Amino Acids, B Vitamins, and Choline and ASD

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Autism spectrum disorder (ASD) is a developmental disorder of variable severity, characterized by difficulties in social interaction, communication, and restricted or repetitive patterns of thought and behavior. In 2018, the incidence of ASD was 2.4 times higher than estimated in 2000. Through examining plasma profiles, urine samples, and dietary intake, researchers found that low choline, abnormal amino acid, and low B vitamin levels were present in children with ASD compared to those without ASD.

autism autism spectrum disorder ASD symptoms ASD incidence choline vitamin B folate B12 B6 amino acids

1. Introduction

In the United States, 1 in 44 children were identified with autism spectrum disorder (ASD) in 2018, a major increase from the estimated 1 in 150 in 2000 [1]. Autistic disorder, Asperger syndrome, and pervasive developmental disorder can be categorized under ASD. Currently, there is no known cause for ASD; however, brain scans show that it is likely to be caused by abnormalities in brain structure and function [2]. ASD can result in restrictive, repetitive, and stereotypical behavior patterns and cause impairments in social interaction and verbal and nonverbal communication. Children with ASD experience fluctuations in aggression, hyperactivity, and attention symptoms. In addition to the symptomatic factors, ASD is costly and is a lifelong demand to both individuals with autism and their caregivers. The standard care process for those living with ASD typically involves full-time behavioral and educational therapy [3]. On average, over the individual's lifetime, medical costs for individuals with ASD are estimated to be about USD 293,545 more expensive when compared with an individual who developed typically. Thirteen years of special education for those with ASD may cost on average USD 37,872 more than education for a typically developing student. Moreover, lifetime care costs (medical and at-home care) are estimated at around USD 967,493 for an individual living with ASD. In addition, over the course of the individual with ASD's lifetime, the family may experience a loss of productivity, costing around USD 2,109,358 [3]. Evidence shows that individuals with ASD frequently suffer from disrupted nutrient levels [4]. It has been shown that supplementation with specific nutrients can decrease the incidence of ASD and alleviate the severity of symptoms. Nutritional interventions before and during pregnancy as well as during early ages are a feasible and cost-effective way of preventing and controlling symptoms of ASD.

2. Choline

Choline is typically taken into the body through diet. It is an essential nutrient and plays an important role in neurotransmitter synthesis (acetylcholine), methyl-group metabolism (homocysteine reduction), cell-membrane signaling (phospholipids), and lipid transport (lipoproteins) [5][6]. Choline is also known to affect sensory processing, cognitive functioning, memory, and learning which are often atypical in individuals with ASD [7]. It is known that choline contributes to brain development [8] and assists in the production of methionine, an essential amino acid [9]. Hamlin et al. evaluated choline and betaine effects in children with and without ASD by assessing their dietary intake and blood levels [10]. They showed that the children with ASD had a dietary intake of choline that was below the dietary reference's intake level appropriate for their age. Moreover, plasma levels of choline were significantly lower in a subgroup of children with ASD when compared to the age-matched control children without ASD [10].

Individuals with ASD often experience impaired functioning of the central nervous system (CNS) as well as metabolic disorders [11]. Choline's role in the synthesis of acetylcholine and reduction of homocysteine can help with improving core symptoms of ASD [12]. To evaluate the effects of choline in improving language and core ASD symptoms in children, Gabis et al. conducted a nine-month randomized, double-blind, placebo-controlled trial following 60 children with ASD [5]. They examined choline supplementation (350 mg) alongside donepezil (5 mg), a prescription drug that inhibits the breakdown of acetylcholine (ACh) [4]. The study aimed to increase ACh activity in the synaptic cleft by increasing ACh in the brain via supplementing with choline and preventing its breakdown by giving patients donepezil. Researchers found the combined treatment to improve receptive language skills after 12 weeks of treatment, primarily in young children (10 years and younger). Improvement stayed consistent even six months after treatment. The study reported no side effects for the use of the regimen in children aged under 10 years; however, those above the age of 10 showed some worsening in behavior, specifically with irritability [5].

These effects have been shown in animal studies as well. Agam et al. studied methylenetetrahydrofolate reductase (MTHFR)-deficient mice to resemble the common gene abnormalities associated with an increased risk for ASD [9]. The MTHFR enzyme assists in processing amino acids; particularly, it is important in the conversion of homocysteine to methionine due to its role in the metabolism of folic acid [13]. This gene abnormality has been shown to be present in both mothers and their offspring with ASD. The offspring of MTHFR-deficient mice which received choline supplemented drinking water (0.003%) for two weeks showed a reduction in characteristics related to repetitive behavior and anxiety. Additionally, in male mice, social behavior and abnormal cortical protein levels of autophagy markers (*p62* and *Beclin-1*) were improved [9]. When compared to controls, both up- and down-regulation of autophagy have been associated with autism [14][15][16][17]. One study finds autophagy marker, beclin-1, to be decreased for both males and females, and LC3 to be increased for females and decreased for males [14]. Another study found the autophagy regulator, mTOR, to be overactive in those with ASD-like behaviors [15]. This association can be understood because autophagy plays a role in the brain development of humans, and normal autophagy is associated with the prevention of neurodevelopmental disorders, such as ASD [18].

