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The amino acid profile in blood plasma of young boys with autism

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Summary

The aim of the study: It has been suggested that some amino acids are involved in the pathogenesis of autistic disorders. The aim of the study was to evaluate the plasma amino acids profile in young males with autism.

Method: Total of 27 autistic boys (aged 2–10 years, the study group) without any metabolic disorders and 13 healthy boys (aged 2–9 years, control group) were included in the study. In all subjects fasting blood plasma free amino acids (both exogenous and endogenous) were quantitatively measured by high performance liquid chromatography with UV-VIS detection.

Results: The mean plasma concentration values of citrulline, α-aminobutyric acid, isoleucine, leucine, phenylalanine, tryptophan and ornithine were significantly lower in boys with autism as compared to the control group ($p < 0.03$, $p < 0.04$, $p < 0.02$, $p < 0.02$, $p < 0.05$, $p < 0.02$, $p < 0.05$, respectively). The areas under the Receiver Operating Characteristic curves for these amino acids ranged from 0.637 to 0.726. None of the amino acids measured differentiate autistic children from healthy children. The sum of exogenous amino acids was lower in the study group than in the control group but this difference was not statistically significant.

Conclusions: Lower levels of exogenous amino acids confirm the possible role of these amino acids in autism. Determination of exogenous amino acids in plasma, however, cannot be used as a diagnostic test but it can still support autistic patients care.

Key words: autism, amino acids, boys

Introduction

Autism Spectrum Disorders (ASD) include infantile autism, Asperger syndrome and pervasive developmental disorders not otherwise specified (PDD-NOS). ASD is

defined as a neurobiological disorder characterized by impaired communication, abnormalities of social interactions and stereotyped patterns of behavior [1, 2]. Worldwide the prevalence of autistic disorders is estimated at 12.7/10000. Boys are affected more frequently than girls – male to female ratio is 2–2.6 [3]. Currently, it is estimated that in Poland about 30,000 people are suffering from autism [1, 4].

The etiology of autism remains unclear. Several hypotheses of the possible causes of autism have been proposed. Some researchers present psychoanalytic and psychosocial theories of autism; others indicate, as the main cause of the disorder, genetic etiology or point to early developmental brain damage [4–6]. Besides, it has been suggested that neurotransmitters such as serotonin, dopamine, noradrenaline and acetylcholine play a certain role in the pathophysiology of autism [1]. It has be pointed out that serotonin is also involved in the regulation of other signal transduction pathways, including GABA-ergic and glutamatergic transmissions [1, 7–15]. Serotonergic transmission disorders are among the reasons underlying typical autistic manifestations such as ritualized behaviors and difficulties in verbal and nonverbal communication. Patients with autism have an increased activity of the dopaminergic system, which may result in hyperactivity, aggression (including autoaggression) and increased severity of stereotyped behaviors [8, 14].

People with autistic disorders show abnormalities in plasma amino acid profile. Plasma concentrations of neurotransmitters such as glutamic acid and γ-aminobutyric acid (GABA) have been most frequently studied in autistic patients [16–24]. The glutamic acid has a stimulating effect while γ-aminobutyric acid exerts inhibitory influence on central nervous system (CNS) [25]. It is believed that the inhibition of GABA-mediated transduction may be caused by an excessive stimulation of glutamatergic system [14]. Some hypotheses indicate the adverse influence of glutamic acid on the development of neurons. It seems that the rapid growth of glutamatergic activity before the third year of age may be associated with the onset of autistic symptoms observed in toddlers [14]. Higher concentration of glutamic acid in patients with autistic disorders as compared to the control group has been demonstrated in many studies [16–21].

Based on available research data it can be assumed that some amino acids are involved in the pathogenesis of autism. However, published studies do not provide the clue to which amino acids are involved in the etiology of autism. Lack of clear-cut data may result from differences in research methodology, difficulties in interpreting the results and divergences among the outcomes which prevent researchers from drawing transparent conclusions. So far, no reports on plasma amino acids in autistic patients selected from Polish population have been presented.

Aim

The aim of the study was to evaluate the concentration of selected amino acids in the blood plasma of children with autism.

