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Branch Chain Amino Acid Deficiency Linked to Autism?

Analysis by Dr. Joseph Mercola Fact Checked | March 24, 2023

STORY AT-A-GLANCE

- Some cases of autism are caused by mutations in the branched chain ketoacid dehydrogenase kinase (BCKDK) gene; in those with BCKDK deficiency, BCAAs are broken down too quickly, leading to depletion
- BCAA deficiency is linked to a neurodevelopmental disorder that includes autism, intellectual disability and microcephaly
- In children with BCKDK deficiency, a high-protein diet and BCAA supplements led to significantly increased BCAA levels along with improvements or stabilizations in motor functions and head circumference in nearly all of the patients
- None of the children who started treatment before the age of 2 developed autism; the youngest child was 8 months old when treatment began, and they had normal development at age 3
- The researchers have called for adding BCKDK deficiency to newborn screening tests so BCAA supplementation could be started right away, potentially preventing autism development

Some cases of autism are caused by mutations in the branched chain ketoacid dehydrogenase kinase (BCKDK) gene.[1] The BCKDK gene is involved in the metabolism of branched-chain amino acids (BCAAs). In those with BCKDK deficiency, BCAAs are broken down too quickly, leading to depletion.[2]

This, in turn, is linked to a neurodevelopmental disorder that includes autism, intellectual disability and microcephaly. Dietary changes, including supplementing with BCAAs, appears to be an effective treatment for some and, if started early, may even prevent autism from developing.

BCAA Supplements May Benefit Autism

In 2012, researchers found that supplementing with BCAAs reversed some of the associated neurological characteristics in mice, and explained:[3]

> *"By supplementing the diet of human cases with BCAAs, we have been able to normalize their plasma BCAA levels, which suggests that it may be possible to treat patients with mutations in BCKDK with BCAA supplementation."*

Joseph Gleeson, a professor with the University of California, San Diego, who was involved with the study, noted:[4]

> *"In a 2012 study, we determined that mice with a mutation in BCKDK that are on a diet low in branched-chain amino acids have traits similar to those of autistic children; feeding the animals high levels of the amino acids eliminates the traits.*
>
> *Supplementing the diets of autistic children who have a BCKDK mutation improved their behavior remarkably. One young woman became calmer and spoke in full sentences; another was more energetic and attentive.*
>
> *Although mutations in BCKDK appear to be rare, metabolic problems in autism may not be. One clinical trial found that nearly 17 percent of autistic participants showed signs of unusual amino-acid metabolism.[5] And in 2012, researchers tied mutations in a gene involved in the synthesis of carnitine (a compound derived from an amino acid) to autism.[6]*
>
> *The genetic risk factor is present in 1 in 350 boys, only 2 to 4 percent of whom have autism. However, if a boy with autism carries this mutation, a readily*

available supplement might treat the underlying cause."

Could Early BCAA Supplementation Prevent Autism?

A 2023 study provides even more framework for using BCAAs to improve traits, such as head circumference and motor skills, in those with BCKDK deficiency.[7] It used data from 21 children with BCKDK mutations, who were diagnosed with BCKDK deficiency when they were between 8 months and 16 years of age.

At the time of diagnosis, all the children had BCAA levels — including leucine, valine and isoleucine — below reference values in plasma and cerebrospinal fluid. All the children also had neurodevelopmental delays, including gross motor function impairment, intellectual disability, language impairment, autism spectrum disorder (ASD), epilepsy, clumsiness, hearing loss and/or feeding difficulties.

While none of the children had microcephaly at birth, 17 individuals developed it during the follow-up period.[8] The children were treated with a high-protein diet (all protein-containing foods contain BCAAs) and BCAA supplements, which led to significantly increased BCAA levels along with improvements or stabilizations in motor functions and head circumference in nearly all of the patients.

Further, none of the three children who started treatment before the age of 2 developed autism. The youngest child was 8 months old when treatment began, and they had normal development at age 3. "This work highlights the potential benefits of dietetic treatment, in particular early introduction of BCAA," according to the study.[9]

One of the best food sources of BCAAs is whey, which is rich in leucine. Grass fed beef and bison, organic, pastured eggs and grass fed dairy products are also good sources of BCAAs. The researchers have called for adding BCKDK deficiency to newborn screening tests. In the study, six of seven children with available newborn screening results had low amino acid levels.[10]

"Those children starting treatment younger, when they were younger than 2 years of age, evolve much better than the others," lead study author Ángeles García-Cazorla told

Spectrum News. “There is really a window of treatment where you can reverse or improve the disease a lot.”[11]

García-Cazorla informed Catalonia, Spain health officials in charge of newborn screenings about the study findings, and they added BCKDK deficiency to the screenings.

In the U.S., Spectrum News reported, “adding diseases to newborn screening can be a cumbersome and slow process. But many newborns already have their amino acid levels checked for another rare disease, maple syrup urine disease, [Gaia] Novarino [researcher on the 2012 study] notes. ‘So it should be a no-brainer to go ahead.’”[12]

The Vitamin B12 Connection

It’s interesting to note that vitamin B12 is also sometimes used as a treatment for autism, with studies showing it typically has positive effects on symptoms[13] such as expressive communication, daily living and coping social skills, sleep, gastrointestinal symptoms, hyperactivity, tantrums, vision, eye contact and more.

