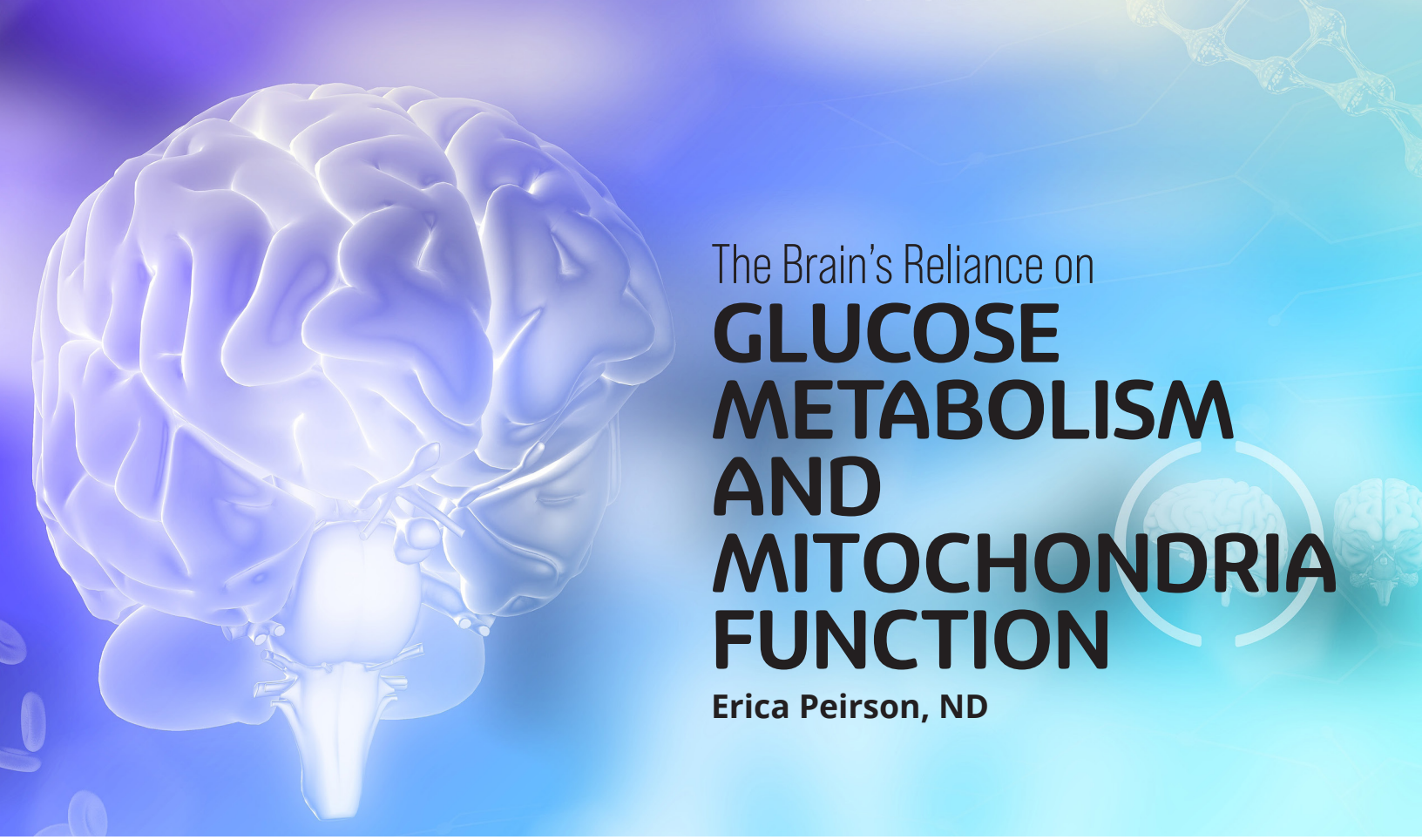

The Brain's Reliance on GLUCOSE METABOLISM AND MITOCHONDRIA FUNCTION

Erica Peirson, ND

Brain Energy Requirements

The brain is one of our most metabolically active organs. It requires a great deal of energy during the day and at night when we are sleeping. It's been estimated that it consumes approximately 20 to 25 percent of total body energy expenditure in adults.[1] During infancy, childhood and adolescence, this number is even higher and can reach 44 to 87 percent of resting metabolic rate (RMR).[2] The peak age of energy expenditure by the brain occurs around the age of four to five years old, a period which accounts for a decrease in growth that also occurs at that age. It is worth asking where this energy comes from, how it gets to the brain and what the consequences are when the brain is not provided with the energy it needs during key developmental years.