Material

Total of 27 autistic boys aged 2–10 years (mean age: 4.37±2.19 years) without metabolic diseases (study group) and 13 healthy boys aged 2–9 years (mean age: 5.00±2.74 years) (control group) were included in the study. Autistic patients were examined at the Outpatient Clinic of Metabolic Disorders and the Outpatient Genetics Clinic of the University Children's Hospital in Krakow in order to exclude any metabolic disorders or genetic defects which could manifest similar clinical symptoms.

Method

Fasting venous blood samples were collected on lithium heparin from all children. Blood was centrifuged for 10 minutes at 1200 g and plasma was kept at – 70°C until analysis. Quantitative determination of free amino acids in the plasma was performed by the Pico-Tag method (Waters, USA). Methionine sulphoxide at a concentration of 0.8 mM in 0.1M HCl (Sigma-Aldrich, Germany) was used as an internal standard. The following analytical stages were performed: 1) the samples were deproteinized using ultrafiltration (Microcon filter, Millipore, Ireland); 2) they were derivatized using phenylisotiocyanate; 3) samples were determined by HPLC-UV/VIS; 4) individual amino acids were identified and their concentrations were calculated. Sample separation was performed on a reversed-phase mode on the C18 Pico-Tag chromatography column (Waters, Ireland) and absorbance of analytes was measured at 254 nm. The Empower program (Waters) was used to collect and compile data. The following amino acids were determined: aspartic acid (Asp), glutamic acid (Glu), hydroxyproline (Hypro), serine (Ser), asparagine (Asn), glycine (Gly), glutamine (Gln), taurine (Tau), histidine (His), citrulline (Cit), threonine (Thr), alanine (Ala), arginine (Arg), proline (Pro), α-aminobutyric acid (Aab), tyrosine (Tyr), valine (Val), methionine (Met), isoleucine (Ile), leucine (Leu), phenylalanine (Phe), tryptophan (Trp), ornithine (Orn), and lysine (Lys). Method for amino acids analysis used in the present study is controlled by the European Research Network for Inherited Disorders of Metabolism (ERNDIM, MCA Lab, Netherlands).

Statistical analysis

The amino acid concentrations were given in μmol/l. Mean values and standard deviation were used in the statistical assessment of the obtained results. The sum of concentrations of: Tyr, Phe, Val, Leu and Ile (CAA1), the sum of concentrations of: Trp, Phe, Val, Leu, Ile (CAA2), the ratio: Trp/CAA1 and the ratio: Tyr/CAA2 were calculated. For citrulline, α-aminobutyric acid, isoleucine, leucine, phenylalanine, ornithine and tryptophan the ROC curves (Receiver Operating Characteristic) were constructed and the AUC (the Area under the Curve) was computed.

Statistica software version 10 (StatSoft) and Microsoft Office Excel 2003 were used to perform statistical analysis. To evaluate the distribution of continuous variables in terms of its compliance with the normal distribution the Shapiro-Wilk test

was employed. The Student's t-test was applied to compare the mean concentrations of amino acids between the study group and control group. To determine the relationship between the concentrations of amino acids and the age of patients the Pearson linear correlation coefficient was used. The p value less than 0.05 was considered statistically significant.

Results

Regardless of the study group no relation between the patients' age and the level of each amino acids has been noted. Table 1 presents the mean values of plasma amino acids concentration (±SD) obtained in boys with autistic disorders and in the control group. The mean concentration values of citrulline, α-aminobutyric acid, isoleucine, leucine, phenylalanine, tryptophan and ornithine were significantly lower in boys with autism as compared to the control group ($p < 0.03$; $p < 0.04$; $p < 0.02$; $p < 0.02$; $p < 0.05$; $p < 0.02$; $p < 0;05$, respectively). Mean value of other amino acids were similar in both studied groups. The sum of exogenous amino acids was lower in the study group than in the control group but this difference was not statistically significant. The mean value of CAA2 in children with autism was significantly lower than the value obtained in the control group ($p < 0.05$). There were no differences for CAA1, TRP*100/CAA1 and TYR*100/CAA2 between studied groups.

