Role of amino acids in the pathophysiology of autism spectrum disorders in Saudi and Egyptian population samples

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Role of amino acids in the pathophysiology of autism spectrum disorders in Saudi and Egyptian population samples

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Abstract. Autism spectrum disorders are complex developmental disorders with increasing incidence and poorly understood etiology. Imbalance of amino acids profoundly influences brain function, and is thought to be one of the key players in the pathophysiology of autism. This study aimed to measure the plasma amino acid profiles of 20 Egyptian and 20 Saudi autistic patients in comparison to matching healthy controls to clarify the role of impaired amino acid concentrations in the etiology of autism. Plasma amino acids profiles were measured using high performance liquid chromatography. While plasma levels of glutamic, aspartic, and glycine recorded the most significant percentage elevated amino acids, glutamine, asparagine, arginine, tyrosine and isoleucine recorded the most remarkable percentage decrease in autistic patients from both populations compared to controls. Among the calculated relative values, only acidic/basic, and glutamate/glutamine ratios were significantly higher in autistics compared to controls. Non-essential/essential and glucogenic/ketogenic ratios were unaltered in autistics compared to controls. Increased plasma glutamate/glutamine ratio, together with increased glycine, arginine, aspartate, aspargine levels, and acidic/basic amino acid ratio can serve as a predictive tools for the early detection of autism. These findings suggest that glutamatergic abnormalities in the brain may be associated with the pathobiology of autism.

Keywords: Autism, amino acids profile, glutamate, glutamine

1. Introduction

The autism spectrum disorder (ASD), including classical autism, are regarded as a group of complex developmental disorders associated with life-long disability, of which prevalence during growth is considerably greater than previously thought [1]. Despite decades of research,, the etiology of ASD remains unclear, and biological causes are poorly understood [2].

The brain depends on a diverse array of amino acids for normal development and function. Amino acids level must be tightly regulated within brain neuronal, astrocytic, extracellular, and synaptic compartments. Virtually all organic compounds involved in neurotransmission or modulation of neuronal excitation are either amino acids or amino acid metabolites. Amino acids with such functions include glutamate, glycine, and proline. Amino acid metabolites, which partici-
pate in neurotransmission, include gamma-aminobutyric acid (GABA), N-methyl D-aspartate, nitric oxide, serotonin, melatonin and histamine. Two of the four carbons and one of the nitrogen atoms in purines come from glycine. Aspartate provides two of the five carbon atoms in adenosine nucleotides, one of the four nitrogens in guanosine nucleotides and one of the nitrogen in pyrimidine nucleotides (uridine, thymine, and cytosine) [3].

The endothelial cells of brain capillaries form a highly effective seal that separates the luminal space from the brain [4]. Passage of amino acids from circulation into brain has to be mediated by specific transporters on both sides of the endothelial cell. Amino acids that are not accepted by one of the available transporters cannot cross. Amino acids are also transported out of the brain into the capillary lumen, which is essential to remove excess excitatory amino acids [5].

Imbalances in amino acids profoundly influence brain function, as shown by the irreversible mental retardation that occurs in phenylketonuria and maple syrup urine disease and by the neuronal degeneration and death that occurs with excessive excitotoxic amino acid release in hypoxia, hypoglycemia, ischemia, and seizures. Recent studies highlight the involvement of amino acid imbalance and/or signaling in the pathophysiology of autism [6]. Autistic children have been identified with high toxic metal levels [7], low levels of metallothionein (MT), with MT systems that work ineffectively, with low levels of glutathione [8], with low levels of sulphur-related detoxification mechanisms [9] and with malfunctioning digestive systems (including “leaky” gut and food allergies). Various different theories for the cause of these malfunctions include genetic predisposition, oxidative stress and nutritional deficiencies in pregnancy.

A huge component of the MT metal regulating system is the essential amino acid, cysteine. The entire MT is composed of sulfur and protein. One of the problems identified in autism patients are digestive systems that cannot fully break down all protein into its basic components, the amino acids so that many necessary amino acids are unavailable to make systemic proteins such as MT [10].

