

Autism and Mitochondrial Disease and Dysfunction;

Lyme-induced Autism

Julie A. Griffith, M.D., M.S., C.M.T.

Northern California Center for Learn. & Behavioral Disorders

Pediatric & Adult Neurology

120 Ross Valley Drive

San Rafael, Ca 94901

Phone (415) 925-1616

Facsimile (415) 259-4011

www.mybrainhealth.org

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- Bruce Kaminsky on behalf of FEAT
- Dr. Ann Corson, slides on Lyme-Induced Autism

Disclaimer

- Any recommendations for supplements, antibiotics or other medications or therapies presented in this lecture should just be to consider. For actual therapies for a given patient, the patient is recommended to see a health care provider, who can determine if the recommendations are best, given the patient's actual clinical presentation.

Basic premise:

- The autisms are caused by genetic predisposition and environmental factors, both of which are variable.

Genetic

- Nuclear DNA abnormalities
- Mitochondrial DNA abnormalities
- Genetic predisposition (will not express disease, unless there are environmental factors to trigger phenotypic expression)

Environmental

- Toxins
 - heavy metals
 - other
- Infections
 - BRC (Lyme disease)
 - fungal (Candida, Rhodotorula, others)- most common infection, likely due to immune suppression from multiple factors (heavy metal poisoning, measles vaccine and weaker children due to general heavier toxin load)
 - parasitic
 - Babesia (Lyme co-infection)
 - others, chronic infection
 - viral -HHV6 (Roseola) is the most common that I and other practitioners see, Rubella, varicella, CMV have all been reported in the literature to be associated with autism) measles (JAG)
- Electropollution (Dr. Dietrich Klinghardt, German literature)
 - Wireless networks
 - Cell phones/cell phone towers
 - mobile phone
- Vaccines

Big picture

- There are multiple subsets of autisms, clustering with possible similar genetic predisposition and environmental exposure history, leading to similar metabolic abnormalities and phenotypes
- At this time I see the 2 main contributing environmental factors are :
 - a) Heavy metal poisoning and
 - b) Lyme disease, properly termed “Borrelia related complex”

From the major environmental exacerbating factors, there are downstream effects:

- Mitochondrial dysfunction (Oliveira et al, 2005)
- Nutritional deficiencies (40-60%_{ARI}), JAG suspect higher percentage when testing comprehensively
- Immune dysregulation
 - allergies
 - inflammation
 - chronic infections
- Excitotoxicity
- Hormonal deficiencies (hypothyroidism common; steroid hormone deficiency seen in girls affecting sex hormone levels associated with cholesterol deficiency; growth hormone deficiency seen rarely (boy later diagnosed with Lyme disease))

ARI Publ, 34/Feb 2006

Oliveira, et al, 2005, Dev Med Child Neurol 47(3):185-9.

Today:

1) mitochondrial disorders

a. mitochondrial disease –genetic abnormality of the mitochondrial DNA and

b. mitochondrial dysfunction, in which there may be a genetic weakness or there may be a strong environmental factor causing mitochondrial dysfunction and

