

AUTISM SCIENCE DIGEST

The Journal of AutismOne



AUTISMONE

APRIL 2011 ISSUE 1 \$8.95

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REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION

JENNY MCCARTHY

ON THE AUTISMONE/
GENERATION RESCUE
CONFERENCE



FRAN KENDALL, MD, has extensive experience in the diagnosis and management of children and adults with a wide array of inborn errors of metabolism, specifically mitochondrial and metabolic disorders. She was trained and on staff at Boston Children's Hospital and Harvard Medical School for a number of years, was the previous 50% owner of a successful genetics laboratory/ healthcare provider, currently serves on the Medical Advisory Board to MitoAction.org and is a frequently requested speaker. Dr. Kendall has authored numerous research articles on various rare diseases that include mitochondrial disease and an array of other inborn errors of metabolism, and has a long-term interest in research and clinical aspects of metabolic disorders. She currently brings this vast experience to her patients at Virtual Medical Practice. www.virtualmdpractice.com.

BRIDGING THE GAP BETWEEN ASD AND MITOCHONDRIAL DISEASE

BY FRANK KENDALL, MD

Many recent studies have linked autism spectrum disorder (ASD) to poor mitochondrial functioning. Understanding mitochondrial disorders and evaluating their symptoms may help ASD families determine whether further testing may be important for their child.

WHAT ARE THE MITOCHONDRIA?

Housed within our body's cells (Figure 1), the mitochondria create energy, known as ATP. In lay terms, the mitochondria act as our body's cellular power plants, busily converting the food we eat into the fuel we need to function. The mitochondria are long, cylindrical shaped organelles (parts of cells) composed of an inner and outer membrane (Figure 2). It is within the inner membrane that we find the well-oiled mitochondrial machinery that produces energy. Each cell contains many of the "power plants" needed to keep our internal engines running.

WHAT IS MITOCHONDRIAL DISEASE?

Some people are born with changes in their mitochondria, or sustain injury to the mitochondrial system through other mechanisms, either of which can result in decreased energy production and the onset of disease. Mitochondrial disorders are a group of diseases that alter the body's ability to adequately convert food into the energy needed for bodily functions.

These diseases, which affect up to 1 in 4000 individuals, can result in widespread clinical problems. These include vision and hearing loss, seizures, low muscle tone, muscle weakness, migraines, chronic fatigue, developmental delays, autism (ASD or autistic features), kidney and liver disease, diabetes and other endocrine problems, and alterations in blood pressure, heart rate and

temperature regulation. Affected individuals can have some or many of these symptoms and problems. Often, but not always, the symptoms of mitochondrial disorders progressively worsen over time, particularly when individuals are subject to stressors such as illness or surgery. Although some forms of mitochondrial disease only affect one person in an extended family, most types

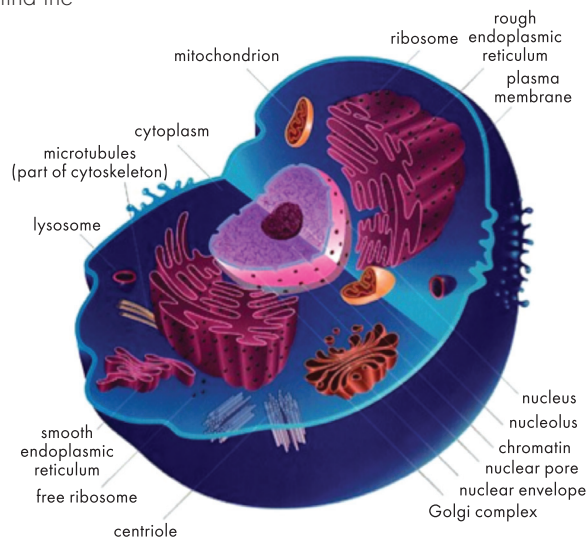


Figure 1: The human cell

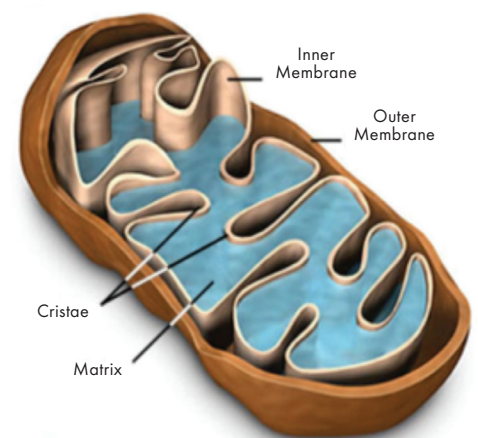


Figure 2: Mitochondria structural features

Table 1
Possible Symptoms of Mitochondrial Disease

BRAIN

- Developmental delays
- Dementia
- Neuropsychiatric disturbances
- Migraines
- Autistic features
- Mental retardation
- Seizures
- Atypical cerebral palsy
- Strokes

NERVES

- Absent reflexes
- Weakness (may be intermittent)
- Fainting
- Dysautonomia (e.g., temperature instability)
- Neuropathic pain

