Role of Plasma Amino Acids Profile in Pathogenesis and Prediction of Severity in Patients with Drug Resistant Epilepsy

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ABSTRACT

Background: Abnormal plasma levels of free amino acids may predict the severity in patients with drug resistant epilepsy (PRE), having probability to affect their therapeutic approach.

Objectives: We aimed to illuminate the effect of plasma free amino acids (PFAAs) profiles on the etiology of patients with PRE and their contribution on the frequencies of epileptic fits.

Patients and Methods: We collected clinical and metabolomic data of 90 subjects; 45 of them were PRE patients, and other 45 age and sex matched healthy controls. Quantitative measurements of PFAAs profiles using SykamAutomatic Amino Acid Analyzer S433, in addition to fasting blood sugar, liver function tests, kidney function tests and lipid profile also, were determined.

Results: The plasma levels of glutamate, glycine and Gamma amino butyric acid(GABA) plasma levels were significantly increased in PRE group compared to controls ($p<0.0001$),their plasma levels also showed significant increase with increased frequency of epileptic fits. Plasma leucine, phenylalanine, aspartate ,ornithine, citrulline, serine and alanine levels ($p<0.0001$) were significantly increased in PRE group in relation to healthy controls. Interestingly, on the other hand, histidine, isoleucine, lysine, threonine and the amino acid derivative taurine levels were significantly decreased in PRE patients compared to healthy controls.

Conclusion: Few biomarkers of PRE are available to find the severity and rate of progressionof PRE. The present study showed that altered plasma amino acids and their derivatives may be candidate markers for PRE, help explaining its pathogenesis, and for further researches concerning normalization of the disturbed amino acid/s or its derivative/s (GABA and taurine) in managing PRE patients.

Keywords: Aminogram; Plasma free amino acid profile; Pharmacoresistant epilepsy, amino acids.

Abbreviations: Anti-epileptic drugs (AEDs**),** Branched-chain amino acids (BCAAs**)**, Plasma free amino acids (PFAAs)**,**Pharmaco-resistant epilepsy (PRE).

INTRODUCTION

Epilepsy is the most common chronic neurological disease. It affects over 70 million people worldwide [(1)]with increased risk of mortality, and socioeconomic consequences that impairing quality of life [(2)]**.** It is diagnosed with either recurrent two or more unprovoked seizures occurring at least 24 hours apartor a single seizure, accompanied by evidence from clinical, or neuroimaging tests that an increased risk exists for future seizures over the next 10 years[(3)]. Approximately 40% of patients with epilepsy exhibit resistance to pharmaco therapy over the past two decades[(4)].Drug or pharmaco resistant epilepsy (PRE) is defined as the failure of tolerable trials of two tolerated and suitably chosen mono therapies singly or in combination to achieve sustained seizure freedom for more than one year [(5)]. PRE patients have increased risk of mortality due to sudden unexpected death in epilepsy [(6)].

Amino acids not only are dynamic structural building blocks of proteins but are also active signaling molecules regulating metabolism.

Several neurotransmitters in the brain synthesized from amino acids. The concentration of amino acids in plasma regulate the invivo synthesis of individual amino acids in the brain so it can affect the brain functions[(7)].

Glutamate is the most abundant excitatory neurotransmitter in the brain, which means increases the probability that the neuron will have an action potential[(8)].Glutamate action mediated through activation of G protein coupled metabotropic receptors and ionotropic receptors so, altered glutamate amino acid transport or metabolism may be a contributory factor in some genetic and acquired forms of epilepsy[(9)].

Inhibitory neurotransmission is mediated by several neurotransmitters, as GABA and glycine[(10)]**.** Gamma amino butyric acid (GABA)increases the permeability of depolarized membranes to ions which leads to acceleration of return to resting potential of all membrane segments. It is also, decreasing membrane sensitivity to stimulation so, stabilizes undepolarized membrane segments. Functional and structural alterations of GABAergic pathway participate to the pathophysiology of many brain disorders including epilepsy [(11)].