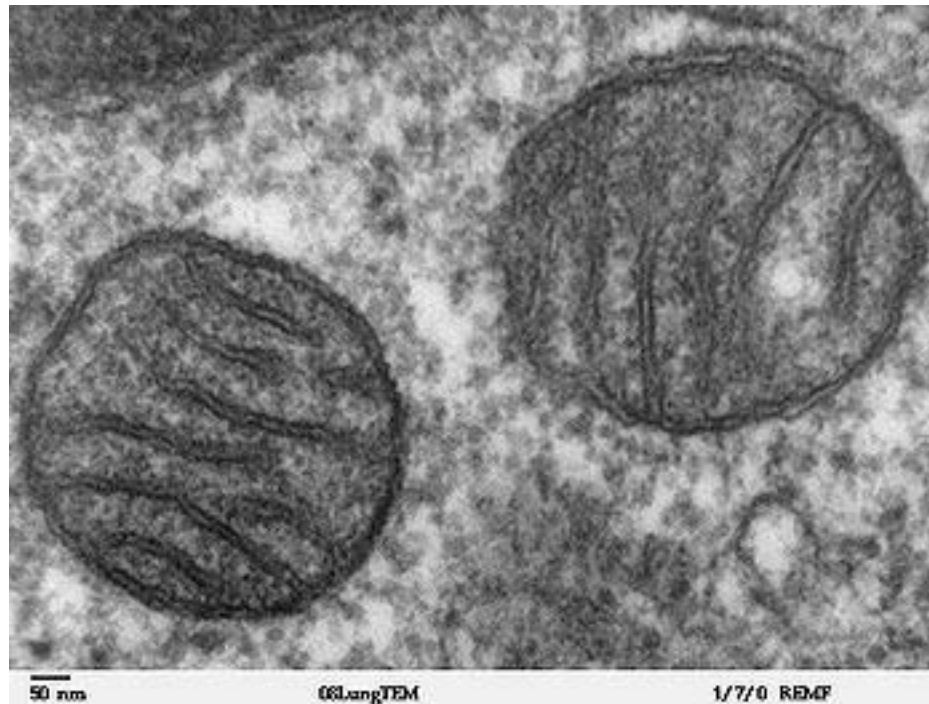
2) Lyme disease, an environmental factor which is due to an infection

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Mitochondria

- Organelle which is the energy powerhouse of the cell, takes fats and sugars to make energy
- inherited only from mother
- Contain their own DNA
- Divide
- Possibly the mitochondria was once a bacteria that entered a eukaryotic cell (highly organized nucleus bound by a nuclear membrane)
- Mitochondria are most closely related to microbe *Rickettsia prowazekii*, carried by body lice, epidemic typhus (Ethiopia, central Africa, Central and South America). (high fever, rigor, centrifugally spreading macular rash, spared head, hands, soles, floating thrombus on echo). R.p. in flying squirrels in U.S.
- Lyme disease is from a Rickettsial organism, also.

Mitochondria from lung



Mitochondrial structures

- Outer membrane
 - permeable to many molecules
 - convert lipids into useable form by the inner membrane
- Inner membrane is folded into cristae. 3 prot:
 - oxid reactions
 - ATP synthase
 - transport proteins taking molecules into and out of matrix
- Matrix-100's of enzymes
 - Oxid of pyruvate and fatty acids
 - TCA cycle
 - Mitochondrial DNA

Mitochondria

- Metabolize sugars, fats to make energy
 - 1 molecule of glucose makes 36 molecules of ATP (when oxidized by O₂ to CO₂ and H₂O)
- (without mito, glycolysis without oxygen ->2ATP)
- High energy electrons fall to successively lower energy levels, releasing energy, which is used to pump protons across the membrane (electrochemical gradient), which is later harnessed to make ATP, or it can be used to drive metabolites into or out of organelles
 - **Body needs energy to kick out toxins

Mitochondria

- Are associated with microtubules of the cytoskeleton
- Are placed in the cell where energy is needed
- Are made of lipid membranes and proteins
(thus nutritionally, need amino acids and essential fatty acids to form the mitochondria, need coenzyme Q 10 for energy production, need ribose 5 phosphate to form the ATP molecule)

Mitochondrial disorders, genetic mutations

Mitochondrial disorders

- HEADD syndrome
 - hypotonia, intractable epilepsy, autism and developmental delay
 - reduced levels in specific respiratory activities were found solely in enzymes with subunits encoded by mitochondrial DNA in 7 out of 8 bx sk. Muscle
 - 5 cases large scale mitochon DNA deletions
 - mitochondrial structural abnormalities in 3 of 4 patients

Mitochondrial disorders and Autism

- 1 child with mitochondrial coenzyme Q10 deficiency
- 1 child with combined partial deficiencies of respiratory chain complex II to III and complex IV.

Tsao et al, 2007. September 22(9): 1121-1123.

A3243GmtDNA mutation and autism.

Pons et al, 2003. J Pediatrics Jan 10.023: 81-85

Mitochondrial dysfunction in autistic patients with 15q inverted duplication.