Table 1. **Mean concentration values of plasma amino acids (±SD) in the control group and in the study group**

Amino acid	Control group n = 13	Study group n = 27	p
	mean ± SD [μmol/l]		
Isoleucine	70.6±20.4	56.2±16.1	0.02
Leucine	128±30.0	106±25.2	0.02
Lysine	156±28.7	134.7±42.9	0.11
Methionine	25.5±9.24	23.8±7.66	0.54
Phenylalanine	56.8±8.92	50.1±9.94	0.05
Threonine	110±28.7	112±26.9	0.82
Tryptophan	66.0±13.4	54.0±14.6	0.02
Valine	247±50.9	221±58.4	0.19
Σ_1	836.7±149.2	744.9±146.1	0.09
Arginine	77.7±26.8	85.2±23.5	0.37
Histidine	86.0±12.4	75.7±19.7	0.09
Tyrosine	64.9±16.3	57.1±11.5	0.11
Σ_2	230.7±46.1	217.6±39.1	0.39
Aspartic acid	7.00±5.75	5.13±2.54	0.19
Glutamic acid	48.4±17.9	60.8±24.0	0.11

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Hydroxyproline	22.6±9.11	19.8±6.13	0.25
Serine	150±27.3	136±26.5	0.12
Asparagine	69.3±14.0	68.1±15.4	0.81
Glycine	231±53.2	253±54.9	0.25
Glutamine	622±109	632±103	0.78
Taurine	41.1±9.69	39.1±6.57	0.46
Citrulline	26.7±10.1	21.2±5.40	0.03
Alanine	358±132	440±140	0.08
Proline	198±66.3	229±88.1	0.26
α-aminobutyric acid	24.2±7.31	19.6±5.98	0.04
Ornithine	59.5±9.29	50.8±14.3	0.05
CAA1	556±115	483±100	0.06
CAA2	555±108	480±102	0.05
TRP*100/CAA1	11.8±2.92	11.3±2.62	0.61
TYR*100/CAA2	11.8±2.13	12.2±2.43	0.65

Σ_1– the sum of: Ile, Leu, Lys, Met, Phe, Thr, Trp, Val concentrations; Σ_2– the sum of Arg, His, Tyr concentrations; CAA1 – the sum of Tyr, Phe, Val, Leu, Ile concentrations; CAA2 – the sum of Trp, Phe, Val, Leu, Ile concentrations

The ROC curves for citrulline, α-aminobutyric acid, isoleucine, leucine, phenylalanine, ornithine, and tryptophan are presented in Figure 1. None of the measured amino acids differentiate autistic children from healthy children. The AUC computed for above-mentioned amino acids were very similar. The best area under the curve has been noted for Trp and Leu.

Discussion

The reference values for plasma amino acids depend on age and gender. In healthy children most commonly published reference ranges for amino acids are: for the children below 11 years of age, from 11 to 16 years of age and over 16 years of age separately for boys and girls [26, 27]. Although data on the plasma amino acid concentrations in patients with autistic disorders has been already published, amino acid concentrations in different papers were analyzed in different age groups: 3–12 years [21] and 12–18 years of age [15]. Croonenberghs et al. [15] found a positive correlation between serum tryptophan concentration and age when they combined both ASD and control patients ($r = 0.48$, $p < 0.01$). Tirouvanziam et al. [21] showed a negative correlation between glutamic acid as well as aspartic acid and age in the control group and positive correlation between both isoleucine and lysine with age in children with autism. In the present study, the children from 2 to 10 years of age has been examined. No relationship between the plasma amino acid concentrations