From Glucose to Energy

The source of energy for all of the cells of the body is ATP (adenosine triphosphate). This energy is stored in the high energy bonds that hold phosphate groups together within the ATP compound (see Image 1).

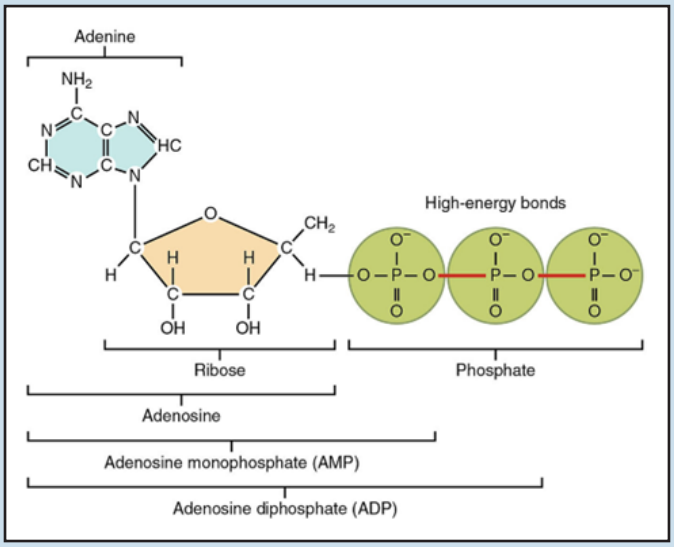

Image 1. Adenosine triphosphate (ATP).

ATP is generated by mitochondria within the cells of our body. Mitochondria are fascinating organelles that are thought to have evolved as independent organisms 1.45 billion years ago when life on earth was dominated by single celled organisms. Their DNA is different from the DNA of our cells. It's theorized that they were once a single celled organism that was engulfed by another single celled organism and ultimately evolved into multicellular animals of today. They are considered the "powerhouse" of the cell because they are the energy or ATP factory of the cell.

When we eat carbohydrates, fats and protein we are essentially feeding our mitochondria to make energy for us in the form of ATP. This ATP is used to drive nearly all cellular processes within the body. When mitochondria do not function properly ATP production declines resulting in lower overall cellular function and metabolism. The first organs of the body that will struggle in this situation are those that are the most highly metabolic, like the brain.

The main source of energy and ATP production in the brain is glucose (see Image 2).[3] The energy from glucose comes from the electrons that are contained within its chemical structure. Through a multistep process that requires oxygen and multiple enzymes functioning optimally within mitochondria these electrons are ultimately used to create ATP. It's like a relay race in which one runner passes the baton to another.

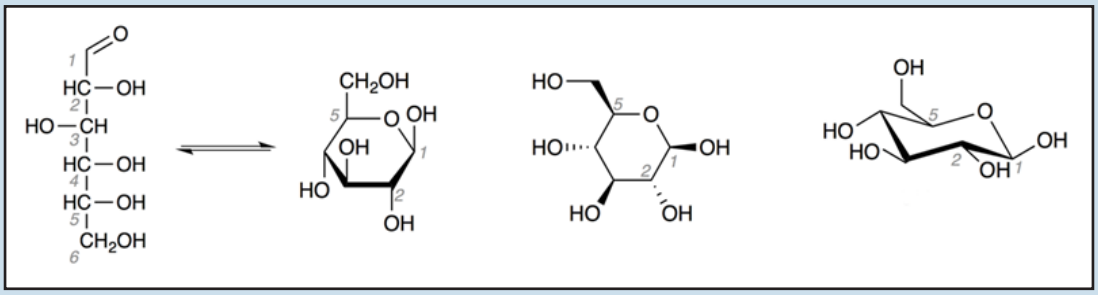

Image 2. Glucose represented by various structural models.

Another great analogy for the energy that is contained within glucose is that of a burning log. Wood is made up of long chains of glucose in the form of cellulose (see Image 3). The energy we get from burning wood comes from the electrons contained within the glucose. This process requires the presence of oxygen, just as it does in our body. Humans cannot access the chemical energy from glucose contained in wood because our bodies don't make the enzyme that's specific for breaking the bonds that link glucose together in the form of cellulose. We also don't burn up from getting energy from glucose like a log does. Our bodies use about 14 different enzymes, 11 of which are within mitochondria, to carefully pull energy from glucose one electron at a time to make ATP.