Adequate intake of choline is also essential during gestation, as it contributes to brain development. An inadequate amount of choline could also influence the brain development of those with ASD, resulting in symptoms being more severe. A study evaluated the impact of choline consumption during pregnancy and nursing to evaluate social interaction and anxious behaviors [8]. Social behavior, anxiety, and repetitive behaviors pre- and post-choline supplementation was examined in a particular mouse strain that displays autism-like phenotype behavior. Through analysis, researchers found choline supplementation to reduce deficits in social interaction, lower anxiety levels, and reduce marble-burying behavior in mice [8]. Marble-burying is an animal model used in scientific research to depict anxiety or obsessive-compulsive disorder (OCD) behavior [19].

The reported benefits of choline supplementation may be partially due to its role in the improvement of potassium, calcium, and sodium chloride ions transportation. Olson et al. studied the potential positive effects of dietary choline intake on improving sensory processing function in ASD [7]. The established idea that acetylcholine supports ion transport in the body was used to suggest that proper intake of choline through the diet would increase acetylcholine and sequentially increase ion transport in the body, which would improve sensory processing in ASD.

3. B Vitamins

B vitamins are taken into the body through diet and supplementation, including fortification and enrichment. B vitamins are essential to many of the body's processes involving the CNS, oxygen transportation, blood cell production, and amino acid production and conversion [20][21][22]. Folate is known to assist in converting homocysteine to methionine [9]. Vitamin B6 contributes to the conversion and degradation of amino acids via the transfer of nitrogen. It also contributes to the production of neurotransmitters (serotonin and dopamine), glutathione, and hemoglobin [22]. Earlier research suggested that vitamin B6 and magnesium supplementation may result in improved ASD symptoms [23][24][25]. Each of these vitamins plays a distinctive role in CNS function. Deficiency of folate may cause behavior changes and cognitive impairment, while deficiency of vitamin B6 can result in irritability [26]. The deficiency of vitamin B12 has features of neurological impairments such as motor disturbances, cognitive impairment, irritability, and brain cell loss, all commonly known as symptoms of ASD [20][26].

Evidence has shown that adequate intake of B vitamins is important in preventing behavioral and cognitive disorders, significant concerns in those with ASD. Schmidt et al. examined the associations between autism and maternal vitamin supplement intake during the periods of preconception and prenatal development. They recruited 545 children between 24 and 60 months of age from the large, population-based, case-control study, Childhood Autism Risks from Genetics and Environment (CHARGE) [27]. Children were grouped based on diagnoses and their cognitive function and assessed using validated questionnaires, behavioral scales, and learning scales. Mothers answered questions specific to vitamin supplementation and fortification intake at any time during three months before conception, through pregnancy, and during the period of breastfeeding. The prenatal vitamins used by mothers typically contained iron, vitamin B6, vitamin B12, and folic acid (800 µg). Findings of the study showed that prenatal vitamin intake during the three months before conception and the first month of pregnancy was associated with a reduced risk for autism. Additionally, researchers studied vitamin intake in normal participants and those with abnormalities in folate, methionine, and transmethylation pathways. Genotyping was determined through blood collection from all family members. Through genetic testing, folate-related pathways were found to be more abnormal in those who were genetically susceptible to developing autism [27].

Another study by Raghavan et al. aimed to determine if multivitamin supplementation during pregnancy and maternal levels of plasma folate and B12 had an association with the incidence of ASD [28]. Through the Boston Medical Center, researchers recruited and reported on 1257 mother–child pairs that were followed from birth throughout childhood. Mothers who reported multivitamin supplementation from three to five times per week were found to have a lower chance of birthing a child with ASD. Those supplementing less than three or more than five times per week were found to have a higher chance of birthing a child with ASD. Very high blood levels of folate (>2.2 micrograms per deciliter) and B12 (>19.5 micrograms per deciliter) were

associated with having a two and a half times higher risk of birthing a child with ASD [28]. Similarly, Steenweg-de Graaff et al. examined the association between human folate concentrations during pregnancy and the severity and presence of autistic traits in their offspring during six years after birth in a population-based birth cohort in the Netherlands [29]. Maternal weight, age, and previous pregnancies were taken into consideration and excluded where appropriate to reduce exposure to other risks known to increase the chances of birthing a child with ASD. Plasma folate levels were taken amongst 5591 mothers in early pregnancy between 10.5- and 17.2-week gestation. At the children's age of six, researchers were able to obtain information on the autistic traits of 70% of the cohort. After analysis and adjustment for confounders, researchers did not find folic acid supplementation to be protective at a significant level in lowering the chances of birthing a child with autistic traits [29]. In contrast, another study with a larger population (n = 85,176) found folic acid to decrease the incidence of ASD. Surén et al. studied the association between folic acid supplementations prior to pregnancy and the risk of children developing ASD [30]. Children aged 3–10 years were studied in a population-based, prospective cohort study in Norway. The study attained information on folic acid intake four to eight weeks after the start of pregnancy in the mothers of the studied children. Of the 85,176 children studied, 114 were diagnosed with ASD after following up between the ages of 3–10 years. Of those diagnosed with ASD, 64 mothers were supplementing with folic acid, while 50 were not. Interestingly, after adjustments for demographics, those with Asperger syndrome and pervasive developmental disorder did not show an association between mothers' folic acid intake and ASD incidence [30].