Filipek et al, 2003. Ann Neurol 53:801-804

Mitochondrial dysfunction

The Poling case

- US Health and Human Services conceded vaccine-
induce autism symptoms (Hannah Poling, 2007).
9 vaccines in 1 day, regression into autism
- HHS stated Hannah's case was rare
- Poling et al, 2006 stated many children might
have pre-vaccination susceptibility related to
mitochondrial dysfunction which is different from
classically described, genetically identified
mitochondrial disorder (mitochondrial DNA
mutations)
- Poling et al, 2006. J Child Neurol Feb 21(2): 170-2.

Hannah Poling

- 19 mo
- CK, aspartate aminotransferase, bicarbonate abnormalities led to
- Muscle biopsy-type 1 myofiber atrophy, increased lipid content, reduced cytochrome c activity
- Marked reductions in enzymatic activities for complex 1 and III
- Complex IV was near the 5% confidence level

Poling et al, 2006

- 159 patients with autism, retrospective
38% elevated aspartate aminotransferase with
autism , compared to 15% of controls, $P < .0001$
CK elevated 47% of 47 patients with autism

Infection-induced mitochondrial dysfunction

- Molds
 - Fusarium molds cause liver toxicity by
 - opening the mitochondrial permeability transition pore complex
 - loss of mitochondrial transmembrane potential
 - increase in free radical O₂- production
 - cytochrome C release
 - capsase activation (which can cause apoptosis)

Fusarium molds are found in cereals, barley, corn, soil, water damaged carpets

Infection-induced Mitochondrial dysfunction

- Mold toxins (ochratoxin, zearalenone and T2-toxin) induce a caspase-dependent mitochondrial apoptotic pathway
 - loss of mitochondrial transmembrane potential
 - cytochrome c release
 - produce reactive oxygen species

Ochratoxin is from *Aspergillus* (air and house dust samples, grains –rice, corn, wheat, cereals and meats ,sewage sludge

Infection-induced mitochondrial dysfunction

- *Cryptococcus gattii* caused a fatal fungal outbreak in Vancouver island. The hypervirulence of this cryptococcus was found to be due to an upregulation of the mitochondrial genes which were associated with mitochondrial activities.
- Ma et al, 2009. Proc Natl Acad Sci Aug 4 106 (31):12980-5.

Bacteria infection-induced mitochondrial dysfunction

- Streptococcus causes ultrastructural mitochondrial membrane remodeling, loss of mitochondrial depolarization and cytochrome C release, which suggests that streptococcus toxin directly initiates the intrinsic apoptosis pathway.
- Timmer et al, 2009 J.Biol Chem. Jan 9; 284 (2): 862-71.

Herpes viruses induce mitochondrial dysfunction

- HSV reduced mitochondrial respiration, which was caused by a block in the mitochondrial electron-transport chain.

- Derakhshan et al, 2006 J Gen Virol Aug; 87 (Pt8): 2155-9

- HHV6 caused a loss of mitochondrial membrane potential.

- Yeo et al, 2008 J Virol Jan; 82 (2): 1011-20

Heavy metals cause mitochondrial dysfunction

- Thimerosal (ethylmercury) , substance that has been in vaccines, causes:
 - depolarization of the mitochondrial membrane
 - generation reactive reactive oxygen species
 - release of cytochrome c
 - release of apoptosis-inducing factor

Lead induced mitochondrial dysfunction

- Lead decreased the activity of mitochondrial MAO in all the brain regions, in a dose-dependent manner.

Devi et al, 2005 Int J Dev Neurosci Jun; 23(4):375-81.

- Arsenic causes dysfunction of mitochondria in osteoblasts

Tang et al, 2009 Toxicol Appl Pharmacol Aug 18.

- Aluminum triggers mitochondrial dysfunction and causes ineffective ATP production.
- Lemire et al, 2009 J Neurosci Res May 1; 87(6): 1474-83

Mitochondrial disorder

- Oliveira et al, 2005 showed that lab abnormalities consistent with mitochondrial dysfunction (elevated lactate) was present in 14 out of 69 autistic patients (20%).
 - 5 of 11 were classified with definite mitochondrial respiratory chain disorder (5 of 69), or 7%.
 - some children may have had artifactually elevated lactate due to lab error
 - 13% of the autistic children may have elevated lactate for other reasons
 - taking lactobacillus acidophilus probiotic
 - lab artifact
 - toxins
 - infections

Oliveira, et al, 2005, Dev Med Child Neurol 47(3):185-9.

