
- HBOT
- Vagal nerve stimulator
- Surgery

Supplements with potential antiseizure activity

- Taurine
- Vitamin B6 / P5P
- Magnesium
- Omega-3 fatty acids
- DMG
- L-Carnosine
- Folinic acid
Case study #1

- 14 year old male: diagnosed at 3 years old with autism; has poor attention and limited speech (says one word at a time)
- Currently on: cod liver oil, MB12 injections, and Aripiprazole
- PMH: anemia, reflux and constipation
- Previous **one hour EEG** - no abnormal discharges or seizures

Case study #1 continued

- He has been receiving ABA therapy for 8 years without much progress
- Various blood testing - unremarkable except low Vitamin D and mild anemia with low serum ferritin

  - **24 hour EEG** showed intermittent left temporal lobe epileptiform spikes throughout sleep (seizure-like activity)
Case study #1 continued

• Patient was treated with Vitamin D3 2000 IU per day and iron 20 mg per day
• He was started on lamotrigine and titrated up over several months to 5 mg/kg/day dose
• Mother reported he went from single words to 4-5 word sentences over a 6 month period
• After a year, he no longer required an aide 100% of the time at school due to increased attention and focus

Seizures in autism

• Obtain a **24 hour EEG**!
• Consider treating epileptiform activity on EEG
• Some reports have suggested that the location of focal discharges correlate with specific symptoms
• ASD children with seizure-like activity **often improve** with seizure meds [Frye, 2010]
Seizures in autism

Take Home Message:
• Obtain an overnight EEG on all kids with ASD - one hour is usually **not enough time** to pick up abnormalities
• Consider treating **any abnormal activity**
• May consider repeating an EEG even if it has been normal in the past - esp. if suspicious

Mitochondrial Dysfunction
Mitochondria

• Possible descendent of an ancestral purple, non-sulfur, photosynthetic bacteria
• Many cells contain 500 to 2000 mitochondria
• Found in every cell, generate ATP (energy)
  - Also generate heat
• Has its own DNA (genome)
• Liver mitochondria detoxify ammonia

Rossignol and Frye, 2012  Mol Psychiatry 17(3):290-314
Symptoms / Signs of mitochondrial dysfunction

- “Any symptom in any organ at any age”
- Growth or developmental delay
- Motor delay
- Clumsiness
- Developmental regression
- Seizures
- Hypotonia (low muscle tone)
- Migraines
- GI Abnormalities (diarrhea, constipation)
- Slow cognitive processing speed
- Fatigue / lethargy
- Ataxia
- Cardiomyopathy
- Myopathy
- Oxidative stress

Mitochondrial dysfunction in autism spectrum disorders: a systematic review and meta-analysis

The prevalence of mitochondrial disease (MD) in the general population of ASD was 5.0% (95% confidence interval 3.2, 6.9%), much higher than found in the general population (approximately 0.01%). The prevalence of abnormal biomarker values of mitochondrial dysfunction was high in ASD… Eighteen publications representing a total of 112 children with ASD and MD (ASD/MD) were identified. The prevalence of developmental regression (52%), seizures (41%), motor delay (51%), gastrointestinal abnormalities (74%), female gender (39%), and elevated lactate (78%) and pyruvate (45%) was significantly higher in ASD/MD compared with general ASD…

Rossignol and Frye, 2012 Mol Psychiatry 17(3):290-314
• Prevalence of mitochondrial disease in ASD ~5% (probably an underestimation)
• Biomarker data suggest that mitochondrial dysfunction is present in ~1/3 children with ASD
• Mitochondrial dysfunction has been correlated with autism severity
• The significant variability in biomarkers suggests that a spectrum of mitochondrial dysfunction in ASD exists
• Mitochondrial dysfunction in many cases may be secondary in nature (e.g., non-genetic)

Rossignol and Frye, 2012 Mol Psychiatry 17(3):290-314

We observed significantly lower levels of complexes III and V in the cerebellum (p < 0.05), of complex I in the frontal cortex (p < 0.05), and of complexes II (p < 0.01), III (p < 0.01), and V (p < 0.05) in the temporal cortex of children with autism as compared to age-matched control subjects, while none of the five ETC complexes was affected in the parietal and occipital cortices in subjects with autism. A significant increase in the levels of lipid hydroperoxides, an oxidative stress marker, was also observed in the cerebellum and temporal cortex in the children with autism.

