Essential and Conditionally Essential Amino Acid Profile in West Kazakhstan Children with Suspected Inborn Errors of Metabolism

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Abstract: Measuring the concentration of amino acids in the blood and compiling a metabolic profile of amino acids, taking into account the influence of factors such as age, gender, body weight, region of residence, is extremely important in the diagnosis of amino acid metabolic disorders, especially when conducting selective screening for inborn errors of metabolism (IEM). Aims: To describe the metabolic profile of essential and conditionally essential amino acids in samples of dried blood spots from children in Western Kazakhstan with suspected IEM using LC-MS/MS technology (liquid chromatography-tandem mass spectrometry). Methods: The cross-sectional study included 200 clinical-risk children of West Kazakhstan aged one day to 18 years, 52.5 % male and 47.5 % female. Depending on their age, the children were divided into the following groups: group A (newborns, age 1-30 days), group B (age 1 month -7 years) and group C (age 8-18 years). Blood samples on Guthrie cards were collected and quantified by LC-MS/MS. Nonparametric statistical approaches were used. The concentrations of arginine, glycine, leucine, isoleucine, hydroxyproline, methionine, phenylalanine, proline, tyrosine, valine in dried blood spots of children with suspected IEM were determined. Results: Significant differences were established between children with suspected IEM of different age groups in the concentrations of hydroxyproline, arginine, glycine, isoleucine, leucine, phenylalanine, proline, tyrosine and valine. A negative correlation with age for the majority of essential and conditionally essential Amino Acids indicates their decline with age in children with suspected hereditary metabolic diseases. Significant differences between groups of female and male children with suspected IEM were established only in the concentration of methionine in dried blood spots. The highest values were determined in female group. Conclusion: The results of this study may be important in conducting selective screening for IEM in various age groups of the pediatric population.

Keywords: Essential amino acids, Selective screening, Inborn errors of metabolism, Tandem mass spectrometry

Introduction

Inborn errors of metabolism (IEMs) are a large class of genetic disorders that result from defects in enzymes involved in energy production and nutrient metabolism (Phipps, Jones & Patel, 2019). Deficiency or alteration in the activity of essential enzymes or proteins in metabolic intermediate pathways results in a wide range of diseases with clinical heterogeneity (Golbahar et al., 2013; Han et al., 2015; Sarker et al., 2019). Disorders of amino acid metabolism, organic acid metabolism and the urea cycle make up a significant part of IEM (Phipps et al., 2019).

Amino acids serve as key building blocks and energy sources for cell repair, survival, regeneration and growth. In addition to their role as building blocks of protein, amino acids are also a source of energy (ketogenic, glucogenic, or both), are building blocks of Krebs cycle intermediates (also known as the tricarboxylic acid cycle) and other metabolites, and are metabolized as needed. Nine amino acids (histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, valine) are considered "essential", i.e. essential in the diet, since humans are not able to synthesize them endogenously (Aliu et al., 2018).

Diagnosis of hereditary disorders of amino acid (AA) metabolism is based on qualitative and/or quantitative analysis of AA, mainly in blood and urine (Piraud et al., 2011). For many years, the most common method was ion exchange chromatography followed by post-column derivatization with ninhydrin. The advent of tandem mass spectrometry (MS/MS) coupled with liquid chromatography (LC) has made it possible to measure many metabolites for the diagnosis of inborn errors of metabolism (Piraud et al., 2011). High-performance technologies based on liquid chromatography-tandem mass spectrometry (LC-MS/MS) are now widely used, which allow the simultaneous quantification of several metabolites, such as amino acids and acylcarnitines, from a very small amount of a biological sample (Sarker et al., 2019).

Amino acid profiles are important tools needed to diagnose inherited disorders of amino acid metabolism. Age reference cutoff ranges for each analyte should be established first for each population by individual laboratories prior to screening/diagnosis of patients (Yang et al., 2018; Sarker et al., 2019), as cutoff values are highly dependent on various factors. such as genetic background, geographical location of the population, diet and age (Dietzen et al., 2016; Sarker et al., 2019). According to Uaariyapanichkul et al. (2018), compared with Caucasians, the levels of most amino acids in the blood of Thai children were higher.