Pathophysiology of mitochondrial dysfunction in autism

- Dr. Jill James et al, 2009 showed that lymphoblastoid cells from autistic children had a reduced glutathione reserve capacity in both the cytosol and mitochondria that may compromise antioxidant defense and detoxification capacity under prooxidant conditions

Dr. Margaret Bauman and Dr. Natowicz et al, 2008 showed:

- 25 patients with autism who had mito dysfunc
 - 1) 21 had significant nonneurological med probs
 - 2) 19 had constitutional sx, including fatigue
 - 3) 15 had neurological abnlities with marked delay in gross motor milestones (32%), and regression (40%)
 - 4) Labs abnormal: blood lactate (76%), alanine (36%), ALT and or AST (52%)

Lab tests to detect mitochondrial dysfunction

- Plasma amino acids, check for alanine
- Lactic acid on ice (without tourniquet, do first, put on ice, process at hospital immediately) and pyruvic acid
- ALT , AST
- Aspartate aminotransferase
- Creatinine Kinase
- Reduced l-glutathione (Genova absolute deficiency , Stanford relative deficiency)
- Urine quantitative organic acids, academic lab
- Mitochondrial DNA testing (\$2225 by Athena labs)

Additional labs

- Stool for fungal culture to Specialty lab (Genova, Doctor's Data are possible choices) which do fungal culture and sensitivities for antifungal medications and herbs and garlic, bacterial culture, parasitic, inflammation, level of digestive enzymes
 - Full throat culture (if indicated) for strep (beta hemolytic Group A but also Group C)
 - blood testing for IgE and IgG against molds (i.e. Meridian Valley inhalant panel) also could check IBT lab). Do not use lab that only checks IgE mediated reaction to inhalant allergens
 - urine fractionated porphyrins (highest sensitivity is Laboratoire Philippe August, Paris, France due to fewer number of ages per grouping for pediatric norms, i.e. 0-2 yrs, 2-4 yrs of age, etc)
- RBC heavy metals or 24 hours heavy metals
- HSV Type I IgG/IgM titers
 - HHV6 IgG and IgM titers

Nutrients which optimize mitochondrial function/energy

- Amino acids (plasma amino acids at least midrange)
- Essential fatty acids omega 3 only (80 mg/kg, max 3000 mg/d), go down for bruising. 100 mg/kg for seizures (higher risk of bruising, need to monitor for this). Do not give omega 6 except as food, since omega 6 fatty acids may lower seizure threshold. AAN.
- Carnitine
- Ribose 5 phosphate
- Coenzyme Q 10
- Vitamin B2 (riboflavin)
- Antioxidants:
reduced l-glutathione,
Vitamin C and
Vitamin E
alpha lipoic acid

- Dr. Greg Enns, a metabolic physician at Lucile Salter Packard Children's Hospital (affiliated with Stanford) told me in a phone conversation that patients with mitochondrial disease can take Vitamins C and E, to protect glutathione levels.
- Dr. Enns states that low glutathione has been found in: Autism, and in patients with poor vision and those with hearing loss
- Free radicals overtax the patient's antioxidant system
- patients who took antioxidants did not have depleted glutathione, His research in the Proceedings of the National Academy of Sciences supports this.

Resources

- United Mitochondrial Disorder Foundation
412 856 1297
www.umdf.org

Transition from mitochondrial dysfunction to Lyme disease

- European vector of Lyme disease named “*Candidatus Midichloria mitochondrii*” can enter mitochondria (lineage within the Rickettsiales) . This bacteria is harbored in the *Ixodes ricinus* tick.
- Sasser et al, 2006. Int J Syst Evol Microbiol Nov 56 (PT 11):2535-40.