Secondary mitochondrial dysfunction

- Heavy metals (mercury, lead, arsenic, cadmium, aluminum)
- Pesticides and herbicides
- Diesel exhaust
- Propionic acid from clostridia
- Medications: valproic acid (depletes carnitine), salicylates, antiretroviral HIV meds
- Estrogen increases mitochondrial efficiency
- Decreased metabolic reserve
- Oxidative stress and lowered glutathione
- Hypoxia

Secondary mitochondrial dysfunction: MEDS

- Aspirin
- Indomethacin
- Amiodarone
- Metformin
- Fluoxetine
- Alprazolam
- Valproic acid
- Acetaminophen
- Naproxen
- Tetracycline
- Amitriptyline
- Haloperidol
- Diazepam
- Disulfiram
- Diclofenac
- Lidocaine
- Statins
- Citalopram
- Risperidone
- Phenobarbital
Evidence linking oxidative stress, mitochondrial dysfunction, and inflammation in the brain of individuals with autism

A SYSTEMATIC REVIEW

- ASD is characterized by oxidative stress, mitochondrial dysfunction and immune dysregulation/inflammation
- Recent studies have also reported these abnormalities in brain tissue derived from individuals diagnosed with ASD.
- The brain regions found to contain these physiological abnormalities in individuals with ASD are involved in speech and auditory processing, social behavior, memory, and sensory and motor coordination.
- These findings suggest ASD has a clear biological basis with features of known medical disorders.

Rossignol and Frye, 2014  Front Physiol 5:150

Labs: Mitochondrial dysfunction

- Elevated lactic acid and pyruvate
- Elevated ammonia (>40 µg/dL)
- Low ubiquinone (CoEnzyme Q10)
- Low carnitine, free and total
- Elevated creatine kinase (>150 U/L)
- Fasting plasma amino acids: alanine (>450 µmol/L); alanine/lysine (>2.5)
- Fasting plasma acylcarnitine analysis (3 or more elevations)
- AST / ALT > 2.0
- Elevated urinary Kreb cycle metabolites (urine)
The association between newborn screening analytes and childhood autism in a Texas Medicaid population, 2010-2012

We explored whether there was an association of any analytes measured by newborn screening tests with a later diagnosis of ASD. A database was compiled of 3-5 year-old patients with any ASD diagnosis in the Texas Medicaid system in 2010-2012. Two controls (without any ASD diagnosis) were matched to each case by infant sex and birth year/month. All study subjects were linked to their 2007-2009 birth and newborn screening laboratory records, including values for 36 analytes or analyte ratios. We examined the association of analytes/ratios with a later diagnosis of ASD. Among 3,258 cases and 6,838 controls, seven analytes (e.g., 17-hydroxyprogesterone, acylcarnitines) were associated with a later ASD diagnosis. In this exploratory study, an ASD diagnosis was associated with 7 of 36 newborn screening analytes/ratios. These findings should be replicated in other population-based datasets.

Mitochondrial enzyme dysfunction in autism spectrum disorders; a novel biomarker revealed from buccal swab analysis

METHODS: 92 children with ASD and 68 controls were studied with immunocapture for RC-I and microspectrophotometry for RC-IV. RESULTS: Significant RC activity deficiencies were found in 39 (42%) ASD patients (p < 0.01) and more prevalent in more severe cases. Aberrant RC overactivity was seen in 9 children. RC-I/RC-IV activity ratio was significantly increased in 64% of the entire ASD cohort including 76% of those more severely affected (p < 0.05). CONCLUSION: Buccal swab analysis revealed extensive RC abnormalities in ASD providing a noninvasive biomarker to assess mitochondrial function in ASD patients.

Secondary mitochondrial dysfunction: Treatment

- **Carnitine** (up to 100 mg/kg/day)
- CoEnzyme Q10 (**ubiquinol**) (up to 15 mg/kg/day)
- B vitamins: thiamine (B1) and riboflavin (B2)
- Milk free diet in Cerebral Folate Deficiency
- Avoid fasting. Most patients do better with small meals (e.g., 6 small meals per day)
- MCT oil may help some patients
- **HBOT** may lead to mitochondrial biogenesis
Side Effects and Behavioral Outcomes Following High-Dose Carnitine Supplementation Among Young Males With Autism Spectrum Disorder: A Pilot Study

Carnitine Supplementation. Participating children were administered oral suspension or tablets of levocarnitine in 3 divided doses, starting at 200 mg/kg/day and increasing to 400 mg/kg/day, with a maximum daily dose of 6 g. If a child experienced unpleasant side effects (i.e., fishy body/breath odor, diarrhea), the maximum daily dose was dropped down to 200 mg/kg/day.

Scores on the ABC Hyperactivity subscale, SCQ, PDDBI Social Pragmatic Problems domain, and AIM Social-Emotional Reciprocity Impact domain significantly decreased over time (indicating behavioral improvement) at the unadjusted .05 level. Similarly, PDDBI Social Approach Behaviors, PDDBI Expressive Social Communication Abilities Composite scores, and PDDBI Receptive/Expressive Social Communication Abilities Composite scores significantly increased over time (indicating behavioral improvement).