Vitamin B12 deficiency, meanwhile, may reduce the ability to metabolize BCAAs. In fact, a study on worms called Caenorhabditis elegans (C. elegans) found a B12-deficient diet harms the worms’ health at a cellular level by altering BCAA metabolism: “The research showed that the reduced ability to break down BCAAs led to a toxic buildup of partially metabolized BCAA byproducts that damaged mitochondrial health.”[14]

In a study of 57 children with autism, treatment with methyl B12 improved symptoms,[15] while **vitamin B12 deficiency** in children can mimic signs and symptoms of autism, sometimes leading to a misdiagnosis. For instance, vitamin B12 deficiency can lead to obsessive-compulsive behaviors, aloofness, withdrawal and problems with speech, language and comprehension in children.[16] Good food sources for vitamin B12 include:

Grass fed organic beef and beef liver	Lamb

Venison	Scallops
Organic, pastured chicken and eggs	Raw organic, grass fed milk
Nutritional yeast	

The Mitochondrial Dysfunction Connection

Rates of autism continue to increase in the U.S., with the latest estimates showing 1 in 30, or 3.49%, of children ages 3 to 17 were diagnosed with ASD in 2020.[17] One factor underlying this surge could be mitochondrial health. In October 2020, a scientific review published in Seminars in Pediatric Neurology outlined evidence that mitochondrial function may be related to autism.

It was estimated in 2017 that about 4% of children with autism could be diagnosed with a definite mitochondrial disease, while other research suggested abnormalities of mitochondrial function could affect up to 80% of children with autism.[18]

"Novel abnormalities" in mitochondrial function have been found in children with autism and treatments targeting mitochondrial dysfunction, such as L-carnitine supplementation and a ketogenic diet, have been found to be beneficial. Children whose autism is rooted in mitochondrial dysfunction will typically have a key set of symptoms that include:[19]

- Fatigability
- Gastrointestinal disorders
- Seizures and/or epilepsy
- Motor delay and/or ataxia and/or muscle weakness
- Unusual neurodevelopmental regression, including multiple regressions or regression later than commonly associated with ASD

The review's author, Dr. Richard Frye with Barrow Neurological Institute at Phoenix Children's Hospital in Arizona, pointed out that mitochondria are "very vulnerable to environmental factors" and a novel type of dysfunction of mitochondria "in which the activity of the electron transport chain is significantly increased … may be associated with environmental exposures."[20]

In 2010, the federal vaccine court conceded that Hannah Poling's autism was the result of vaccinations, which "significantly aggravated an underlying mitochondrial disorder, which predisposed her to deficits in cellular energy metabolism, and manifested as a regressive encephalopathy with features of autism spectrum disorder."[21]

Do Antidepressants During Pregnancy Trigger Autism?

Environmental exposures, including to certain medications, are also likely involved. research, published in Brain, Behavior, and Immunity, suggests antidepressant drugs during pregnancy may play a role. The finding could have major implications for public health, considering that among pregnant women using antidepressants, 80% are prescribed antidepressant drugs known as selective serotonin reuptake inhibitors (SSRIs).[22]

The animal study revealed SSRIs may interact with inflammation in the mother's body, producing a reaction that affects the maternal-fetal interface (MFI), which includes the decidua (a mucous membrane lining the uterus) and placenta, and ultimately the fetus' developing brain.

Later in life, adult offspring whose mothers were exposed to inflammation during pregnancy had sex-based behavioral changes, including lessened communication and low interest in social interactions, mimicking those seen in people with autism.[23]

"Moreover," the researchers explained, "the combination of maternal inflammation in the presence of pharmacologic inhibition of serotonin reuptake further transformed MFI physiology and offspring neurobiology, impacting immune and serotonin signaling pathways alike."[24]

Even acetaminophen, brand name Tylenol, which many consider to be completely innocuous, is linked to autism when used during pregnancy. Compared to children of mothers with the lowest acetaminophen burden during pregnancy, children of those with the greatest acetaminophen burden had a 262% higher risk for ASD.

As noted by the authors, their findings "support previous studies regarding the association between prenatal and perinatal acetaminophen exposure and childhood neurodevelopmental risk."[25] Exposure to glyphosate,[26] mercury, lead,[27] aluminum[28] and other chemicals, including phthalates[29] and air pollution,[30] has also been implicated in autism.

The Gut-Brain Connection in Autism

Another avenue being explored is that the gut plays an important role in the development of ASD. Gut dysfunction in autism may be due to mutations in genes found in both the gut and brain that affect neuronal communication and cause gut dysfunction.[31]

Russian neurologist Dr. Natasha Campbell-McBride believes brain toxicity stemming from gut toxicity, otherwise known as Gut and Psychology Syndrome (GAPS), is a key factor that sets the stage for autism, especially when vaccines are added into the mix. Having an imbalanced gut microbiome may also render children more susceptible to the adverse effects of environmental toxins.

Interestingly, BCAAs are also involved in regulating intestinal health and maintaining intestinal barrier function, while dietary supplementation with BCAAs promoted intestinal development and increased intestinal absorption of amino acids in animal studies,[32] pointing to another avenue of potential benefit of BCAAs to this complex condition.