The essential branched-chain amino acids BCAAs (leucine, isoleucine, and valine) have lately used as a treatment for PRE. Circulating BCAAs can readily enter the brain, where they supply glutamate biosynthesis and may either suppress or prompt acute seizures [(12)].

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Homocysteine and taurine are considered to be neurotransmitters and neuromodulators. Homocysteine has a hyperexcitability role, while taurine has inhibitory and neuroprotective properties [(13)]. After acute epilepsy seizures, amino acid changes in the cerebrospinal fluid (CSF) were observed and may be limited to a reduction in the level of taurine[(14)]. The taurine neuroprotective effect is linked with its anticonvulsive properties, it is mediated by its interactions with glutamate, GABA pathway and oxidative stress [(15)].

Aromatic amino acids mainly phenylalanine can be implicated in neuronal survival and differentiation through regulating expression of brain-derived neurotrophic factors [(16)].

MATERIALS AND METHODS

The current study is a case-control study that was conducted on 45 patients with PRE (group A)who were selected from the outpatients and inpatients of Epilepsy clinic, Neurology and psychiatry Department of Assiut University Hospital, together with, 45 age and sex matched healthy persons(controls, group B) who were selected randomly from the same population as the patients, with no known personal history or family history of epilepsy or any neurological or psychiatric diseases,they were presented to the outpatients clinic with non-specific complaints. The study in collaboration with Metabolic and Genetic Disorders Unit (MGD) in the period from March 2017 to July 2018, Faculty of Medicine, Assiut University, Egypt.

Ethical approval: The study protocol was approved by the Ethics Committee of Faculty of Medicine, Assiut University (code number: IRB00008718).

All participating subjects gave written informed consent after the purpose and method of the study were briefly discussed to each participant.

Diagnosis of PRE was depending on the presence of uncontrolled seizures with an average frequency of one fit per month for two years with usage of at least three different tolerated and appropriately chosen anti-epileptic drugs (AEDs) (singly or in combination) [(17)]. Group (A) patients were receiving valproic acid, clonazepam and oxycarbazine in different combinations.

Epileptic patients with other types of neurological diseases, chronic medical diseases (cardiac, hepatic or renal or malignancies or those currently pregnant or breast-feeding) all were excluded from the study.

Data collection, Clinical examination and Imaging studies:

Personal data including age, residence and occupation,handedness, smoking or drug addiction, family history of epilepsy, consanguinity between parents, history of febrile convulsions, personal or family history of migraine, history of head trauma orany CNS infections, detailed history of epileptic fits, past and current medications,and careful therapeutic history together with detailed clinical examination were taken by a neurologist.

An Electroencephalography (EEG) was performed by specialized neurologist, additionally, magnetic resonance imaging (MRI) was done when indicated.

Laboratory workup:

After an overnight fasting, 4ml of antecubital venous blood samples were drawn from patients and controls. The blood samples were collected in heparinized tubes, Plasma products were separated by centrifugation of blood samples at 3000 rpm for 10 min, then stored at −20 °C for measurement of the PFAA profiles.

Ion exchange separation method using high performance liquid chromatography using a Sykam Automatic Amino Acid Analyzer S433 supplied by Sykam GmbH, Germany (catalog no. 1120001).Free amino acid samples were prepared from plasma by acidic protein precipitation, where 200µl of 10%sulfosalicylic acid solution was added to 800 µl plasma, mixed by vortex, then solution was allowed to cool down at about 4 °C for 30 min, and then was centrifuged for 10 min at 14000 rpm. Supernatant liquor was diluted with same amount of sample dilution buffer (catalog no. S000015). One hundred µl of each of prepared samples and ready to use amino acid physiological standard (Catalog no. 6006005) wereinjected directly.