Newborns are currently screened or diagnosed with more than 30 IEMs using LC-MS/MS in newborn screening programs in most developed countries and some developing countries around the world (Mak et al., 2013). Currently, screening of newborns using MS/MS is not mandatory in Kazakhstan, but we have developed and are conducting a pilot project for selective screening for hereditary metabolic disorders using MS/MS. During the study, reference intervals were developed for the concentration of 57 metabolites, including amino acids and acylcarnitines in dried blood spots for different age groups of the pediatric population, including newborns (Syrlybayeva, Zharmakhanova & Kononets, 2023; Zharmakhanova et al., 2023). From October 2022 to December 2024, we assessed the frequency of 37 inherited metabolic disorders using LC-MS/MS technology in a group of high-risk children in Western Kazakhstan. The data obtained from examining a group of high-risk children will be compared with the reference intervals we previously established.

Study Objectives

To describe the metabolic profile of essential and conditionally essential amino acids in samples of dried blood spots from children in Western Kazakhstan with suspected IEM using LC-MS/MS technology.

Tasks

1. To determine the level of essential and conditionally essential amino acids in samples of dried blood spots in children with suspected IEM, taking into account age and gender.
2. To evaluate factors that may affect essential and conditionally essential amino acids levels.
3. To compare findings of the determined analytes in newborns of Western Kazakhstan DBS with the results of previously published studies in other populations.

Methods

Data Sources

The data of this study were obtained during the examination of 200 clinical-risk children aged one day to 18 years to describe the metabolic profile of essential and conditionally essential amino acids (Figure 1). In this research, we recruited a sample of eligible 200 children across the region (200 children aged one day to 18 years suspected of IEM). Western Kazakhstan is divided into four regions (provinces, oblasts) according to the administrative division: Aktobe, West Kazakhstan, Atyrau and Mangystau (Figure 2).
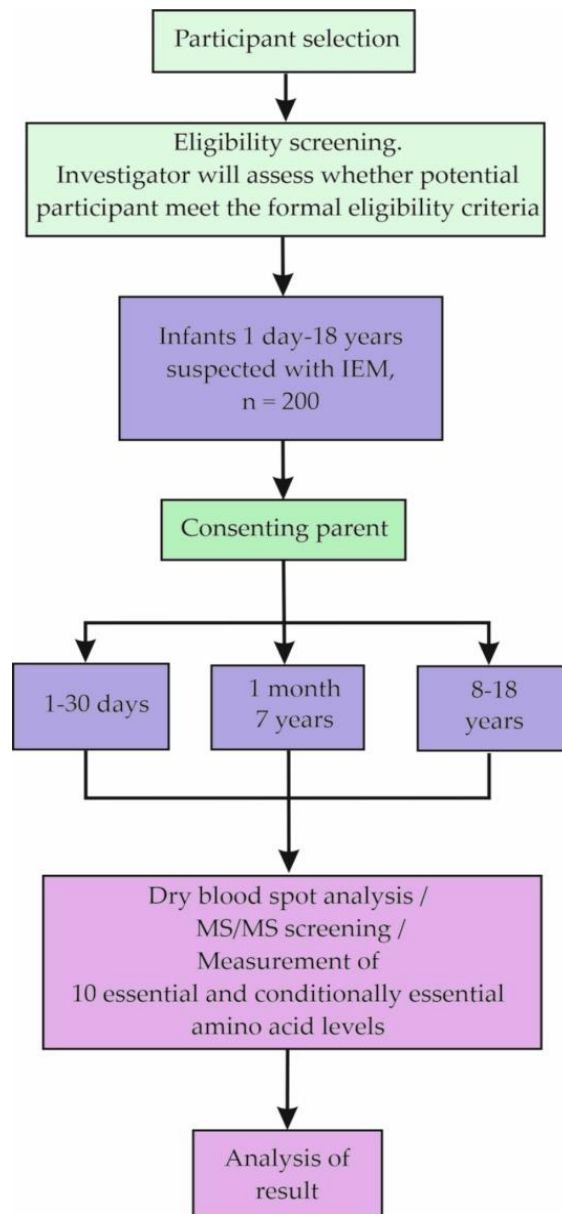
Figure 1. Study flowchart

Figure 2. Sites for data collection throughout western Kazakhstan.