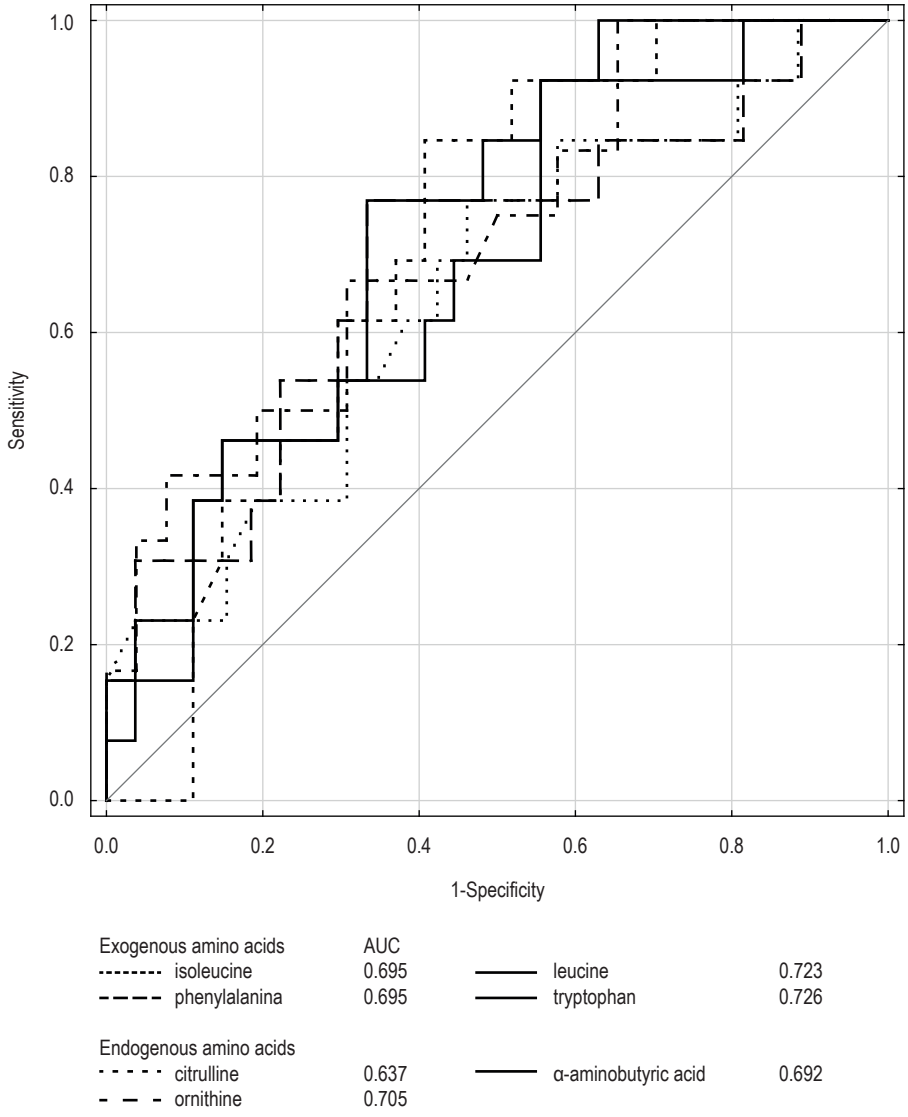

Figure 1. **ROC curves for citrulline, – aminobutyric acid, isoleucine, leucine, phenylalanine, ornithine, and tryptophan**

and the age of children has been found either for children with autistic disorders or for the control group.

Some amino acids, which are essential for the normal human development, are not synthesized in the body and must be taken with food (exogenous amino acids like isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, valine)

[25]. Arginine, histidine, tyrosine can be synthesized from exogenous amino acids, but with an inadequate diet their amount may be insufficient [25, 28]. Autistic disorders are frequently accompanied by the dysfunction of the digestive system, thus the therapy comprises pharmacological, psychological and dietary treatment [7, 29].

Amino acids are the basic elements of proteins, they are ubiquitous in the body's tissue and fluids. In addition they feature in processes of cellular energy metabolism, detoxification and neurotransmission. A measure of amino acids concentration can provide a valuable indication of metabolic activity associated with many of the body's tissues [30]. The dysfunction of the digestive system within the autistic population is often linked to protein malabsorption and protein metabolism. Patients with ASD are often on gluten-free and casein-free diet [31, 32], what could cause lower plasma levels of essential amino acids [33]. The important component of the treatment is to improve the nutritional status of the patient, therefore determination of plasma amino acids may be useful.