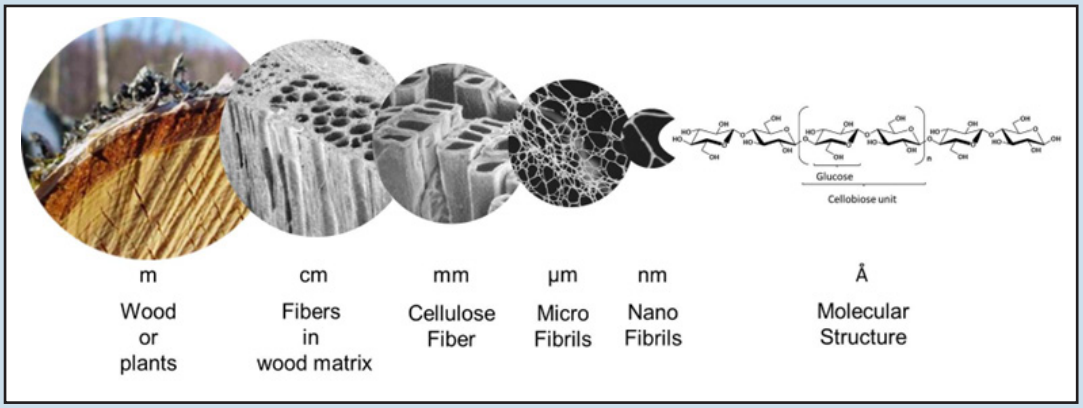

Image 3. Wood composed of chains of glucose.[4]

The function of these 14 enzymes is dependent on cofactors. In this case, the cofactors are vitamins. In fact, all water-soluble vitamins are cofactors for enzymes because that's how vitamins work in the body. They assist in enzyme function. Enzymes are like the hands of the relay race runners. In order to grab onto the baton, however, they require some assistance in order to get them into the right shape to grab the baton. In the presence of a vitamin deficiency, these enzymes won't function properly. As a result, the "baton" is dropped and energy production is impaired.

Requirements for Optimal Mitochondria Function

The B vitamins are the ones that are necessary for optimal function of enzymes within mitochondria. These B vitamins are needed within the citric acid cycle, which is the first phase of mitochondria function (see Image 4). Other cofactors that are not classified as vitamins include iron, glutathione, coQ10, alpha-lipoic acid, magnesium and manganese. A deficiency in any one of these micronutrients will result in mitochondria that do not function optimally. This can ultimately lead to low production of ATP and a lower metabolic rate for the many processes that keep the brain healthy.