The study was approved by the Bioethics Committee of the West Kazakhstan Marat Ospanov Medical University (Ref. No. 7, 09/09/2020.) Written informed consent (IS) was obtained from the parents and/or legal guardians of children after birth to collect a DBS sample. Demographic and anthropometric data of study participants are presented in Table 1.

Table 1. Demographic and anthropometric data of study participants children suspected IEM (n=200)

	Group A newborns 1-30 days (n=130)	Group B 1 months- 7 years (n=52)	Group C 8-18 years (n=18)	The whole sample (n=200)
Weight in grams, by birth Median (IQR)	3180 (2500;3725)	3095 (2300;3465)	3200 (2950;3400)	3155 (2480;3628)
Gender				
Male, n, %	71 (54.6 %)	24 (46.2 %)	10 (56.6 %)	105 (52.5 %)
Female, n, %	59 (45.4 %)	28 (53.8 %)	8 (44.4 %)	95 (47.5 %)
Geographic distribution				
Urban population, n, %	68 (52.3 %)	27 (51.9 %)	11 (61.1 %)	124 (62,0 %)
Rural population, n, %	62 (47.7 %)	25 (48.1 %)	7 (38.9 %)	76 (38,0 %)

Depending on their age, the children were divided into the following groups: group A (newborns, age 1-30 days), group B (age 1 month -7 years) and group C (age 8-18 years). Children from a West Kazakhstan population with suspected metabolic disorders were assessed for inborn metabolic disorders and referred by primary care neonatologists and pediatric consultants between October 2022 and August 2024 based on clinical symptoms associated with metabolic disorders. The study included newborns and children undergoing treatment in maternity hospitals and pediatric clinics of 7 children's hospitals in the region. Patient information was obtained from Individual Record Cards (IRCs) completed by parents or guardians of study participants. The completed questionnaires were reviewed by the researchers. In cases of improper collection, data were removed from the study if they could not be adequately verified. A sample IRC, as well as other supplementary materials, is available at the registry at clini-cal.trials.gov (https://www.clinicaltrials.gov/study/NCT05910151).

Criteria for Inclusion in the Study

Children from 1 day to 18 years of age enrolled for selective screening for IEM if one of the main criteria or two or more additional criteria (symptoms) are identified. The inclusion criteria for IEM selective screening are:

Main Criteria (Symptoms)

Sudden deterioration of the child's clinical condition after a period of normal development (days, weeks, months):
• acute metabolic encephalopathy,
• lethargy (coma),
• seizures resistant to antiepileptic therapy;
Hepatomegaly (hepatosplenomegaly);
Metabolic acidosis with increased anion gap;
Multiple fractures;
Child mortality in the family from diseases with similar symptoms.

Additional Criteria (Symptoms)

Treatment-resistant seizures;
Abnormal muscle tone: dystonia, hyperkinesis, hypotension;
Speech retardation;
Mental retardation of unknown cause;
Cardiomyopathy;
Tachypnea;
Frequent spitting up (vomiting);
Osteoarticular anomalies (joint stiffness, chest deformity, rickets-like changes);
Hernias (umbilical, inguinal-scrotal);

Persistent or recurrent hypoglycemia;

Metabolic alkalosis;

Hyperammonemia;

Thrombocytopenia;

Abnormal odor of urine, body, earwax, any unusual odor;

Hair growth disorders, alopecia;

Ophthalmic anomalies;

Unusual appearance, dysmorphic features;

Parents' consanguinity;

Positive family history with metabolic disorders.

