

Review Article

Increased Glutamate and Homocysteine and Decreased Glutamine Levels in Autism: A Review and Strategies for Future Studies of Amino Acids in Autism

Ahmad Ghanizadeh^{1,2}

¹ *Research Center for Psychiatry and Behavioral Sciences, Shiraz University of Medical Sciences, Shiraz, Iran*

² *Department of Psychiatry, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran*

Correspondence should be addressed to Ahmad Ghanizadeh; ghanizadeha@hotmail.com

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There are many reports about the significant roles of some amino acids in neurobiology and treatment of autism. This is a critical review of amino acids levels in autism. No published review article about the level of amino acids in autism was found. The levels of glutamate and homocysteine are increased in autism while the levels of glutamine and tryptophan are decreased. Findings regarding the plasma levels of taurine and lysine are controversial. The urinary levels of homocysteine and essential amino acids in both the untreated and treated autistic children are significantly less than those in the controls. The current literature suffers from many methodological shortcomings which needed to be considered in future studies. Some of them are age, gender, developmental level, autism symptoms severity, type of autism spectrum disorders, medical comorbidities, intelligent quotient, diet, concomitant medications, body mass index, and technical method of assessment of amino acids.

1. Introduction

Autism is one of the different subtypes of autism spectrum disorders. Its main characteristics are deficits in social communication and relationship, verbal communication and language impairments, and repetitive/restrictive behaviors and interests.

Many children with autism are picky eaters. They do not like a variety of different foods. Eating problems are risk factors for nutritional deficiencies. Some of these children do not like to try new foods and have food selectivity [1]. Food refusal and food selectivity are reported in 90% of these children [2]. Children with autism intake vitamin B6 and vitamin E more than the controls [3]. However, their take of vitamin B12 is less than that of the typical controls [4]. In addition, the level of vitamin B6 in plasma is very high in autism [5].

Moreover, there are contradictory reports about the level of intake of proteins by children with autism. For example, a study reported that the protein intake of children with autism is significantly less than the typical controls [4]. Meanwhile, others reported that daily protein intake of children with autism is higher than that of the controls [3, 6]. Nevertheless,

another study could not find a difference between autism and controls [7].

Children with autism suffer from deficiency of essential plasma amino acids displaying their poor protein intakes [8]. While the rate of at least one essential amino acid (valine, leucine, phenylalanine, and lysine) deficiency in autism was 58%, the rate in the control group was 4% [8]. Another study compared plasma level of 25 amino acids between high-functioning autism children and the healthy controls [9]. The study showed that only the levels of glutamate and glutamine were different between the two groups. While the level of glutamate was increased, the level of glutamine was decreased (Table 1) [9]. The levels of other amino acids were not different between high-functioning autism children and healthy controls [9]. The authors suggested that the plasma level of these two amino acids may differentiate high IQ autism and normal children. The deregulation of amino acids in autism was also reported in siblings and parents of these children [10].

Glutamate is involved in neuroinflammation in autism [11]. Moreover, targeting glutamate receptors through glycine

TABLE 1: A summary of the studies regarding amino acids in children with autism.

Study	Methodological issues	Main findings
Shimmura et al. [9]	Comparing the levels of 25 amino acids, including glutamate and glutamine, in the platelet-poor plasma of drug-naive, male children with high-functioning autism (HFA) would be altered compared with those of normal controls using high-performance liquid chromatography	Plasma glutamate: HFA* group > control, plasma glutamine: control > HFA Other 23 amino acids: no significant group difference
Moreno-Fuenmayor et al. [15]	Plasma amino acid levels were measured by high-pressure liquid chromatography (HPLC) in 14 children with autism aged less than 10 years	Glutamic acid: autism > normal values Aspartic acid: autism > normal values Taurine: autism > normal values Glutamine: autism < normal values Asparagine: autism < normal values
Aldred et al. [10]	Plasma amino acid levels were compared between autistic and Asperger syndrome children and their siblings, parents, and their aged matched controls	Glutamic acid: autism > controls Phenylalanine: autism > controls Asparagine: autism > controls Tyrosine: autism > controls Alanine: autism > controls Lysine: autism > controls Glutamine: autism < controls
Tu et al. [16]	Plasma amino acids profiles of 20 children with autism were compared with those of age and gender matched group of children	Lysine: autism > controls Glutamic acid: autism > controls Homocysteine: autism > controls Leucine: autism < controls Tryptophan: autism < controls Valine: autism < controls Taurine: autism < controls Tyrosine: autism < controls Glutamine: autism < controls
Tirouvanziam et al. [17]	Compared plasma amino acid levels in children with Autism spectrum disorders (ASD, $N = 27$) and neurotypically developing controls ($N = 20$)	Glutamate: autism > controls Glutamine: autism < controls Threonine: autism < controls Asparagine: autism < controls Citrulline: autism < controls Serine: autism < controls Tyrosine: autism < controls Leucine: autism < controls

*High functioning autism.

site on NMDA receptor is supposed as a target for treating autism [12]. In addition, methionine sulfoximine may improve inflammation in autism [13]. Besides, many children with autism suffer from irritability and aggression. The levels of homocysteine and glutamate are associated with each other, and this is supposed to be a target for treating aggression [14].