Cation separation column LCAK06/Li was used (catalog no. 5112008) with size: 150 mm× 4.6 mm, specification range: met efficiency: >48000, asymmetry: 0.8–1.5, resolution THR/SER: > 1700, and column pressure: 45–80bar. Buffer: Sykam LiA-1,LiB-1,LiC-4.The ready to use ninhydrin reagent (catalog no. S000025) and citrate buffers in different pH (2.9, 4.2, and 8.0) were used. Analysis at wave length 440nm:570 nm. The sample chromatogram is compared to the standard measurements curve (Fig:1A) to obtain various amino acid values, then results were multiplied by a dilution factor of 2.5[(18)].

Routine blood investigation including: fasting blood glucose, liver function , kidney function tests and lipid profile were analyzed using enzyme colorimetric kits supplied by Biodiagnostics, Egypt. Additionally, blood level of anti-epileptic drugs were measured for the included patients at Assiut University Hospitals, Egypt.

Statistical Analysis

Data were collected and analyzed using SPSS (Statistical Package for the Social Science) version 20. Continuous data was expressed as mean ± SD or median (range), while nominal data was expressed as frequency (percentage).Student's t test tested

statistical significance for two groups and ANOVA test for threegroups.

RESULTS

The mean age of the patients (group A) was 22.56 ± 9.45 years while that of healthy control group (group B) were 22.09±6.78 years (P=0.98). Duration of Epilepsy for patients (group: A) ranged from 2-26 years. Both of patients and control groups included 29 males and 16 females. Regarding risk factors in patients; consanguinity was positive in 26 (57.8%) of patients. Positive family history of epilepsy found in18 (40%) of patients, while history of febrile convulsion presented in two patients only(4.4%).
General biochemical studies showed non-significant difference regarding serum glucose, lipid profile, liver or renal functions.

Concerning the age ofonset, it was noticed that age of onset of the majority about 35.6%of patients were at adolescence (12- 18 year) followed by20% at early adulthood (>18 year), 20% at late childhood (6-12 year), 13.3% Early childhood (1- 6 year),and 11.1% at infancy (<1 year). Of patients 55.6% and 42.2% had daily (severe), and weekly (moderate) seizures respectively. Only one case (2.2%) was mildly affected and had a monthly fits. Serial fits presented in 35 (77.8%) patients while 9 (20%) patients had history of status epilepticus.

The plasma free amino acids levels in the study groups have been shown in (Table 1& Fig.1B &C). Plasma amino acids profile in patients and controls showed interesting significant differences, where plasma levels of glutamate, glycine, leucine, phenylalanine, aspartate, ornithine, citrulline,serine and alanine levels and amino acid derivative GABA,were all increased in PRE group compared to controls($p<0.0001$). On the other hand, plasma levels of histidine, isoleucine, lysine, threonine and the amino acid derivative taurine levels were significantly decreased in PRE patients compared to controls ($p<0.0001$ each).

Regarding the frequency of epileptic fits, the severely affected patients (those complained of fit daily) had significantly higher glutamate, glycine and GABA plasma levels (P-value <0.000 each) compared to moderately affected patients (table 2), their serum ornithine, aspartate and alanine also showed also, significant increase in severely affected PRE patients. On the contrary, serum phenylalanine showed significant decreased in severely affected PRE patients compared to those moderately affected.

Subgrouping PRE patients according to presence or absence of status epileptics, (table: 3) showed also significant higher levels of glutamate amino acid in patients with recurrent attacks of status epileptics (p-values= 0.023).

We further subdivide the patient group (n=45) into five subgroups according to age of onset of epilepsy .We found no significant difference either in the plasma amino acid profiles between the subgroups (except for arginine amino acid)(Table:4) nor, in the correlation studies between plasma amino acid profiles and age of onset)(results not showed).

Correlation studies between frequencies of fits and levels of PFAA, confirmed previous results and showed significant positive correlation among GABA, glycine, glutamate, aspartate and alanine amino acids and the frequency of fits, although, significant negative correlation found between the frequency of fits and only phenylalanine amino acid(table:5) .