This information initiated our interest in a pilot study to measure amino acid profiles of two groups of Egyptian and Saudi autistic patients compared to age-matched control subjects of both populations in a trial to screen and understand the role of amino acid profile abnormalities in the etiology of autism in both investigated groups. Although autism occurs in all cultures and countries, most of the published researches have come from Western countries. To our knowledge, few studies compared established cases of autism in Arab countries simultaneously. There were no statistically significant differences in clinical variables like regression, hyperactivity, epilepsy, or mental retardation. Delayed language development was significantly higher in the Egyptian group while delay in all development milestones was more significant in Saudi group [11].

2. Materials and methods

2.1. Patient selection

Twenty Egyptian and 20 Saudi autistic patients with ages between 3–4 yr, and 40 age, gender and ethnic matched healthy controls were enrolled in the study. They were recruited from outpatient clinics for autistic disorders, Medical Research Centre of Excellence, National Research Centre, Cairo, Egypt; Autism research and treatment centre clinic, medical college, King Khalid hospital of King Saud university. Both autistic groups (Egyptian and Saudi) were diagnosed by the Diagnostic and Statistical Manual of mental disorders, fourth edition (DSM IV), text revision criteria, the Autism Diagnostic Interview-Revised, the Autism Diagnostic Observation Schedule and 3DI (developmental, dimensional diagnostic interview). All the studied patients were simplex cases and their DNA was negative for fragile X gene study. Subjects were excluded from the investigation if they had dysmorphic features, or other serious neurological (e.g., seizures), psychiatric (e.g., bipolar disorder), fragile X syndrome or any other known medical conditions. All participants were screened via parental interview for current and past physical illness. Children from both tested populations, with known endocrine, cardiovascular, pulmonary, liver, kidney or other medical disease were excluded from the study. All children have an intellectual disability (mental retardation) with average IQ between 55–70.

2.2. Ethics approval and consent

This work was ethically approved by the Ethical committee of King Khalid hospital, King Saud uni-
versity, and the Ethics Review committee of the National Research Centre. A written consent was obtained from the parents or caregivers for all participants before the study.

2.3. Samples collection

Blood samples were collected in the morning following at least 10 hr fast. Plasma was collected in heparinized tubes using standard clinical practices and stored at −80°C until thawed for analysis.

2.4. Amino acid profile and determination of glutamate/glutamine (Glu/Gln) ratio

The plasma samples were derivatized and proteins were precipitated according to Mondino et al. [12] then the samples were homogenized with sulfo salicylic acid, centrifuged immediately at 12,000 rpm 4°C for 10 min to remove precipitated protein and brought to pH 2.2 with lithium hydroxide. After filtration, the protein-free supernatant is used for high-performance liquid chromatography (HPLC) determination of amino acids. The resultant peaks are compared to standards, and the level of each amino acid is automatically calculated as described by Turnell and Cooper [13]. All standards, quality-assessment specimens, and test specimens were stored at −20°C and thawed immediately before analysis. To 20 μL of standard amino acid solution, or plasma in a polypropylene tube, 20 μL of internal standard solution and 200 μL of acetonitrile precipitation reagent were added. The contents of all tubes were vortex-mixed, centrifuged at 12,000 g for 2 min. A 20 μL of the supernatant was taken into another polypropylene tube, and 100 μL of iodoacetic acid reagent was added. Contents were mixed with 100 μL of ortho-phthalaldehyde/mercaptoethanol reagent and 20 μL were injected onto column for gradient HPLC system Altex 420 (Altex Scientific Inc., Berkeley; Whatman Inc., Clifton). Amino acids derivatives were detected with Schoeffel FS970 fluorescence detector (Kratos Inc., Westwood), excitation wavelength 230 nm and emission cutoff filter at 418 nm. Data from the chromatography was processed by SP4100 computing integrator (Spectra-Physics, Santa Clara). Amino acid derivatives were identified by their retention times relative to the reference peaks produced by homocysteic acid, norvaline, and homoserine. Amino acid concentrations were automatically quantified by comparing their peak areas with that of homocysteic, internal standard.