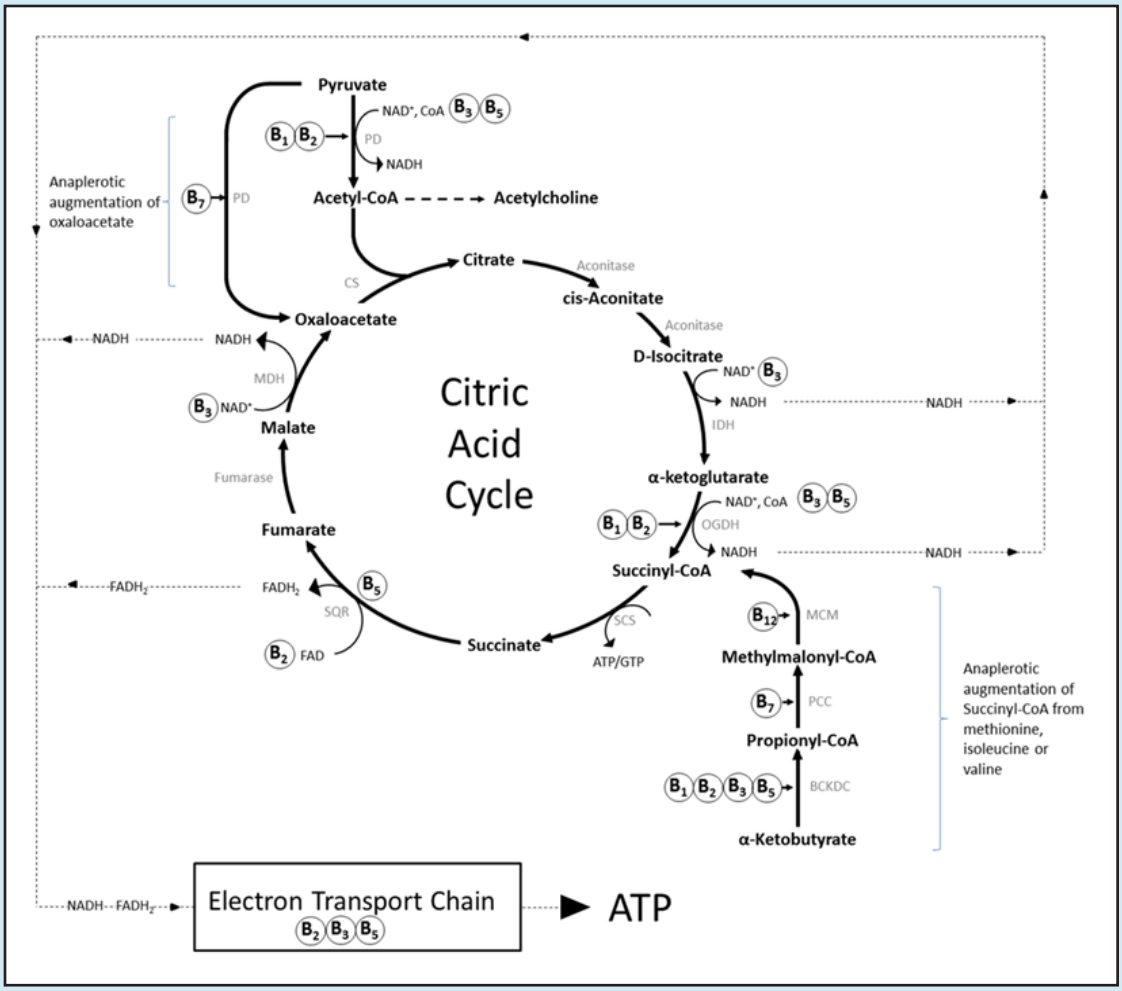

Image 4. B vitamin cofactors needed for mitochondria function.[5]

Two key B vitamins that are needed for mitochondria function that act as "keys to the front door" are thiamine (vitamin B1) and riboflavin (vitamin B2). They are cofactors for a very large enzyme complex called pyruvate dehydrogenase (PDC). PDC is the gate to the citric acid cycle that is the first phase of mitochondrial function. Its job is to transfer pyruvate — the end product of glycolysis — into mitochondria where it can be used to continue the process of energy production. If this front gate does not open due to a thiamine or riboflavin deficiency, the whole process of mitochondrial function slows or shuts down.

In 2002, Dr. Derrick Lonsdale and colleagues published a paper outlining their use of thiamine tetrahydrofurfuryl disulfide (TTFD). They reported that "8 out of 10 children improved clinically." They also studied urine samples of children with autism and found high levels of arsenic, a substance that is known to cause thiamine deficiency.[6] While this was a small pilot study, these results were significant. A team of researchers at the University of California, Davis, reported activity of PDC in children with autism was half that of children without autism. They found that the mean PDHC activity has a value of 1.0 in children with autism compared with a value of 2.3 in control children.[7]

Another consequence of a deficiency in thiamine and/or riboflavin deficiency is a low production of acetylcholine secondary to low acetyl-CoA production, as seen at the top of Image 4. Acetylcholine is an extremely important neurotransmitter that is needed for the function of all organs of digestion, gut motility, skeletal muscle function and neuron-to-neuron communication within the brain, among other things.

Signs and Symptoms of Mitochondrial Dysfunction

Since mitochondrial function is necessary for nearly all organ function, the signs and symptoms of mitochondrial dysfunction can be seen in more than just brain function. They include:

- low muscle tone
- difficulty swallowing
- failure to thrive
- learning disability
- fatigue
- delayed gut motility
- pancreatic dysfunction
- heat/cold intolerance
- migraines
- lactic acidosis
- liver disease, or elevated liver enzymes
- immune system problems
- heart problems
- kidney problems
- neurological problems
- autonomic nervous system dysfunction

Elevated liver enzymes and liver dysfunction result because the liver, like the heart and kidneys, is also a very metabolically active organ of the body.