The Effect of Mitochondrial Supplements on Mitochondrial Activity in Children with Autism Spectrum Disorder

We examined citrate synthase and Complex I and IV activities using a validated buccal swab method in 127 children with autism spectrum disorder with and without mitochondrial disease, a portion of which were on common mitochondrial supplements. Mixed-model linear regression determined whether specific supplements altered the absolute mitochondrial activity as well as the relationship between the activities of mitochondrial components. This study provides empirical support for common mitochondrial treatments and demonstrates that the relationship between activities of mitochondrial components might be a marker to follow…

Delhey, et al., 2017 J Clin Med 6(2)
Case study #2

- 3 year old male with regression at 2 yo - lost over 100 words and all social interaction
- Started SIBs such as head banging
- Walked at 17 months
- Some hypotonia and clumsiness
- Does poorly with fasting

Case study #2 continued

- “Normal” 24 EEG and normal MRI
- Normal comprehensive stool analysis
- Genetic counseling - no significant abnormalities- minor SNPs including MTHFR A1298C heterozygous
- Normal IgG & IgE food and environment panel
- Mother presented after declining Risperidone from primary care doctor
<table>
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<tr>
<th>Test Name</th>
<th>Value</th>
<th>Reference Range</th>
<th>Loc</th>
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<tbody>
<tr>
<td>CARNITINE, LCMS/MS</td>
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<td></td>
<td></td>
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<tr>
<td>CARNITINE, TOTAL</td>
<td>72</td>
<td>32 - 62 UMOL/L</td>
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<tr>
<td>CARNITINE, FREE</td>
<td>33</td>
<td>25 - 54 UMOL/L</td>
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</tr>
<tr>
<td>CARNITINE, ESTERS</td>
<td>39</td>
<td>4 - 12 UMOL/L</td>
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<tr>
<td>ESTERIFIED/FREE RATIO</td>
<td>1.18</td>
<td>0.09 - 0.35</td>
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**TEST(S) PERFORMED AT:** QUEST DIAGNOSTICS-NICHOLS INST JON H. NAKAMOTO M.D., LAB DIRECTOR 331980
ORTEGA HIGHWAY SAN JUAN CAPISTRANO, CA 92675 CLIA #05D0443352

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<td>POTASSIUM</td>
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<td>3.5 - 5.5 MEQ/L</td>
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<td>CHLORIDE</td>
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<td>96 - 111 MEQ/L</td>
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<tr>
<td>CO2 (BICARBONATE)</td>
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<td>20 - 34 MEQ/L</td>
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<tr>
<td>ANION GAP (CALC.)</td>
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<td>0.0 - 25.0 MEQ/L</td>
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<td>GLUCOSE</td>
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<td>65 - 99 MG/DL</td>
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<td>BUN (BLOOD UREA NITROGEN)</td>
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<td>CREATININE</td>
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<td>9.0 - 28.0 RATIO</td>
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<td>CALCIUM, TOTAL</td>
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<td>8.6 - 10.8 MG/DL</td>
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<td>Total Protein</td>
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<tr>
<td>ALBUMIN</td>
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<td>3.7 - 5.1 G/DL</td>
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<td>1.1 - 2.5 RATIO</td>
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<td>AST (SGOT)</td>
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<td>CALCIUM, IONIZED (CALC.)</td>
<td>4.6</td>
<td>3.9 - 5.3 MG/DL</td>
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Case study #2 continued

- Pt started on an ALL organic diet
- Treated patient with acetyl-L-carnitine (ALCAR) 500 mg twice daily
- Folinic acid 20 mg per day (empirically)
- Mother reported increased energy levels and cognition
- Follow up after 6 months: added ubiquinol (active CoQ10) 100 mg twice daily and MCT oil twice daily
- Parents reported syllables increased to full sentences over next 6 month period

Case study #3: 12 month old sibling of child with autism

- He takes Vitamin D, probiotics, and DHA.
- He is pointing. He is saying one word. He has bowel movements every 1-2 days. He is sleeping ok. There are no current concerns.
**CARDIAC PROFILE**

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<tr>
<th>Test</th>
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<th>Unit</th>
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<tbody>
<tr>
<td>Creatine Kinase (CPK), Total</td>
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<td>&lt;150 H</td>
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**SPECIAL CHEMISTRY - SENDOUT**

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<tr>
<td>Carnitine, Free</td>
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<td>25-55</td>
<td>umol/L</td>
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<tr>
<td>Carnitine, Total</td>
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<td>umol/L</td>
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Test developed and characteristics determined by ARUP Laboratories. See Compliance Statement B: aruplab.com/CS

Performed by ARUP Laboratories,
500 Chipeta Way, SLC, UT 84108 800-522-2787
www.aruplab.com, Julio Delgado, MD, Lab. Director

Lactic Acid, Plasma

Test(s) performed at: Clinical Pathology Labs, INC.

