

Summary - Psychiatric Disorders in Mitochondrial Disease **Presented by Andrew A. Nierenberg, MD**

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Introduction

Emerging research suggests a relationship exists between many psychiatric conditions and mitochondrial dysfunction. Dr. Nierenberg is very interested in innovative approaches to mitochondrial influences on mental health. Altered brain energy metabolism is not often in the forefront of mitochondrial disease discussions, but the brain is a very energy hungry organ, requiring mitochondria to make energy. This discussion will explore these topics:

- Role of mitochondria in the brain
- Psychiatric manifestations of mitochondrial disease
- Mitochondrial dysregulation in psychiatric disorders

Mitochondria and the Brain (slides 3-6) The brain, using 20 - 25% of the body's energy, is an energy intensive organ. The brain is hungry and selfish, and a body will sacrifice other organs' energy to fuel the brain! Brain metabolism is essential to the entire body. Advanced neuro-imaging shows complex networks of cells in the brain, all requiring a large amount of energy to maintain, right down to the hungry neurons. In the book, Networks of the Brain, Olaf Sporns explains how our brains are functionally organized. Dr. Nierenberg recommends this book, though not light reading, because the book will change the reader's understanding of how the brain works.

The Default Mode Network (slide 7) describes the way our brains organize during rest, when the body is seemingly doing nothing. The brain still uses an enormous amount of energy to sustain the complex communication networks between different areas of the brain even at rest. The area of the brain with the highest resting metabolic rate in the conscious resting state is the posteromedial parietal cortex (slide 5), lighting up as a red or hot area of the brain. Technology can map the areas of the brain working hard and using more energy. These networks, active when the body is at rest, are the same networks that are affected in Alzheimer's, Parkinson's, and Huntington's Disease, as well as ALS, due to a dysregulation of energy and neuronal damage.

A brain facing obstacles and striving to persevere, as may happen in mitochondrial disease, lights up in a specific pattern (slide 8). For some unable to overcome obstacles, it may not just be a matter of giving up, but rather a reflection of how their brains are functioning. Moving to the cellular level of the brain (slides 9-12), a cross section of a single mitochondria shows the inner structure, including the inner membrane, outer membrane, cristae and matrix. Deeper within the inner membrane of each mitochondria, the electron transport chain works as a series of protein complexes, critical to energy production. Deeper still, the exquisite mito architecture depicts that energy production in the various complexes, I-V. Dr. Nierenberg is not surprised that problems arise within the production of energy, and would like to focus on dysregulation

in Complex I, which can produce psychiatric symptoms and disorders. The mito genome is complicated, but relevant as psychiatric disorders can have a genetic cause, such as discovering that MT-ND1 is an area implicated in psychiatric disorders.

Mitochondria supply essential energy for neuronal plasticity (ability to change and adapt), including:

- neurons growing from a neuro stem cell (neurogenesis)
- neurons moving
- neurons growing new arms for new connections (dendritogenesis)
- neurons forming and un-forming connections (synaptogenesis)
- regulation of cell survival and death (apoptosis) (slides 14-15).

Neurons in the brain change and grow constantly even in adults, taking energy from the bank!

Oxidative Stress (slides 16-18) Oxidative stress can cause cellular dysfunction or death, and can also cause dysfunctional electron flow in the mitochondria inner membrane.

- Reactive oxidative stress damage mito
- decreased ATP
- damaged membrane
- abnormal calcium sequestration
- apoptosis - cell death
- neurons are especially susceptible

Psychiatric Disorders in Mitochondrial Disease

Dr. Nierenberg contends that many mito patients diagnosed with mood disorders actually have energy disorders. The brain does not function as it should due to deficiencies in energy production. Patients with Mitochondrial Disease frequently present at some time in their life with a mood disorder of some kind. **Research of lifetime prevalence of psychiatric disorders (slide #20) estimates that 50% of children with mitochondrial disease will present with depression and about 70% of adults diagnosed with mito will also present with a major psychiatric disorder at some time.** The onset of psychiatric disorders averages about 13 years before the diagnosis of mito disease in adults, and can be resistant to some psychiatric medications because some medications may interfere with mitochondrial function. Basically with mitochondrial disorders, brains do not function as well as they should because the energy available to use is limited due to the the compromised energy delivery system. A dysregulation of energy production exists, causing symptoms through the brain and entire body.

Psychiatric presentations most common with mito dysfunction (slide 21):

- major depressive disorders
- bipolar disorder
- OCD

- anorexia
- bizarre hallucinations
- anxiety disorders
- substance abuse
- borderline personality disorders & catatonia

Dysregulation unites all these presentations. Sleep, eating, mood, energy levels, thoughts, executive function, stress, and more are all regulated without thinking about it, and the ease of this regulation is energy dependent.