Autism and Mitochondrial Dysfunction

A search in PubMed for the term "autism mitochondrial dysfunction" results in 394 papers dating back to 1998. One of the first papers, written by Dr. Jay Lombard, is titled "Autism: a mitochondrial disorder?"[8] He states, "Organic acidemias and other disorders of metabolism need to be routinely screened for and identified (in those with autism)." It's now 24 years later, and this advice has not become routine within conventional medical practices. A more recent paper, "Mitochondrial Dysfunction in Autism Spectrum Disorder: Unique Abnormalities and Targeted Treatments" — written by Dr. Richard Frye in 2020 — summarizes the growing amount of literature that supports mitochondrial dysfunction as a potential causative factor in some children with autism.[9]

Gastrointestinal issues can be secondary outcomes of mitochondrial dysfunction. A recent paper reported that, "Gastrointestinal (GI) disorders are among the most common medical conditions that are comorbid with autism spectrum disorders (ASD)."[10] Several gastrointestinal issues like small intestinal bacterial overgrowth and candida overgrowth, which occur secondary to slow gut motility, among other causes, can result in malabsorption of micronutrients that are needed for mitochondria function. An example of this is the production of aldehydes that occur secondary to candida overgrowth in the GI tract. Aldehyde toxicity leads to deficiencies of vitamin B1, B6, folate, zinc and possibly other micronutrients.[11] Small intestinal bacterial overgrowth can result in deficiencies of vitamins B12, B1, B3, A, D and E and iron.[12] The resulting mitochondrial dysfunction secondary to these micronutrient deficiencies leads to further gastrointestinal issues, malabsorption and a vicious cycle (see Image 5).

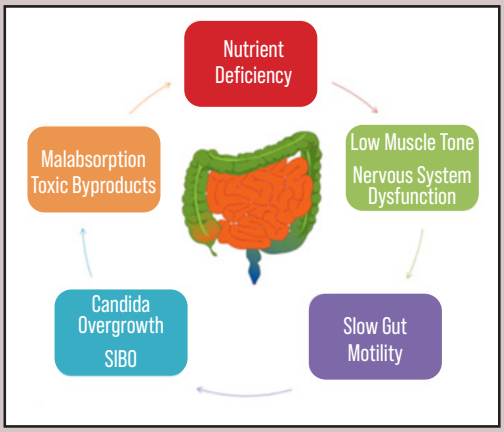

Image 5. Mechanism of nutrient deficiencies in children with low muscle tone.

Diagnosing Mitochondrial Dysfunction

Diagnosing mitochondrial dysfunction includes doing a thorough history, review of symptoms and a physical exam. The most important test for diagnosing mitochondrial dysfunction in children with a diagnosis of autism or early warning signs of autism is a urinary organic acid test. One study stated that, "Quantitative organic acid testing can give information about potential problems, especially with energy production, neurotransmitter metabolism, intestinal dysbiosis and nutritional individuality which is very important in autistic children."[13] Organic acids are metabolites of multiple biochemical pathways in the body. Their levels will be higher in the urine in the presence of vitamin and other cofactor deficiencies (see Image 6).

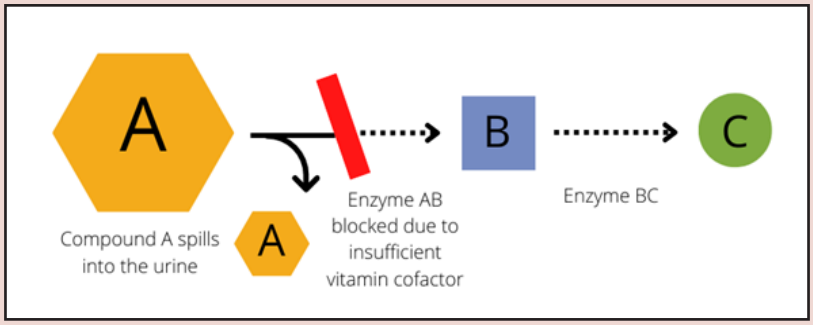

Image 6. Biochemical pathway in the presence of a vitamin deficiency.

An organic acid test can also detect metabolites of yeast and bacteria. Elevations of these metabolites indicate elevated levels of yeast and bacteria in the GI tract, which is a common cause of micronutrient deficiencies. A medical practitioner who is trained in the interpretation of organic acid test results can quickly determine whether the patient is experiencing mitochondrial dysfunction.