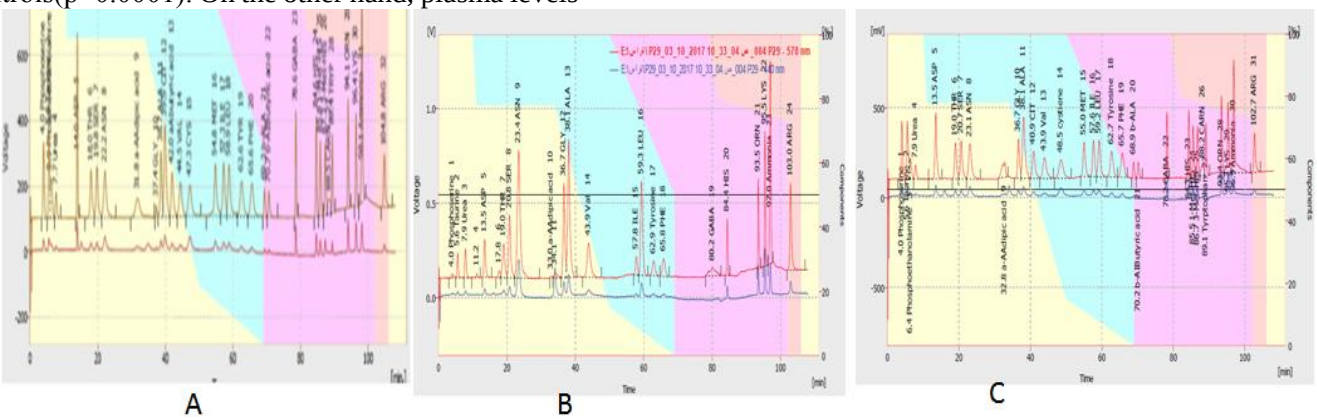

***Fig 1**: Chromatogram of amino acids Aminogram.(A): standard curve: Analysis at wavelength 440nm:570 nm(B) for the studied patients.(C) for the included controls (group B).Abbreviations:-ASP:Aspartate; Ther:Threonine; Ser:Serine; GlY:Glycine; Ala:Alanine; Val:Valine; Met:Methionine; Ile:Isoleucine; Leu:Leucine; PHE:Phenylalanine; GABA:Gamma amino butyric acid; Orn:Ornithine; LYS:Lysine; 8: Glutamate.*

Table 1: Plasma free amino acid levels (µmol/L) in the studied groups (patients and controls).

Variables	Patients (A)N=45	Healthy control (B) N=45	P value

Branched chain Amino Acids (BCAAs)			
Valine	394.86 ±98	401 ± 51.5	0.6718
Isoleucine	145.26 ± 8	220.2 ± 7.3	**0.0001**
Leucine	492.79 ±123	180.8 ± 19.66	**0.0001**
Aromatic Amino Acids (ARAAs)			
Tyrosine	137.7 ±7.9	141.66 ±6.7	0.8
Phenylalanine	198.5 ± 8	82.96 ±6	**0.0001**
Histidine	134.5 ± 5.16	262.3 ± 35.3	**0.0001**
Excitatory Amino Acid			
Glutamate	280.8 ±70	155 ± 20	**0.0001**
Aspartate	192 ±18	26.9 ±15.3	**0.0001**
Amino Acid derivatives			
Urea	438.76 ± 7	402.4 ± 6.8	0.0515
GABA	193 ± 3.7	67.86 ±1.8	**0.0001**
Taurine	47.71 ± 1.9	83 ± 1.7	**0.0001**
Other Amino Acid			
Ornithine	238.8 ± 59	150.2 ± 35	**0.0001**
Lysine	424.95 ±106	521.8 ± 130	**0.0002**
Arginine	348.7 ±87	406.2 ± 101.9	**0.0045**
Citrulline	116 ± 27.7	28.6 ± 1.59	**0.0110**
Methionine	33.8 ±4.49	37.9 ± 3.7	0.1637
Threonine	214.5 ± 7.5	290. 8 ±55.6	**0.0001**
Serine	368.87 ± 85.6	201.3 ±12	**0.0001**
Glycine	575.4 ± 46.9	277.6 ± 20.7	**0.0001**
Alanine	470.8 ±33.5	282.6±22	**0.0001**

Data represented as mean (µ mol/l)±SD, comparison between the two subgroups by using T. Test. P <0.05: significant P <0.01. Significant results are bold and gray shading.