This is a narrative critical review of amino acids levels in autism. There is a positive correlation between cerebrospinal level of glutamate level and its plasma level [18]. Meanwhile, its level in serum is several times more than the CSF level. Therefore, the levels of amino acids in plasma, brain, and urine are reviewed. To the best of author's knowledge, no published review article about the levels of amino acids in autism has been published yet.

2. Amino Acids Levels

2.1. Glutamate. Glutamate is a major excitatory neurotransmitter in the brain. The high level of plasma glutamate level especially in children with normal IQ is supposed to be

a diagnostic screening test [9]. The increased plasma level in adults with autism is also reported [19]. Higher glutamate level is not limited to plasma, and some studies confirmed its higher level in some brain regions (amygdala-hippocampal regions but not in parietal region) of patients with autism compared to the controls [20]. The increased plasma glutamic acid is not limited to patients with autism, but its level is increased in their siblings and parents [10]. Another study measured plasma amino acid levels in 14 young children with autism by high-pressure liquid chromatography (HPLC). The mean glutamic acid was increased [15].

2.2. Glutamine. The low level of plasma glutamine level is suggested as a screening test for detecting autism in children especially those with normal IQ [9]. The decreased level has been reported before in all children with autism [10, 15, 16] (Table 2).

2.3. Taurine. Taurine is an inhibitory amino acid whose plasma level is increased in autism [15]. It is suggested that

TABLE 2: The level of amino acids in patients with autism in comparison to healthy controls.

Amino acid	Status
Leucine	Decreased in CSF [21] Decreased in plasma [8, 16, 17, 21]
Lysine	Increased in plasma [8, 10, 16] No difference in plasma [17]
Tryptophan	Decreased in plasma [16, 17]
Taurine	Decreased in plasma [16] Increased in plasma [15, 22] Increased in serum [16, 23] Increased total homocysteine (tHcy) in serum [24]
Homocysteine	Decreased plasma levels of homocysteine [25] Increased level in urine [26]
Citrulline	Decreased in plasma [17] No difference in plasma [17]
Alanine	Increased in plasma [10]
Glycine	No difference in plasma [17]
Valine	Decreased in plasma [8, 16] No difference in plasma [17]
Aspartic acid	Decreased platelet levels [27]
GABA	Decreased platelet levels [27]
Arginine	No difference in plasma [17]
Isoleucine	Decreased [21]
Threonine	Decreased in plasma [17]
Serine	Decreased in plasma [17]
Proline	No difference in plasma [17]
Asparagine	Decreased in plasma [15, 17] Increased in plasma [10]
Aspartic acid	No difference in plasma [17]
Methionine	Increased in plasma [8] Decreased [21]
Glycine	No difference in serum level [19]
D-serine	No difference in serum level [19]
L-serine	No difference in serum level [19]
Glutamic acid	Increased in plasma [10, 16, 17] Decreased platelet levels [27]
Glutamate	Increased level in plasma [9, 10, 15, 19, 28] Increased in some regions of brain [20]
Aspartate	Increased in plasma [22]
Phenylalanine	Decreased in plasma [8, 17] Increased in plasma [10]
Glutamine	Decreased in plasma [9, 10, 15–17] No difference in serum level [19] Decreased platelet levels [27]
Lysine	Increased in plasma [10]
Tyrosine	Decreased in plasma [16, 17] Increased in plasma [10]

its higher level is a compensatory phenomenon for the increased glutamate level [15]. Nevertheless, others reported that the mean level of taurine is decreased in autism [16].

2.4. Homocysteine. A study reported that the plasma levels of homocysteine were low in autism [25]. However, their subjects were taking supplements of folic acid and vitamin

B12 before being included in the study. These vitamins may be involved in reducing homocysteine level. Homocysteine is converted to methionine [29]. This process needs vitamin B12. Therefore, the deficiency of vitamin may increase the level of homocysteine. Meanwhile, other well-controlled study showed that the serum level of homocysteine is increased in autism [16, 23, 24].

2.5. Other Amino Acids. There are many reports about the increased plasma level of lysine in autism [8, 10, 16]. Meanwhile, a study reported that lysine level in autism is not different with in the controls [17]. The level of aspartic acid is increased as well [16]. All of the studies reported that the level of tryptophan is decreased in autism [16, 17].