2.5. Statistical analyses

Computer statistical package for the social sciences program was used for the analysis of the obtained data, and results were expressed as mean ± standard deviation. All statistical comparisons were made by means of the student’s t-test. Significant difference was considered at P value < 0.05. The Pearson's correlation analysis was used to find a correlation between the measured parameters. Generally, positive or negative correlations above 0.80 are considered high. The receiver operating characteristics (ROC) curve as a fundamental tool for biomarkers evaluation was performed using the same computer program. In a ROC curve, the true positive rate (sensitivity) is plotted in function of the false positive rate (100-specificity) for different cut-off points of a parameter. Each point on the ROC curve represents a sensitivity/specificity pair corresponding to a particular decision threshold. The area under the ROC curve is a measure of how well a parameter can distinguish between autistic and control subjects.

3. Results

Seventeen amino acids were measured using HPLC and represented in figures (Figs 1–4). Significantly, reduced levels of the aromatic amino acids tyrosine and tryptophan were observed in autistic cases in both populations. This could be easily related to increased biosynthetic demands for the serotonergic and dopaminergic systems. This also supported by El-Ansary et al. [7] recent finding of significantly elevated plasma dopamine and serotonin in autistic subjects. In addition, changes in microbiota composition in subjects with ASD compared to healthy control subjects have been reported in several studies, based on bacterial culture and molecular methods [14], higher counts of clostridia overall and more species of clostridia in stools of autistic children compared to healthy children were reported [15]. Differences in the microbiota may result in altered microbial metabolism of aromatic amino acids as phenylalanine, with consequent depletion of tyrosine [16].
4. Discussion

The branched chain amino acids (BCAA) are utilized for energy production and glutamatergic regulation through nitrogen shuttle [17]. This probably contributed to the significantly reduced isoleucine ($P < 0.01$) in plasma of autistic subjects in both populations. Novarino et al. [6] reported inactivating mutations in the gene coding for branched chain ketoacid dehydrogenase kinase in consanguineous families with autism, epilepsy, and intellectual disability. Patients with homozygous branched chain ketoacid dehydrogenase kinase mutations display reductions in plasma branched-chain amino acids. Interestingly, this was not the case for valine, a second BCAA that was found significantly elevated in Saudi and Egyptian autistics ($P < 0.05$). This may be explained by “leucine-isoleucine and valine antagonism” phenomenon, wherein that elevation of one BCAA causes antagonistic effect on the levels of the other two [18].

Histamine plays a role in inflammatory processes besides having several neuromodulatory and cerebral functions [19], including enhancement of excitotoxicity [20]. Significantly reduced histidine in Saudi autistic subjects ($P < 0.05$) could be related to abnormally high production of histamine. This assumption is supported by significant improvements of autistic symptoms after administration of the histamine H1-receptor antagonist niaprazine [21]. On the other hand, the slightly elevated histidine concentration in plasma of Egyptian autistic subjects compared to controls could be due to the fact that this amino acid is related to an immune response suggesting interactions...
between genetic and environmental factors and hence might be greatly affected by population makeup [22]. Increased glycine was one of the most striking abnormalities in the plasma of Saudi and Egyptian autistic patients compared to controls ($P < 0.01$). Although it is considered inhibitory transmitter, the glycineergic synapses can be excitatory in the immature brain [23], an important function for synaptogenesis [24]. The elevation of glycine and its relationship to excitotoxicity in autistic patients could be related to pro-inflammatory induced synaptic function alterations previously recorded in autistics [25]. Tumor necrosis factor-alpha and interleukin-6 as two remarkably high pro-inflammatory cytokines in Saudi autistics [26] which alter excitatory and inhibitory synaptic responses [27]. Elevated glycine could be also explained on the basis of dysfunctional transport due to mutation of glycine transporters recently reported to be involved in autism [28]. The levels of arginine were significantly very low in autistic subjects’ plasma from both populations compared to the controls. This can be related to increased nitric oxide synthesis and excitotoxicity. When glutamate receptors are activated, the resultant $\text{Ca}^{2+}$ influx leads to nitric oxide synthase activation and increased NO synthesis, which could cause L-arginine depletion [29]. This also could be related to the lower level of arginine vasopressin which has been hypothesized to play a role in etiology of autism based on a demonstrated involvement in the regulation of social behaviors [30]. Aspartate is another excitatory neurotransmitter, and was found to be higher in the plasma...
of both autistic populations compared to controls, which is consistent with excitotoxicity suggested in autism [25]. Elevated glutamate and aspartate have been reported in autism [31]. As a matter of fact, the two amino acids are co-localized and co-secreted from the same neurons [32,33]. Aspartate can bind at the glutamate-binding site of N-methyl D-aspartate receptors [31].