Table 2, The levels of plasma free amino acid(µmol/l)in patients group(A)according to frequency of epileptic fits

Variables	Frequency of Fits		P-value
	Moderate(weekly) n=19	Severe (daily) n=25	
GABA	117.23±2.74	163.76±5.91	**0.0106**
Valine	402.32±7.76	421.26±12.99	0.563
Isoleucine	150.35±7.53	156.11±6.52	0.814
Leucine	452.8±11.9	504.73±48.89	0.542
Tyrosine	151.9±7.45	163.57±8.93	0.540
Phenylalanine	216.9±78.93	159.48±8.3	**0.024**
Histidine	152.71±7.71	185.39±9.27	0.216
Glutamate	166.21±24.62	253.52±55.05	**0.000**
Aspartate	135.63±9.59	189.3±3.13	**0.050**
Glycine	325.75±38.6	526.49±39.31	**0.000**
Ornithine	263.28±20.95	265.83±19.58	**0.002**
Lysine	412.96±41.11	416.72±79.81	0.940
Arginine	407.14±58.83	377.64±79.91	0.574
Taurine	122.4±5.05	116.07±4.6	0.645
Citrulline	155.52±34.08	69.47±9.44	0.080
Methionine	32.26±8.4	32.89±8.31	0.805
Threonine	323.08±15.29	313.53±51.25	0.815
Serine	437.35±85.67	457.43±69.68	0.618
Alanine	353.9±177.27	445.81±18.74	**0.04**

*Data represented as mean (µ mol/l)±SD, comparison between the two subgroups by using T. Test: P <0.05: significant **Nb:** Number of epileptic patients =45, only one patient was mildly affected (suffered of epileptic fits once monthly).This patient was not included in this statistic, so number of patients in table (2) were 44 patients. Significant results are bold and gray shading.*

Table 3: Comparison of the levels of plasma free amino acid (µmol/L) in Epileptic patients group(A)(N=45)according to presence or absence of status epilepticus

Variables	Status Epilepticus	P. value

	Present (n=9)	Absent (n=36)	
	Mean±SD	Mean±SD	
GABA	143.16±4.81	143.9±6.85	0.974
Valine	377.01±88.39	417.2±11.95	0.323
Isoleucine	162.72±3.47	151.23±5.35	0.698
Leucine	382.59±95.62	450.08±132.23	0.154
Tyrosine	134.33±2.42	161.89±6.61	0.256
Phenylalanine	143.44±6.48	196.3±4.11	0.094
Histidine	189.26±14.97	165.3±8.82	0.458
Glutamate	256±44.81	202.56±50	**0.005**
Aspartate	143.87±4.36	168.74±8.01	0.470
Glycine	457.07±43.71	426.05±84.19	0.641
Ornithine	229.84±31.05	269.85±16.39	0.373
Lysine	450.48±55.81	406.17±62.67	0.465
Arginine	321.65±88.97	403.88±62.41	0.195
Taurine	104.33±26.14	123.36±27.24	0.059
Citrulline	108.55±9.62	118.99±25.86	0.243
Methionine	31.02±4.13	33.03±8.89	0.515
Threonine	272.71±61.67	325.7±81.61	0.07
Serine	415.63±79.8	452.88±74.78	0.572
Alanine	400.05±55.17	403.69±63.55	0.948

By using Independent Samples. Significant results are bold and gray shading.

Table 4: Plasma free amino acid levels (µmol/l) in patient group (A)(N=45) according to age of onset of epilepsy.