Mass Spectrometry Analysis

Specimen Collection and Storage

Whole blood samples were collected from infants no earlier than 3 hours after feeding by heel prick using a heel stick. Five drops of whole blood (each ~75 µl) were applied to Guthrie cards, Ahlstrom 226 filter paper, and PerkinElmer 226 Five-Spot Card (PerkinElmer Health Sciences, Greenville, USA) to form dried blood spots (DBSs) for LC-MS/MS analysis. Whole blood samples from older children at high-risk were collected after a 4-hour fasting using a standard venipuncture method.

Samples were dried for 4 hours at room temperature and then stored at 4°C in labeled individual zip-lock plastic envelopes with desiccants until analyzed by LC-MS/MS. Samples were sent to the laboratory within five days. In the case of long-term storage of samples, it was carried out at a temperature of –20°C.

Specimen Preparation and LC-MS/MS Analysis

The Neobase2 TM Non-derivatized MSMS kit (PerkinElmer, Wallac Oy, Turku, Finland) was used to quantify 5 essential amino acids and 5 conditionally essential amino acids in dried blood spots according to the manufacturer's instructions. Vial with lyophilized isotope-labeled internal standards (IS) containing $^2H_3$-Leucine (Leu IS), $^2H_3$-Isoleucine (Leu IS), $^2H_3$-Methionine (Met IS), $^{13}C_6$-Phenylalanine (Phe IS), ^{15}N-$^{13}C_5$-Valine (Val IS), $^2H_4$-^{13}C-Arginine (Arg IS), $^{15}N,2$-^{13}C-Glycine (Gly IS), $^2H_3$-Hydroxyproline (Leu IS), $^{13}C_5$-Proline (Pro IS), $^{13}C_6$-Tyrosine (Tyr IS), was being recovered by adding 1.4 ml of the extraction solution that is included in the Neobase 2 kit. The Extraction Working Solution (EWS) IS was prepared by diluting the recovered internal standards with the extraction solution of 1:100 (v/v).

DBS were analyzed using a Shimadzu LCMS-8050 Triple Quadrupole Mass Spectrometer (Shimadzu Corporation, Kyoto, Japan). Level I and Level II (low standard and high standard) dried blood drops were included with each assay lot of the Neobase2 TM Non-derivatized MSMS kit to monitor system accuracy and precision.

To analyze essential and conditionally essential amino acids, stored DBS card samples are brought to room temperature (+18 to +25°C) before extraction. A 3.2 mm disc (equivalent to ~3.1 µl of whole blood) is punched out of one dried blood spot with a diameter of 3.2 mm using a Wallac DBS Puncher (PerkinElmer, Wallac Oy, Mustionkatu 6, FI-20750 Turku, Finland) into the well of the 96-well polystyrene U-bottom microplate supplied with the Neobase2 TM Non-derivatized MSMS kit. After adding 125 µL of working extraction solution to each well of the microplate, the plate is covered with an adhesive aluminum film and incubated for 30 minutes at room temperature on a microplate shaker with a shaking speed of 650 rpm. After incubation, 100 µL of the supernatant is transferred to a new 96-well U-bottom microplate, covered with aluminum foil to reduce evaporation, and incubated for 1 hour. The plate is then placed into the Shimadzu LCMS-8050 Triple Quadrupole Mass Spectrometer autosampler, and 5 µL of supernatant is injected into the LCMS for analysis.

Metabolites to Measurement

Arginine (Arg), Glycine (Gly), Leucine (Leu), Isoleucine (Ile), Hydroxyproline (Pro-OH), Methionine (Met), Phenylalanine (Phe), Proline (Pro), Tyrosine (Tyr), Valine (Val).