Significantly elevated \((P < 0.01)\) plasma levels of glutamate were also found in both groups of autistic children compared to the control groups. The role of glutamate as the major excitatory neurotransmitter is well defined, and it is crucial for normal synaptic plasticity and maintenance of cognitive functions. Glutamate is present in high concentrations in the brain, and its levels in blood were found positively correlated with those in the cerebrospinal fluid [34]. In some neurologic and psychiatric disorders like epilepsy where excitotoxicity also contributes to the etiology, increased glutamate levels were reported in both plasma and cerebrospinal fluid [35]. Similarly, for autism, elevated plasma glutamate reported in this work and other studies [36] can be related to the elevated Glu/Gln ratio detected in autistic brains \(^1\)H-magnetic resonance imaging [37]. Such findings support the implication of glutamate excitotoxicity in the pathophysiology, and suggests the diagnostic importance of plasma glutamate and glutamine levels in autism [38].

Excess glutamate, which is a potent neurotoxin that can cause cognitive dysfunction, neuronal cell death and can compromise the blood-brain barrier may contribute to peripheral elevations of glutamate [39]. It is thought that exposure to immune challenge and activation of peripheral cytokines release would promote the release of several neurotransmitters in the central nervous system; including glutamate, GABA, serotonin, and dopamine [40]. This alters neurotransmission, and can lead to behavioral and psychiatric disorders [41]. The significantly lower plasma levels of asparagine and glutamine in both populations were consistent with previous study [39] and can be explained by increased synthetic demand for their corresponding acidic excitatory amino acid transmitters (aspartate, glutamate).

The association between high plasma glutamate and low glutamine is demonstrated through the significantly elevated (about the triple) Glu/Gln ratio in autistic subjects compared to healthy children. This relationship can be explained when considering an important and remarkable cycle between astrocytes and neurons, the Gln-Glu cycle. The cycle that controls glutamate levels, prevents excitotoxicity, and shuttles nitrogen between astrocytes and neuron involves two important enzymes. The astrocytic glutamine synthetase (GS), rather than glutamate dehydrogenase, removes both glutamate and ammonia by combining them into glutamine. Once released and taken up by neurons, the neuronal phosphate-dependent glutaminase metabolizes glutamine back to ammonia and glutamate [18]. Based on this, the balance between these enzyme activities is critical and must be maintained for controlling normal levels of glutamate, glutamine, and ammonia in the brain. The striking abnormality of Glu/Gln ratio among autistic subjects observed in this study clearly suggests that the Gln-Glu cycle is affected in Saudi and Egyptian autistic children in the study. This indicates possible enzymatic dysfunctions or abnormalities that disrupt the balance between astrocytic glutamine synthesis and the neuronal metabolism. It is suggested that the increased gliosis and astrocyte activation reported in autistic brains [42] leads to dysregulation of Gln-Glu cycle [43]. Supporting this are some immune-glutamatergic studies, where the activated astrocytes and microglia were found to up-regulate the activity of glutaminase [44]. In addition, GS is a key regulator for the metabolism and release of both glutamate and GABA. Ortinski et al. [45] have reported that activated astrocytes down regulate the expression of GS, which results in reduced glutamine and elevated glutamate. Nitration and inhibition of GS were reported in epilepsy causing dysregulation of both glutamatergic and GABAAergic transmission systems [46].