MUSCLES

- Weakness
- Cramping
- Hypotonia
- Muscle pain

GASTROINTESTINAL

- Gastrointestinal problems
- Irritable bowel syndrome
- Dysmotility
- Pseudo-obstruction
- Gastroesophageal reflux
- Diarrhea or constipation

KIDNEYS

- Renal tubular acidosis or wasting

HEART

- Cardiomyopathy
- Cardiac conduction defects (heart blocks)

LIVER

- Liver failure
- Hypoglycemia (low blood sugar)

EARS & EYES

- Visual loss and blindness
- Ptosis
- Ophthalmoplegia
- Optic atrophy
- Hearing loss and deafness
- Acquired strabismus
- Retinitis pigmentosa

PANCREAS & OTHER GLANDS

- Diabetes and exocrine pancreatic failure (inability to make digestive enzymes)
- Parathyroid failure (low calcium)

SYSTEMIC

- Failure to gain weight
- Fatigue
- Unexplained vomiting
- Short stature
- Respiratory problems

Table 2
Genetic Testing for Autistic Spectrum Disorder (ASD) Patients

TIER 1

Basic workup recommended for all patients

- Chromosome microarray studies
- Fragile X
- Complete metabolic panel, CBC, CPK
- Ammonia level
- Lactate and pyruvate levels
- Carnitine, plasma total and free
- Coenzyme Q10 level
- Plasma and urine amino acids
- Urine organic acids
- Plasma acylcarnitines
- Thyroid function tests

TIER 2

Dependent on clinical features and results of Tier 1 testing

- Mitochondrial enzyme and/or DNA testing
- Rett syndrome DNA testing
- Atypical Rett (CDKL5 gene testing)
- PTEN mutational analysis
- NLGN3, NLGN4X, SHANK3, SNRPN gene testing
- Lysosomal enzyme testing
- Peroxisome disease testing (VLCFAs)
- CSF studies for lactate and pyruvate, amino acids and neurotransmitters
- Brain MRI

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are inherited, creating a greater impact on families at large.

The mitochondria create ATP through a complex series of biochemical reactions in the electron transport chain. The electron transport chain, also known as the respiratory chain, is composed of five complexes (Complex I-V) or groups of chemicals whose sole purpose is to create energy from the breakdown products of food using phosphate and oxygen. There are hundreds of different genes (37 inherited from the mother in the form of the mitochondrial DNA and over 850 inherited from both parents in the nuclear DNA) that encode for various proteins that ultimately come together like jigsaw puzzle pieces to create energy. Mitochondrial disorders alter one or more of these genes and proteins, resulting in decreased or ineffective energy production and subsequent malfunctioning of the body's energy-producing processes.

Poor mitochondrial functioning has been linked to the onset of many other disease processes, including Alzheimer's disease, Parkinson's disease, schizophrenia and bipolar disorder. Some medications, such as HIV antiviral drugs, are also known to affect the mitochondria, resulting in poor energy production and mitochondrial disease symptoms. This secondary mitochondrial dysfunction is due to the mitochondria becoming "sick" or "toxic" due to changes in the cells.

HOW IS MITOCHONDRIAL DISEASE DIAGNOSED?

Some patients present with a collection of clinical features and findings that enable them to be diagnosed by a comprehensive history, examination and minimal testing such as blood lactate level and brain MRI.

(See Table 1 for a comprehensive list of mitochondrial-related clinical symptoms.)

For example, individuals affected by Leigh's disease (a particularly aggressive form of mitochondrial disease) have very specific brain MRI changes and often have elevated lactate levels. In this case, diagnosis can be made on the basis of clinical and laboratory findings alone.

In other cases, patients present with findings that are clearly seen in several of the commonly described mitochondrial diseases known to be associated with specific gene changes. An example is a patient who presents with elevated lactate levels, stroke-like episodes and progressive problems who is found to have the common tRNA mtDNA 3243 mutation seen with MELAS (mitochondrial encephalomyopathy lactic acidosis and stroke-like episodes). This diagnosis can be confirmed using a simple blood test.

In the past, for most others, definitive diagnosis of a mitochondrial disease required the completion of special studies on a tissue rich in mitochondria. The body tissues that house the most mitochondria are the brain, kidney, liver, heart, and skeletal muscles. Because collection of brain and heart tissue is impractical, and attainment of kidney or liver tissue for analysis is not only very invasive but potentially damaging and dangerous, muscle tissue became the tissue of choice for investigation of mitochondrial disorders. After collection of the muscle tissue, the mitochondria were removed from the tissue and studied using special instruments such as a spectrophotometer. Although laboratory use of these special instruments allowed physicians to interpret whether or not an individual appeared to be making energy at normal levels, the biopsies also always

carried a risk of false positives and false negatives.