Blood labs that are helpful in determining whether a patient is experiencing mitochondrial dysfunction and what supplements are needed include the following:

- Carnitine panel
- TSH, free T4, free T3, reverse T3
- CBC
- Comprehensive Metabolic Panel
- Serum B12
- Ferritin
- Lactate
- Pyruvate

A blood draw for lactate and pyruvate is not required if an organic acid test is being conducted as both are already included in an organic acid test.

Treatment of Mitochondrial Dysfunction

Treatment of mitochondrial dysfunction should be based on each child's individual needs and lab results. While it is possible to use supplements on a trial-and-error basis or in response to symptoms alone, using lab results avoids the potential negative side effects of supplements. The fact that something is "natural" or "simply a vitamin" does not mean that there are no side effects. A full organic acid test includes over 70 markers. Interpretation of this test does not simply involve treating each individual marker with its coordinating supplement. It also entails looking for patterns, corroborating markers and finding the root cause of abnormal results. Outlining the interpretation of a full organic acid test is outside the scope of this article and should be undertaken by a trained medical practitioner. A brief list of some of the key markers used on an organic acid test and blood labs to assess for mitochondrial function, as well as interventions used for aberrant results, is found below (see Table 1).

Lab	Indication	Intervention if high	Intervention if low
Lactic acid	Pyruvate dehydrogenase (PDC) activity	Vitamins B1, B2, R-lipoic acid	Assess for hypoglycemia
Pyruvic acid	Pyruvate dehydrogenase (PDC) activity	Vitamins B1, B2, R-lipoic acid	Assess for hypoglycemia
Adipic, Suberic, Sebacic acid	Fatty acid metabolism	L-carnitine, vitamin B2	Assess for fat malabsorption or low fat in the diet
Succinic acid	Succinate dehydrogenase (SDH) activity	CoQ10, vitamin B2	may indicate the need for leucine / isoleucine
Glutaric acid	Glutaryl-CoA dehydrogenase (GCDH) activity	Vitamin B2	may indicate the need for leucine / isoleucine
Carnitine	Carnitine levels in the blood	Reduce dose of carnitine and/ or meat in the diet	Carnitine supplementation
Serum B12	B12 levels in the blood	Reduce supplementation or look for cause of elevation if not supplementing	Low = <800 mcg/dL Supplement with methyl, hydroxy or adenosylcobalamin
Ferritin	Iron storage, inflammation	High = possible inflammation[14]	Iron bisglycinate 10-15 mg give on empty stomach

Table 1. Labs to assess for mitochondrial function and treatment for aberrant results.
green = urine organic acid test
blue = blood test

After appropriate and individualized supplementation, improvements in mitochondrial function can be seen as improved gut motility, decreased fatigue, increased alertness and engagement and increased muscle tone and strength. These improvements are typically seen within days or weeks of starting supplementation. For example, a team of pediatricians in Japan tested carnitine in patients with motor and intellectual disabilities and found that levels of free carnitine were significantly correlated with severity of constipation.[15] They also noted, "The severity of constipation (frequency of defecation and form of feces) in constipation group was significantly relieved after supplementation with 10–50 mg/kg/day carnitine." In another study, a team of researchers demonstrated improvements in communication, interaction with peers, sleep and food rejection after three months of supplementing with ubiquinol, a form of CoQ10, at 50 mg twice a day.[16]

Conclusion

As the prevalence of autism increases, so has the number of parents seeking help for their children outside of the conventional medical paradigm. While autism is a complex neurodevelopmental condition with potentially multiple causes, one significant area that should be ruled out in all children with autism is mitochondrial dysfunction. Testing for and treating mitochondrial dysfunction is an actionable way of supporting the brain and overall health of children whose autism is rooted in mitochondrial dysfunction. In addition, detecting early signs and symptoms of mitochondrial dysfunction in infants and toddlers is key to optimizing early brain development in children, which could potentially prevent many cases of autism.

Take Home Points

- When we eat carbs, fats, and proteins, we are feeding our mitochondria to make energy for our body.
- A deficiency in micronutrients will result in mitochondria that do not function optimally.
- The signs and symptoms of mitochondrial dysfunction can be seen in more than just brain function.
- Gastrointestinal issues can be secondary outcomes of mitochondrial dysfunction.
- The most important test for diagnosing mitochondrial dysfunction in autistic children is a urinary organic acid test.
- Treatment should be based on each child's individual needs and lab results.

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