Variables	Age at onset					P. value
	Infancy (n=5)	Early childhood (n=6)	Late childhood (n=9)	Adolescence (n=16)	Early adulthood (n=9)	
	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD	
GABA	124.47±5.93	108.81±8.04	183.06±9.05	152.24±6.67	123.39±5.48	0.097
Valine	431.4±7.15	395.76±9.54	456.61±7.22	406.2±35.77	363.55±9.64	0.469
Isoleucine	159.08±5.29	216.13±28.26	145.71±7.71	136.41±7.68	146.97±9.07	0.318
Leucine	492.43±62.64	551.22±44.86	379.5±66.01	570.01±38.19	356.99±23.91	0.275
Tyrosine	154.53±8.16	159.16±6.87	169.66±6.1	161.98±8.76	132.31±4.17	0.793
Phenylalanine	162.83±6	185.91±9.57	201.49±8.32	204.34±9.67	149.5±5.88	0.557
Histidine	245.84±7.65	140.32±9.42	137.53±8.23	167.52±8.09	184.97±11.59	0.179
Glutamate	222.2±58.6	224.5±57.18	248±62.58	200.69±7.68	198.33±8.29	0.618
Aspartate	147.64±6.4	107.91±28.67	154.4±3.79	173.35±10.01	202.29±18.27	0.377
Glycine	502.55±17.3	436±17.29	507.93±15.4	389.35±20.3	391.31±57.04	0.432
Ornithine	258.15±34.06	190.44±9.37	351.16±12.4	249.48±17.19	244.18±27.23	0.100
Lysine	456.81±16.99	412.26±71.59	365.31±55.07	431.79±62.61	413.59±99.04	0.861
Arginine	308.28±14.68	246.62±15.83	504.44±49.12	392.61±48.39	399.09±70.96	**0.039**
Taurine	103.41±25.29	126.48±31.68	96.17±8.89	134.75±5.31	120.27±5.78	0.270
Citrulline	35.86±2.46	144.98±36.89	89.34±4.36	112.5±27.72	118.6±11.1	0.842
Methionine	35.66±4.91	30.4±8	35.69±8.2	30.88±5.12	32.49±8.53	0.553
Threonine	319.52±6.25	308.28±9.74	333.19±20.37	329.55±74.82	273.43±12.07	0.875
Serine	443.33±82.55	401.31±40.2	531.47±73.97	451.35±88.26	379.45±63.7	0.436
Alanine	455.94±69.68	370.92±89.87	462.11±10.5	404.14±69.42	333.65±39.07	0.371

By using one-way ANOVA test; P >0.05: non-significant, Boldface: P <0.05: significant.Significant results are bold and gray shading.

Table 5: Correlation between frequencies of fits and all quantitative parameters in Patients (group A) (N=45)

Variables	Frequency of fits	
	r	P
Age at onset	-0.117	0.443

GABA	**0.355***	**0.017**
Valine	0.173	0.255
Isoleucine	-0.018	0.906
Leucine	0.191	0.209
Tyrosine	0.146	0.339
Phenylalanine	**-0.424****	**0.004**
Histidine	0.214	0.158
Glutamate	**0.685****	**0.000**
Aspartate	**0.359***	**0.015**
Glycine	**0.589****	**0.000**
Ornithine	0.089	0.562
Lysine	0.092	0.549
Arginine	-0.041	0.788
Taurine	-0.070	0.647
Citrulline	-0.041	0.790
Methionine	0.034	0.826
Threonine	0.062	0.687
Serine	0.139	0.363
Alanine	**0.343***	**0.021**

*By using Spearman's correlation. Significant results are gray shading and boldface: * Statistically significant correlation (p<0.05), ** Statistically significant correlation (p<0.01).*

DISCUSSION

Amino Acid profile in plasma and CSF give strong indication for excitability state and health of the brain. In the present study levels of the excitatory amino acids glutamate in addition to aspartate amino acid were significantly increased in PRE patients compared to healthy controls, also their levels increase significantly with increased frequency of fits.Aspartate may be a key excitatory neurotransmitter besides glutamate in pathogenesis of epilepsy, this in accordance with previous study of **Huxtable *et al.*** [19] that concluded that fasting plasma levels of aspartate and glutamate significantly increase in epilepsy.