Lyme disease

- Borrelia Related Complex is the proper term, which describes the symptoms and signs or clinical disease caused by *Borrelia burgdorferi*, and associated co-infections, including other bacteria (*Bartonella*, *Ehrlichia*) and including parasitic infection by *Babesia*. Also, BRC includes *Mycoplasma* (which is a bacteria without a cell wall, dependent on the host for molecules such as purines, pyrimidines and the ETS).

Lyme-induced Autism

Bransfield et al (2008) hypothesized that tick-born infections may lead to the development of autism. This hypothesis is supported by the fact that:

- Multiple cases of mother's with Lyme disease and children with autism
- Patients with autistic spectrum disorder have positive reactivity for
 - Borrelia burgdorferi* (in 22%, 26% and 20-30% in studies)
 - Mycoplasma* in 58%
- There is improvement in autistic symptoms when antibiotics are given.

Bransfield, wulfman, Harvey and Usman, 2008. *Medical Hypotheses* (70): 967-974.

Lyme-Induced Autism, supporting evidence

- Teenagers and adults infected with Borrelia(BI) or TBI (tick-born infection) often have symptoms suggestive of ASD, including
 - hyperacusis (and other SMI deficits, JAG)
 - emotional detachment
 - mood instability
 - decline of speech and language
 - hypotonia
 - weak grasp (JAG)
 - gut dysfunction
 - cravings for starch carbohydrates and sugars
 - Adults with chronic BI or TBI show a global decline after receiving routine immunizations

Bransfield, wulfman, Harvey and Usman, 2008. Medical Hypotheses (70): 967-974.

ASD and Lyme patients:

- Both have inflammatory bowel disorders associated with gastrointestinal symptoms

Kugathasan, 2001 Curr Opin Gastroenterol 17(4): 350-5

Zaidi and Singer.2002. Clinical Infect Dis 34:1206-12.

- Fried biopsied children with inflammatory bowel diseases and found Babesia, Bartonella, Mycoplasma, Borrelia burgdorferi sensu lato, and Helicobacter pylori.

The GI sx improved with abx.

- Fried. 2001. GI manifestations of LYD. 14th Int Sc Conf LYD and other TBD.

Gestational TBI

- Jones et al reviewed 102 gestational BI/TBI cases.
 - Borrelia, babesia (14%)
 - Strep (7%)
 - Erlichia (6%)
 - Leptospirosis (5)%
 - mycosis (4%)

9% diagnosed with autism

56% diagnosed with ADD

Gestational Lyme d., cont'd

- Psychiatric sx:
 - irritability/moodswings (54%)
 - anger/rage (23%)
 - anxiety (21%)
 - depression (13%)
 - emotional difficulties (13%)
 - OCD (11%)
 - suicidal thoughts (7%)

Gestational Lyme cont'd

- Neurological symptoms:
 - headache (50%)
 - vertigo (30%)
 - developmental delays (18%)
 - tic disorders (14%)
 - seizure disorders (11%)
 - involuntary athetoid movements (9%)
 - hypotonia (7%)

Gestational Lyme, cont'd

- Sensory symptoms:
 - photophobia (43%)
 - hyperacuity (36%)
 - Motion sickness (9%)
 - tactile, taste or smell sensitivities (23%)

Gestational Lyme, cont'd

- Cognitive symptoms:
 - poor memory (39%)
 - cognitive impairments (27%)
 - speech delays (21%)
 - reading/writing deficits (19%)
 - articulation difficulties(17%)
 - auditory/visual processing deficits (13%)
 - word selectivity (12%)
 - dyslexia (18%)

Gestational Lyme, cont'd

- Gut symptoms were common:
 - GERD (27%)
 - abdominal pain (29%)
 - diarrhea or constipation (32%)
 - nausea (23%)