3. Amino Acids Levels in Urine

The level of homocysteine in overnight urine sample in autism is increased [26]. This reduction may be due to the deficiency of folic acid and vitamins B6 and B12.

In addition, the urinary levels of essential amino acids in both the untreated and treated autistic children are significantly less than those the controls [30]. The levels of alanine, a-Aminobutyric acid, valine, leucine, isoleucine, threonine, serine, proline, asparagine, aspartic acid, glutamic acid, phenylalanine, a-Amino adipic acid, glutamine, glycine-proline, lysine, histidine, tyrosine, proline-hydroxyproline, Tryptophan, and total essential amino acids in untreated autism in first urine of the morning are less than those of the controls [30].

4. Discussion

Current findings support that many children with autism suffer from amino acids metabolism impairment. Nearly, all the studies reported higher levels of plasma glutamate in autism than those of the controls. In addition, the lower level of glutamine is frequently reported. Hyperglutamatergic state causes excitotoxicity and neurodegeneration [31]. Glutamate easily passes through blood brain barrier [31]. It is suggested that hyperglutamatergic state is an etiology of autism [32]. This state is associated with exacerbation of inflammation in the brain [33]. Moreover, this increased glutamate level is compatible with the findings that the level of proteins involved in transforming glutamate to GABA is decreased [34]. A well-controlled study confirmed that the plasma glutamate level is increased while the level of glutamine is decreased in children with autism [9]. The increased serum level of glutamate in autism is weakly associated with severity of autism [19]. Another study also reported that there was a statistically nonsignificant increase of platelet-poor plasma glutamate in autism [17].

In summary, children with autism more likely have essential amino acids deficiency, and this may make them prone to a higher deficiency if they are under a specific diet.

4.1. Future Directions. There are many shortcomings in the current literature regarding the level of amino acids in autism.

Many of the following methodological issues have never been considered in the current literature.

- (1) Further studies should investigate whether the levels of different amino acids are associated with age and gender in autism. At least one study reported that the pattern of amino acids is associated with age while it is not associated with gender [17]. Although it is suggested that the increased level of glutamate is stable in later ages [9], it needs to examine whether the findings can be generalized to different ages. A study reported that some biomarkers are gender related in patients with Asperger's syndrome [35]. The rate of autism is gender dependent as well [36].
- (2) Besides, it is not examined whether the profile of amino acids in autism is associated with the developmental level, autism symptoms severity, and psychiatric disorders comorbidities. The rate of psychiatric comorbidity is up to 74% [37]. About half of children with autism meet diagnostic criteria for ADHD [38].
- (3) Autism is one of the disorders in the spectrum of pervasive developmental disorders. Whether the pattern of amino acids is different between the different types of autism spectrum disorders needs to be clarified. Whether current findings can be generalized to all the types of autism needs to be investigated.
- (4) In addition, many children with autism have some medical comorbidities such as Down's syndrome, Fragile X syndrome, epilepsy, and/or tuberous sclerosis. These comorbidities need to be considered as covariates in further studies.
- (5) The intelligent quotient of about two-thirds of children with autism is less than 75 [39]. In other words, majority of children with autism suffer from mental retardation. Few studies considered IQ as a possible covariate [9].
- (6) Moreover, future studies should examine the possible role of any diet regime or food habits as covariate factors. It should be clarified whether the possible profile of amino acids in autism is secondary to the food and diet pattern. Some instruments assess the diet or food pattern of children. However, these instruments are very different. For example, some of them may evaluate the food pattern during a few days while others may assess it during a few months.
- (7) Gastrointestinal problems are not uncommon in children with autism. About one-fourth of them have at least one of the problems of constipation, abdominal pain, bloating, diarrhea, and/or nausea lasting three or more months [40]. Is there any role for these problems to impact amino acids levels in autism?
- (8) Further studies should investigate why glutamate level is increased in autism. Is it due to dietary origin, metabolic problems, vitamin B6 involvement, glutamate receptor problems, and glutamate transporters problems or all of them?

- (9) There is a speculation about the possible role of human gut microbiota in the etiology of autism [41]. Some of the microbial metabolites may affect brain function [42] through impacting aromatic amino acids metabolism [43].
- (10) The ratio of the different amino acids is another item which needs to be considered in future studies. Because one study indicated that several amino acids, individually or combined, differentiate autism spectrum disorder and healthy controls [17].
- (11) Past history of medication is another covariate. We do not know whether the changes are due to the effect of drugs. The levels of some amino acids in urine of treated children with autism are different from those of untreated ones [30].
- (12) Body mass index and creatinine level may impact on amino acids levels.
- (13) The technical method of assessment of amino acid should be considered to decrease the possibility of plasma contamination from other resources of amino acids such as platelets. Serum, platelet-poor plasma, and platelet-riched plasma should be differentiated. Further studies should consider 24-hour collection rather than spot collection.

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