Dysregulation of Glu-Gln cycle suggested by the abnormal Glu/Gln ratio would help to explain the marked but non-significant elevated ammonia levels (19.75%) in autistic subjects’ plasma. In addition, the very low levels of the urea cycle intermediate arginine could contribute to both ammonia elevation and urea slight reduction in autistics as previously suggested [47] and reported in the same Saudi autistic samples used in this study [48]. As for the remaining amino acids, threonine and lysine showed some variations between Saudi and Egyptian patients, respectively. This could be attributed to the different dietary levels of these essential amino acids. Alanine levels was significantly lower in autistic subjects compared to controls while phenylalanine and methionine did not show a significant difference. The few variations in
Table 1
Relative values of amino acids in Saudi autistics compared to control

<table>
<thead>
<tr>
<th>Parameters</th>
<th>n</th>
<th>Mean ± SD</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonessential/essential</td>
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<td></td>
<td></td>
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<tr>
<td>Control</td>
<td>19</td>
<td>7.38 ± 0.33</td>
<td>0.525</td>
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<tr>
<td>Autistic</td>
<td>20</td>
<td>7.45 ± 0.40</td>
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<tr>
<td>Glucogenic/ketogenic</td>
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<td></td>
<td></td>
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<tr>
<td>Control</td>
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<td>17.89 ± 1.05</td>
<td>0.124</td>
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<tr>
<td>Autistic</td>
<td>20</td>
<td>18.63 ± 1.82</td>
<td></td>
</tr>
<tr>
<td>Acidic/basic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>19</td>
<td>6.93 ± 0.64</td>
<td>0.001</td>
</tr>
<tr>
<td>Autistic</td>
<td>20</td>
<td>12.40 ± 0.84</td>
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</tr>
<tr>
<td>Glutamic/glutamine</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>19</td>
<td>0.46 ± 0.03</td>
<td>0.001</td>
</tr>
<tr>
<td>Autistic</td>
<td>20</td>
<td>1.37 ± 0.06</td>
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</table>

Tables 1–3 demonstrate relative values of non-essential/essential, glucogenic/ketogenic, and acidic/basic amino acids ratios. While nonessential/essential ratio did not show any significant difference between autistic and control populations, glucogenic/ketogenic ratio was significantly different only in Egyptian autistics compared to controls. In contrast, acidic/basic amino acids ratio recorded high significant difference, almost more than 100% increase in autistics compared to control subjects of both populations. This could be related to the pathology of autism because glutamate and aspartate function as excitatory neurotransmitters but are known to be neurotoxic when both reach supraphysiologic concentration. On the other hand, lysine and arginine as basic amino acids are known to protect against brain membrane damage by placing their positive charge near negatively charged phospholipid head groups. Impaired acidic/basic amino acid ratio recorded in Egyptian and Saudi patients is supported by the previous reports of Meguid et al. [49] and El-Ansary et al. [50], in which they reported impaired plasma phospholipids in Egyptian and Saudi autistic patients, respectively, compared to control subjects. The significant differences in the three calculated relative ratios between Egyptian and Saudi autistics could be related to the different and characteristic nutritional habits of both populations (Table 3).