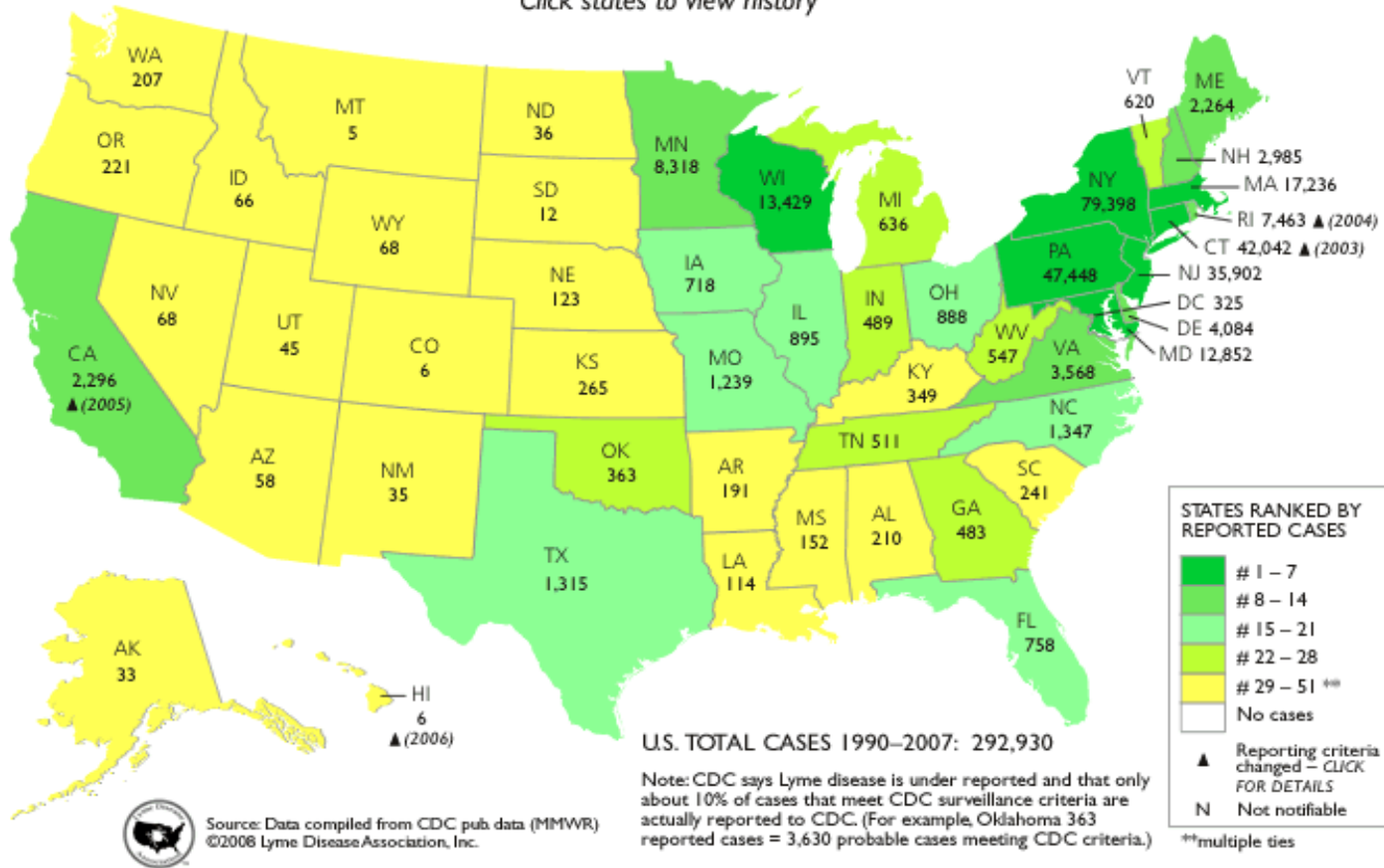
Lyme can be transmitted-sexually (Bach, 2000. Am PsychAssn Inst Psych Services)

-transplacentally

-breast milk (Jones, s LIA Conf 2007); Schmidt et al, 1995. Diagn
Microbiol Infect Dis 21(3): 121-8)

TOTAL LYME CASES REPORTED BY CDC 1990–2007

Click states to view history



Risk Map of California

The ticks that carry Lyme disease have been found in all but two counties in California. Infected ticks have been found in 42 of 58 counties. Studies have not been conducted in all areas