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**CHEMISTRY**

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<td>135 - 146</td>
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<td>CO2 (Bicarbonate)</td>
<td>16 L</td>
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<td>Glucose</td>
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<td>5 - 18</td>
<td>mg/dL</td>
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<td>Creatinine</td>
<td>0.4</td>
<td>0.2 - 0.8</td>
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<tr>
<td>BUN/Creatinine Ratio (Calc.)</td>
<td>35.0 H</td>
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<td>Ratio</td>
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<tr>
<td>eGFR-African American (Calc.)</td>
<td>226</td>
<td>&gt;60</td>
<td>mL/min</td>
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<tr>
<td>eGFR-Non African American (Calc.)</td>
<td>195</td>
<td>&gt;60</td>
<td>mL/min</td>
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Note: eGFR is not reported on individuals less than 1 year of age. Reference values not established.

Calcium, Total

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<th>Lower Limit</th>
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<td>10.5</td>
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Total Protein

<table>
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<th>Upper Limit</th>
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<td>5.6 - 7.5</td>
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Albumin

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<th>Upper Limit</th>
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<td>3.0 - 4.8</td>
<td>g/dL</td>
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MOLECULAR GENETIC ANALYSIS - SENDOUT

MTHFR Mutation C677T  
MTHFR Mutation A1298C  - NEGATIVE  - HOMOZYGOUS

The sample is homozygous for the MTHFR C677T mutation and negative for the A1298C mutation. This is associated with increased plasma homocysteine levels, which is a risk factor for venous thromboembolism. Women with this result are at increased risk for recurrent pregnancy loss and have a modestly increased risk (odds ratio 1.6) of having offspring with a neural tube defect.
Algorithm for calculating the probability of mitochondrial dysfunction

**Care Plan:**

1. **Carnitine:** Start 250 mg of Acetyl-L-Carnitine 2 times per day. Carnitine is an amino acid derivative. Two studies have reported improvements using carnitine compared to placebo in children with autism. In several studies of carnitine in children with autism, improvements were found in sleep, energy level, communication, expressive speech, autism behaviors, and muscle strength. Side effects include hyperactivity and loose stools.

   In a few days to one week add the next step (it is best to add one treatment at a time and observe for effects.)

2. **Ubiquinol (active form of CoEnzyme Q10):** Start 100 mg of ubiquinol once per day in the morning. Ubiquinol can help with mitochondrial function. It generally helps to increase attention, cognition and energy levels. Side effects include hyperactivity in a small number of people.
### Section I: Clinical signs and symptoms

**Muscular presentation**
- Exercise intolerance
- Muscle weakness
- Abnormal EMG
- Rhabdomyolysis

**CNS presentation**
- Seizures
- Myoclonus
- Cortical blindness
- Extrapyramidal signs
- Brain stem involvement

**Multisystem disease**
- Heart
- Kidney
- Vision
- Hearing
- Neuropathy
- Recurrent/familial

Total Points Section I: [Formula](#)

---

### Section II: Metabolic/imaging studies

- Elevated lactate (2 points)
- Elevated lactate/pyruvate ratio (2 points)
- Elevated alanine (2 points)
- Elevated CSF lactate (2 points)
- Elevated CSF protein (2 points)
- Elevated CSF alanine (2 points)
- Leigh syndrome/MRI (2 points)
- Stroke-like picture MRI (2 points)
- Urinary tricarbonyl acid excretion (2 points)
- Erythromelalgia (2 points)

Total Points Section II: [Formula](#)

---

### Section III: Morphology (muscle biopsy)

- Ragged red/orb fibers (4 points)
- Reduced SDH staining (4 points)
- Con-negative fibers (4 points)
- SDH positive blood vessels (2 points)
- Reduced COX staining (4 points)
- Abnormal mitochondria/EM (2 points)

Total Points Section III: [Formula](#)

**SCORE:**

1. Mitochondrial disorder unlikely
2. Possible mitochondrial disorder
3. Probable mitochondrial disorder
4. Definite mitochondrial disorder

Total Score: [Formula](#)

---

**Mitochondrial Dysfunction**

**Take Home Message:**
- Remove offending mitochondrial agents
- May need *multiple* mitochondrial support agents working synergistically (one or two alone may not be enough)
- Treat even if only clinical suspicion
- Children with autism often respond well to mitochondrial support