This also, observed by **Janjua *et al.*** [20] who found these amino acids act as excitatory neurotransmitter playing a key role in the pathogenesis of PRE epilepsy and are also compatible with neurochemical and neurophysiological evidence implicating glutamic acid in the mechanism of seizure. Also, this increases in aspartate and glutamate concentrations may be explained by the prescription of phenytoin as mentioned by **Huxtable *et al.*** [19].

Regarding inhibitory amino acid glycine, it shows a significant increase in patients as compared to controls. This can be explained by either the administration of valproate which increases the plasma levels of glycine (by inhibition of the glycine cleavage system),or defect in receptor and signaling pathway in the brain as documented by **Rainesalo*et al*.** [14] .

The current study revealed that plasma levels of GABA showed a significant increase in PRE patients compared to healthy controls (P-value<0.0001) which can be explained by the administration of anti-epileptic drugs that increase local GABA concentration and another explanation is resistance of GABA receptors to central GABA that can be reflected in part in by elevated plasma GABA. That was in accordance with a previous study by **Löscher et al.** [21] who demonstrated in animal study that increased central GABA concentration by anticonvulsant inhibitors of GABA catabolism are reflected in part in plasma GABA.These results suggest that the GABA in plasma may be useful to indirectly monitor the effect of such drugs on brain GABA concentration in humans.

The role of BCAA on human brain is somewhat controversy. Current study showed significant increase of levels of leucine in patients with PRE compared to healthy controls, the finding that may partially explained by that of **Evangeliou *et al.*** [22] who concluded that constant oral supplementation of BCAAs worsens seizure propagation and causes neuron loss in animals with mesial temporal lobe epilepsy.

Although, phenylalanine concentration is mildly significantly elevated in patients compared to controls. Yet, its levels were negatively correlated with age of onset, this in accordance with **Huxtable *et al.*** [19], who found decreased concentrations of aromatic amino acids as tyrosine and phenylalanine in plasma after acute seizures.

Suárez *et al*. [23] stated that the biosynthesis of taurine is depending on nutritional state, protein intake, and cysteine accessibility, so it recorded highly variable among individuals. In current study, taurine level was decreased in patients compared to controls, this finding may be due to the lack of neuroprotective role of taurine in epileptic patients as explained by **Hrncic *et al*.** [13].

Our results of significantly decrease histidine amino acid in PRE patients than controls is in accordance with previous work by **Gietzen *et al.*** [24], who demonstrated that deficiencies of histidine exacerbate seizures, furthermore, limitation of histidine amino acid may excite the anterior pyriform cortex of the cerebrum, which contains a zone of high epileptogenicity.

Arginine amino acid showed tend to significant increase in PRE patients compared to controls this finding in accordance with **Carlson *et al.*** [25] who showed five times increase in arginine levels in patients with focal epilepsy. **De Sarro*et al.*** [26] results also support contribution of arginine to the origins of seizure activity through the action of nitric oxide which is formed from L-Arginine upon excitatory amino acid receptor activation within the prepiriform cortex.

The study has public health implications, as according to **Kobow and Blümcke** [27], about 50 million people worldwide have epilepsy, thus its considered the most common worldwide chronic and severe neurological disease. Above 30% of epileptic patients have insufficient control of their seizures with pharmacological therapy. In addition, few biomarkers of PRE are available to assess the severity and rate of progression. The present study showed that plasma amino acids and their derivatives may be a candidate

marker for selection in future risk scores for PRE if larger sample size studies can also replicate these findings**.**

CONCLUSION

Significant differences among plasma amino acids profile between patients and controls establish an interesting connection between plasma amino acid changes and pathogenesis of PRE.

Identification of PFAA changes may contribute to drug failure in PRE, allowing better understanding of its cellular and metabolic mechanisms and is critical for improvement of new and targeted therapeutic approaches. The use of altered PFAAs profile may explain pathogenesis and severity of epilepsy. They also, may act as prognostic factor for the frequency of fits and status epileptics in PRE patients, raising the question of whether such findings had an effect in frequency of PRE fits.

Conflict of Interest: The authors declare that they have no conflict of interest.

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