Table 2
Relative values of amino acids in Egyptian autistics compared to control

<table>
<thead>
<tr>
<th>Parameters</th>
<th>n</th>
<th>Mean ± SD</th>
<th>P value</th>
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</thead>
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<tr>
<td>Nonessential/essential</td>
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<tr>
<td>Control</td>
<td>20</td>
<td>7.59 ± 0.64</td>
<td>0.515</td>
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<tr>
<td>Autistic</td>
<td>20</td>
<td>7.70 ± 0.34</td>
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<tr>
<td>Glucogenic/ketogenic</td>
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<td></td>
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<td>Control</td>
<td>20</td>
<td>18.41 ± 1.83</td>
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<tr>
<td>Autistic</td>
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<td>20.28 ± 1.72</td>
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</tr>
<tr>
<td>Acidic/basic</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>20</td>
<td>7.41 ± 1.11</td>
<td>0.001</td>
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<tr>
<td>Autistic</td>
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<td>11.80 ± 0.79</td>
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<tr>
<td>Glutamic/glutamine</td>
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<td></td>
</tr>
<tr>
<td>Control</td>
<td>20</td>
<td>0.53 ± 0.11</td>
<td>0.001</td>
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<tr>
<td>Autistic</td>
<td>20</td>
<td>1.29 ± 0.08</td>
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Table 3
Relative values of amino acids in Egyptian autistics compared to Saudi autistics

<table>
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<tr>
<th>Parameters</th>
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<th>Mean ± SD</th>
<th>P value</th>
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<td>20</td>
<td>7.45 ± 0.40</td>
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<tr>
<td>Egyptian</td>
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<td>7.70 ± 0.34</td>
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<td>Egyptian</td>
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<td>20.28 ± 1.72</td>
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<td>Acidic/basic</td>
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</tr>
<tr>
<td>Saudi</td>
<td>20</td>
<td>12.40 ± 0.84</td>
<td>0.027</td>
</tr>
<tr>
<td>Egyptian</td>
<td>20</td>
<td>11.80 ± 0.79</td>
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<tr>
<td>Glutamic/glutamine</td>
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<tr>
<td>Saudi</td>
<td>20</td>
<td>1.37 ± 0.06</td>
<td>0.001</td>
</tr>
<tr>
<td>Egyptian</td>
<td>20</td>
<td>1.29 ± 0.08</td>
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</table>
transport [54]. In the future, we recommend a tightly controlled, large-scale study of amino acids in autistic subjects, encompassing all the different aspects of amino acids absorption, transport, and metabolism. This could be very helpful to clarify the possible reasons behind the striking abnormal amino acid profiles reported in autistic subjects in this study.

The present study suggests that plasma glutamate/glutamine ratio, together with glycine, arginine, aspartate, asparagine, and acidic/basic amino acid ratio may serve as a possible tools for the early detection of autism, however, further extended large scale studies are recommended to confirm these results. Also these findings indicate that glutamatergic abnormalities in the brain may play a role in the pathophysiology of autism. The changes in amino acid profile in both populations were discussed in relation to genetic makeup, and defective transport mechanism.

Fig. 5. The receiver operating characteristics curve of amino acids profile (µmol/L) in the Saudi autistic group (A = Cysteine, and glutamic; B = Aspartic; C = Histidine, and asparagine; D = Glutamine; E = Lysine, methionine, valine, and glycine; F = Tyrosine, alanine, arginine, and threonine; G = Isoleucine, phenylalanine, and tryptophane; H = Glucogenic/ketogenic ratio, nonessential/essential ratio, and glutamic/glutamine ratio; I = Acidic/basic ratio). (Colours are visible in the online version of the article; http://dx.doi.org/10.3233/JPN-140660)
Fig. 6. The receiver operating characteristics curve of amino acids profile (µmol/L) in the Egyptian autistic group (A = Cysteine, and glutamic; B = Aspartic; C = Histidine, and asparagine; D = Glutamine; E = Lysine, methionine, valine, and glycine; F = Tyrosine, alanine, arginine, and threonine; G = Isoleucine, phenylalanine, and tryptophane; H = Glucogenic/ketogenic ratio, nonessential/essential ratio, and glutamic/glutamine ratio). (Colours are visible in the online version of the article; http://dx.doi.org/10.3233/JPN-140660)

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