In ASD patients the plasma profile of exogenous amino acids has already been analyzed. Naushad et al. [20] demonstrated reduced levels of Trp, Met, His and Phe in children with autism in comparison to the control group and no differences in Tyr, Ile, Leu and Val concentrations between the analyzed group were observed. Croonenberghs et al. [15] conducted studies on serotonergic and noradrenergic signal transduction markers as well as the concentrations of exogenous amino acids. They showed a significant decrease in Ile, Leu, Phe and Trp concentrations and no differences for Tyr and Val between study group and control group. Tirouvanziam et al. [21] noted a significant deficiency of exogenous amino acids such as Leu, Thr and Tyr in children with ASD and normal level of Phe, Trp, His, Met, Ile, Lys, Val, Arg. Our study revealed statistically significant decrease of concentration levels of Ile, Leu, Phe and Trp in boys with autism as compared to healthy subjects and no differences for Lys, Met, Thr, Val, Arg, His, Tyr. Tryptophan is a serotonin precursor. Decreased concentration of this amino acids can lead to the insufficient synthesis of serotonin in the CNS. Serotonin may be involved in the pathogenesis of autism spectrum disorders. Tryptophan and the neutral amino acids circulating in the blood such as Phe, Val, Leu and Ile reach the brain by the same transportation system. Elevated levels of these amino acids may be the reason why the amount of tryptophan reaching the brain is reduced [34]. Naushad et al. [20], Tu et al. [19] and Croonenberghs et al. [15] demonstrated significantly lower concentrations of tryptophan in the plasma of autistic patients compared to the control group. Similar results were obtained in this study. These observations differ from the results obtained by Aldred et al. [18] and Shimmury et al. [16]. They analyzed the plasma concentrations of tryptophan and did not find any differences between the autistic children and the control group.

Croonenberghs et al. [15] observed not only decreased concentrations of tryptophan but also reduced CAA1 and CAA2 values in autistic children in comparison to the control group. However, they did not show any differences in the Trp/CAA1 and Tyr/CAA2 ratios between the studied groups. Similar results were obtained in the present study: lower mean values of CAA1 and CAA2 were noted in autistic boys compared to the control group and no differences in Trp/CAA1 and Tyr/CAA2 between the stud-

ied groups were demonstrated. In contrast, Naushad et al. [20] obtained a statistically significantly lower Trp/CAA1 ratio in children with autism compared to the control group and found no differences between the studied groups for Tyr/CAA2. It can be speculated that dietary habits may be responsible for these discrepancy.

Glutamic acid is one of the most important excitatory neurotransmitters in the CNS. It easily crosses the blood-brain barrier. According to the literature, a higher concentration of glutamic acid is found not only in the blood plasma [16–20] of autistic patients but also in certain regions of their brain [35]. Some researchers have suggested that a hyperglutamatergic state triggers autism [36]. In the present study, the mean value of glutamic acid was higher in plasma of autistic children compared to control subjects, however, the difference was not statistically significant. Too small number of patients may be the reason of lack of statistical difference.

Tirouvanziam et al. [21] reported reduced mean value of citrulline in patients with autism, which was also confirmed in the present study. No publications on the concentrations of α-aminobutyric acid and ornithine in the blood plasma of autistic patients are currently available. In our study statistically significantly lower mean concentrations of α-aminobutyric acid and ornithine were obtained in the group of young autistic males in comparison to the control group. It is difficult to find a simply explanation for these differences; they may result from altered amino acid metabolism.

Only few publications address the diagnostic value of measuring plasma amino acid concentrations in order to detect autistic disorders. Tirouvanziam et al. [21] demonstrated a high diagnostic value for threonine and glutamine (AUC = 0.8; AUC = 0.87, respectively). However, there is no research devoted to the diagnostic value of citrulline, α-aminobutyric acid, isoleucine, leucine, phenylalanine, ornithine and tryptophan in patients with ASD. AUC obtained in the present study for Cit, Aab, Ile, Phe, Leu, Orn, Trp, and CAA2 in boys with autism show low usefulness of these amino acids determination as diagnostic tool. However, amino acids profile can be indicative for the physician taking care of autistic children.

Conclusions

1. Lower levels of exogenous amino acids confirm the possible role of these amino acids in autism.
2. Determination of exogenous amino acids in plasma, however, can not be used as a diagnostic test but it can still support autistic patients care.

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