Common psychiatric symptoms in mito (slide 22) all can be traced back to the notion of regulation. Hostility, for example, may not be regulated well in a person with mitochondrial disease because that machinery for regulation is dysfunctional. Anglin, et al. 2012 (slides 23-25) searched the literature, publishing both psychiatric and physical symptoms:

- depression with psychotic features/delusions - believing something is real that cannot be real
- psychosis - hallucinations and delusions
- cognitive deterioration - memory: recall, sort, and store
- anxiety disorders
- bipolar disorders - full dysregulation of mood and energy
- frontal lobe syndrome - impulsive, inability to plan, and memory issues
- Physical manifestations in this population which is also typically seen in mito:
 - muscle weakness or atrophy
 - seizure disorders
 - migraine or headache
 - hearing loss
 - short stature
 - Type 2 diabetes
 - severe constipation, often with ileus
 - ataxia
 - dysarthria
 - stroke

MRI finding support these findings:

- white matter lesions
- cerebral or cerebellar atrophy
- ischemia or an old infarct
- basal ganglia calcifications or hyperintensities (movement and mood regulation)

Mitochondrial neurologic findings again give cause to dysfunction in the brain. White matter deterioration, underlying defects in the respiratory chain, oxidative stress, neuronal death, and replacement of neurons by glial cells are all of caused by is insufficient energy to sustain healthy function. (slide 26)

Among mitochondrial mutations (slide 27) for MELAS, MERF, CPEO, and MNGIE, no clear genotype psychiatric phenotype relationship has been established, meaning a prediction of psychiatric manifestations cannot be accurately made based on the mito mutation. Genotype refers to the genes or genetic make-up of a cell while phenotype refers to observable or physical traits expressed by those genes. Physical manifestations (slide 28) may be Wolf-Parkinson-White Syndrome, ophthalmoplegia, ptosis, cardiomyopathy, cardiac conduction defect, and abnormal movements.

Deterioration with the use of Psychotropic drugs: (Slide 29)

- typical & atypical antipsychotics - impair complex 1
 - SSRI's and tricyclic antidepressants - inhibit mito respiratory chain & oxidative phosphorylation
 - Valporic acid - induces carnitine deficiencies

Treatment for psych problems that can co-occur with mitochondrial disease are now starting to be used in the psychiatric world (slide 30). Evidence that supplements are effective is limited: Creatinine monohydrate, Alpha Lipoic Acid, Vitamins E, C, & Riboflavin, Antioxidant idebenone. Negotiate with doctor to reduce or discontinue psychotropic drugs that do not work or have a negative impact.

Mitochondrial Dysregulation in Psychiatric Disorders

The other side of the coin is the growing evidence of mitochondrial dysregulation in psychiatric disorders, meaning those who present with certain psychiatric disorders also demonstrate mitochondrial dysfunction. Kato's research in the 1980's demonstrated mitochondrial changes in the genome of patients who suffered from Bipolar Disorders. Further research by Young & Andriaza in Canada also notes problems in the electron chain, specifically Complex I, with Bipolar Disorder (slides 32-38). Bipolar Disorder, Parkinson's Disease, Major Depressive Disorder, and Schizophrenia have ties with specific mito genes.

In Bipolar Disorder, altered mitochondrial gene expression decreases brain energy metabolism, alters calcium metabolism, dysregulates calcium channel genes and decreases oxidative stress with lithium and valproate, all giving evidence to support that mitochondria are altered in Bipolar disorders. Research at McLean Hospital in Massachusetts and other institutions relates mitochondrial function and the abnormal cellular energy production which occurs in patients with Bipolar Disorder (slides 40-51).

Magnetic Resonance Spectroscopy demonstrates altered levels of metabolic, or energy related, metabolites, depicting decreasing levels of creatinine and phosphocreatinine in Bipolar Disorders (slides 52-63). Peripheral markers of oxidative stress associated with Bipolar Disorder include TBAR's Thiobarbituric Acid Reactive Substances, Superoxide Dismutase (SOD), Catalase, Glutathione, and Nitric Oxide.

Researchers worldwide have been trying to find the genetic basis of Bipolar disorder because it is heritable - even more heritable than breast cancer. The gene that keeps emerging involves calcium which is central to energy metabolism and mitochondrial

function (slides 64-67). This research leads to the question: Can Bipolar relapse rates be decreased by modulating mitochondria? Would supplements used for mitochondrial disease decrease bipolar symptoms and relapses even without a clear mitochondrial issue?

Mito modulators are (slides 69-73):

- N-acetyl-cysteine (NAC) - precursor to Glutathione, GSH, one of the most important antioxidants the brain produces.
- Acetyl-L-carnitine (ALCAR)
- Alpha lipoic acid
- Coenzyme Q10
- S-adenosylmethionine (SAME)

A double blind, randomized placebo-controlled trial of NAC for depressive symptoms in Bipolar Disease by Berk, et al. in 2008 demonstrated that NAC prevented depression but needs more study. Carnitine and Alpha Lipoic Acid and also need additional study (slides 74-79).

Summary

The reason that psychiatric disorders appear in those with mitochondrial dysfunction is due to the brain's need for constant energy in order to perform. If brain energy is dysregulated, then the numerous brain functions are also dysregulated. Some psychiatric disorders do not have a clear mitochondrial gene mutation but seem to have a dysregulation in energy - maybe not a true mitochondrial myopathy but mitochondrial dysfunction or dysregulation.