Recently, non-invasive enzyme tests have been developed that use tissues other than muscle tissue, such as buccal swabs and lymphocytes. Gene testing also has expanded, so that a simple blood draw can provide information on over 700 mitochondrial-related genes. These newer tests open the door to a larger patient population, facilitating widespread access to mitochondrial testing without the risks, cost and invasiveness associated with traditional muscle biopsies.

BRIDGING THE GAP BETWEEN MITOCHONDRIAL DISEASE AND AUTISM

Although mitochondrial dysfunction has long been linked to neurological conditions, its association with ASD is a topic of more recent interest, research and discussion. ASD, a complex neurobiological disease, currently affects an estimated 1 in 110 individuals. ASD influences individuals' ability to communicate and relate to others, while predisposing them to rigid routines and repetitive behaviors.

Studies completed by a group in Portugal in 2005 and 2007 (Oliveira et al., 2005; Oliveira et al., 2007) suggested that 4.1% of patients with autism had underlying mitochondrial disease. This analysis would classify mitochondrial disorders as a rare but definable cause of ASD. However, a more recent study in the US published in the *Journal of the American Medical Association* (JAMA) (Giulivi et al., 2010) suggests a much stronger link between autism and mitochondrial dysfunction, reporting that children with autism are far more likely to have defects in their ability to produce energy

However, a more recent study in the US published in the *Journal of the American Medical Association* (JAMA) suggests a much stronger link between autism and mitochondrial dysfunction, reporting that children with autism are far more likely to have defects in their ability to produce energy than typically developing children. In addition to other signs of mitochondrial impairment, the study discovered widespread reduced mitochondrial enzyme function among the autistic children.

However, the authors also emphasized the need for ASD children to be screened for possible mitochondrial dysfunction, citing improvements in children with ASD and mitochondrial abnormalities after initiation of mitochondrial disease management.

than typically developing children. In addition to other signs of mitochondrial impairment, the study discovered widespread reduced mitochondrial enzyme function among the autistic children. Complex I was the site of the most common deficiency, found in 60% of the autistic patients, and occurred five out of six times in combination with Complex V. Other children had problems in Complexes III and IV. Although many questions remain to be answered, the study results point to a stronger link between mitochondrial dysfunction and autism than was previously believed to exist. Importantly, this association was established utilizing a cell population (lymphocytes, a type of white blood cell) that is easily obtainable via blood draw.

Even more recently, a review in *Molecular Psychiatry* (Rossignol & Frye, 2011) reported findings that suggest that children on the autism spectrum also reside along a spectrum of mitochondrial dysfunctions of varying severity. This article, like the JAMA report, pointed to the need for more research to understand this association. However, the authors also emphasized the need for ASD children to be screened for possible mitochondrial dysfunction, citing improvements in children with ASD and mitochondrial abnormalities after initiation of mitochondrial disease management.

WHICH ASD PATIENTS SHOULD BE EVALUATED FOR MITOCHONDRIAL DISEASE OR OTHER GENETIC DISORDERS?

All ASD patients should undergo a basic genetics workup (see Table 2). Although **some** of the first tier tests in Table 2 can be obtained without a subspecialist's input, interpretation of the data may be difficult without the involvement of a genetics specialist. Decisions regarding whether a

specific patient requires a more in-depth investigation for mitochondrial or other rare metabolic or genetic diseases should be undertaken by a mitochondrial expert and/or a biochemical geneticist. Such a decision should be based on a number of factors, including screening results, laboratory testing, family history, physical findings, and clinical features. In general, the genetics workup and ongoing management of an ASD patient (should a genetics diagnosis be made) is best completed by someone trained in genetics with mitochondrial and metabolic disease experience and expertise.

WHY IS IT IMPORTANT TO KNOW IF AN ASD PATIENT HAS MITOCHONDRIAL DISEASE?

Most people or families seek a diagnosis for two general reasons. First, a mitochondrial diagnosis can lead to interventions that will improve the life and health of the affected person. Although mitochondrial disease is not yet curable, an affected person's quality and duration of life can be improved by aggressive metabolic management by a mitochondrial expert. Knowing that a patient has a mitochondrial disorder is also important for ER staff and other healthcare professionals, as certain protocols should be followed to prevent the adverse affects that can occur particularly at times of illness and stress. Secondly, obtaining a clear diagnosis may assist families with future pregnancy planning, as well as providing a basis for determining risks to other family members. In addition, mitochondrial medicine is rapidly changing, with a number of clinical trials under way. Enrollment and participation in ongoing treatment trials and research protocols requires that a patient be definitively diagnosed with a mitochondrial disease.

CONCLUSION

Navigating the road of complex medical problems can be confusing and overwhelming. Many parents and families find themselves alone and sometimes bewildered as they try to determine the best course of action for their loved one. Understanding the facts and options, and what constitutes an appropriate evaluation and workup, can empower families to obtain the best care for their child or loved one and help provide them with the best possible outcome and quality of life. Making use of resources such as foundations, support organizations and chat rooms (particularly to seek opinions about subspecialists being considered for care) can alleviate stress, avoid potential conflicts of interest with providers, and guarantee the best care.

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