In a clinical trial of 57 children aged 3–7 years, Hendren et al. directly studied the impact that 75 micrograms (about 63% more than the recommended dietary allowance for this group) of vitamin B12, in the form of methylcobalamin, would have on improving symptoms in children with autism [31]. The study aimed to improve the methylation of methionine and metabolism of the antioxidant glutathione, which were measured at baseline and after eight weeks of treatment. Results showed that methylcobalamin treatment improved ASD symptoms. These findings were correlated with improvements in transmethylation metabolism, which is known to be abnormal in individuals with ASD [31].

B vitamins also influence oxidative stress and inflammation in the body by assisting in antioxidant reactions. Wang et al. studied the relationship between B vitamins supplementation and autism-like behavior and neurodevelopmental impairment in an animal study [32]. They showed that supplementation with folate, B6, and B12 significantly reduced neurobehavioral impairment in autistic mice, including reduced social communication disorder, reduced stereotyped repetitive behavior, and reduced learning and spatial memory impairment. Moreover, reductions in mitochondrial damage, pro-inflammatory cytokines, and increases in gene activities that assist in the synthesis of superoxide dismutase, glutathione, and glutathione peroxidase were observed. In addition to the B vitamin's ability to reduce oxidative stress, they can also lower the plasma concentration of homocysteine, which adds to the antioxidant capabilities of these vitamins by further reducing oxidative stress and inflammation [33].

B vitamins, particularly B6, B12, and folate, influence both the central and peripheral nervous system's function by contributing to maintaining a healthy nervous system and improving neurological conditions, even when a deficiency is not determined [34][35]. The effects of B vitamins on CNS function can be partly due to their roles in metabolizing amino acids. Kałużna-Czaplińska et al. showed that supplementation with vitamins B12, B6, and magnesium would better stabilize urinary tryptophan concentration in children with ASD [11]. Urinary tryptophan levels in the supplementation group were from 0.07 to 19.67 µmol/mmol, while in the control group, they were from 0.01 to 348.94 µmol/mmol [11]. Along with other AAs, tryptophan serves as a precursor for many major neurotransmitters, especially serotonin [11]. Therefore, controlled urinary tryptophan levels might show that tryptophan was used for the synthesis of neurotransmitters in this population.

4. Amino Acids

Essential amino acids must be consumed in the diet, while non-essential amino acids can be created by conversion processes in the body. Amino acids are known to have a significant impact on the CNS, controlling the body and mind [36][37]. Certain amino acids play an important role in regulating CNS neurotransmitters, including serotonin and dopamine. Tryptophan is known to increase serotonin levels, while tyrosine increases dopamine levels [38][39]. Serotonin is involved in brain development, as it influences cell division, cell proliferation, migration, differentiation, cortical plasticity, and synaptogenesis [40][41]. Moreover, serotonin influences memory, learning ability, and mood [42][43]. Dopamine regulates motor activity, motivation, attention, and reward processing [44][45][46]. Individuals with autism have impaired dopamine and serotonin levels [47][48]; therefore, adequate levels of tryptophan and tyrosine might support normal concentrations of dopamine and serotonin. Inadequate levels of tyrosine have been shown to decrease focus and increase hyperactivity in children without ASD [49][50].

Differences in the plasma levels of amino acids amongst individuals with ASD and individuals without ASD have been documented. **Table 1** reports the differences found in the reported amino acid plasma levels between individuals with ASD and individuals without ASD. Individuals without ASD are shown to have normal levels across the plasma levels of the listed amino acids, while individuals with ASD exhibit a range of high and low levels.

Table 1. Plasma levels of amino acids in individuals with ASD compared to individuals without ASD.

Amino Acid	ASD
Tryptophan	High [37] Low [51][52][53]
Tyrosine	Low [51][52][53]
Phenylalanine	High [37][54][55]
Homocysteine	High [51][56][57]
Lysine	High [51][54] Low [53]

High levels of amino acid lysine have been supported via examining plasma levels [51][54]. Although infrequent, high levels of essential amino acid lysine have been associated with an intellectual disability or behavioral issues [58]. Deficiencies in amino acid lysine among children with ASD have also been supported by earlier research [53]. Inadequate levels of essential amino acid lysine can cause agitation [37][59]. This might be due to a lack of synthetization of glutamate, which is responsible for producing the neurotransmitter GABA [60]. GABA is the main inhibitory neurotransmitter, and a low level of GABA is associated with mood disorders [61].

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