Statistical Analysis

Shapiro-Wilk and Kolmogorov-Smirnov tests were used to check the normality of the distribution. The data obtained in the study demonstrated that the distribution of essential and conditionally essential amino acids in DBS differs from normal. Me (median) and quartiles (IQR interquartile range) were used for descriptive statistics of the samples. Nonparametric tests (Mann-Whitney U test, Kruskal-Wallis H test) were used to test differences in essential and conditionally essential amino acids concentrations depending on various factors (gender, age, place of residence). Considering the skewed distribution, correlations between body weight, age, and the concentration of essential and conditionally essential amino acids in dry blood spots were performed using Spearman's test. Two-sided levels <0.05 are assumed to be statistically significant. Statistical analysis was done using the software IBM SPSS v. 23.0 (IBM, Armonk, NY, USA) and Statistica (StatSoft, Inc., Tulsa, OK, USA, v. 10).

Results and Discussion

Descriptive statistics on the concentrations of 10 essential and conditionally essential amino acids in samples of dried blood spots from children in Western Kazakhstan with suspected IEM, divided into subgroups according to age, are presented in Table 2.

Table 2. Essential and conditionally essential amino acid profile in dried blood spots of 200 children with suspected IEM in Western Kazakhstan.

Amino acid, µmol/l		All children (n = 200)	Group A newborns 1-30 days (n=130)	Group B 1 months- 7 years (n=52)	Group C 8-18 years (n=18)	Kruskal – Wallis *H* test	p-values
5-Oxo Pro	Median	30.76	66.68	19.90	23.34	28.43	0.000
	Range	19.62;93.66	22.01;106.76	16.44;31.18	18.23;62.59		
Arg	Median	23.18	17.89	45.23	44.38	75.38	0.000
	Range	15.73;39.03	13.87;24.38	32.78;55.11	35.02;56.95		
Gly	Median	493.51	547.56	311.37	315.84	73.99	0.000
	Range	362.36;632.40	472.18;660.36	251.52;423.37	273.64;407.04		
Ile	Median	56.12	51.41	34.15	54.49	18.12	0.000
	Range	49.22;65.13	47.82;59.52	25.12;44.53	47.19;62.24		
Leu	Median	144.49	156.21	115.46	129.50	34.25	0.000
	Range	117.08;176.12	130.20;186.43	98.94;145.51	107.94;141.56		
Met	Median	29.02	30.58	23.15	21.92	5.39	0.068
	Range	21.38;57.25	24.31;54.42	18.53;83.94	16.68;31.68		
Phe	Median	54.50	58.51	43.95	46.83	54.14	0.000
	Range	44.38;64.77	51.01;68.82	37.68;49.99	35.66;55.12		
Pro	Median	148.89	157.84	117.86	128.10	32.78	0.000
	Range	120.27;174.98	134.29;185.77	93.29;156.40	104.76;138.22		
Tyr	Median	85.33	104.83	57.57	59.26	70.87	0.000
	Range	60.42;126.79	83.39;149.64	46.74;69.35	19.80;70.65		
Val	Median	124.98	127.04	119.68	157.59	8.77	0.013
	Range	105.62;151.65	105.95;148.56	103.25;147.28	124.57;182.02		

Differences in the distribution of the level of essential and conditionally essential amino acids in dried blood spots between groups of children with suspected IEM of different ages, determined using the Kruskal-Wallis test, are noted in Table 2. Statistically significant differences between age groups were noted in the concentration of hydroxyproline, arginine , glycine, isoleucine, leucine, phenylalanine, proline, tyrosine and valine (Table 2).

In addition, significant negative correlations of moderate strength with age were established for the concentrations in dried blood spots of glycine, phenylalanine and tyrosine, weak negative correlations for hydroxyproline, isoleucine, leucine, methionine, proline and an moderate positive correlation with age for arginine (Table 3).

Age had a significant effect on the concentrations of most essential and conditionally essential amino acids, with Spearman's r correlation coefficients ranging from 0.053 to 0.619 for positive relationships and from -0.153 to -0.613 for negative relationships (Table 3). Only arginine and valine had a positive correlation with age. Most essential and conditionally essential amino acids showed a negative correlation with age, indicating a decrease in these amino acids with age in children with suspected hereditary metabolic diseases (Table 3).

Table 3. Statistical analysis according to age (Spearman's correlation) and gender (Mann-Whitney U test)

Analyte	Spearman correlation		Male N=105		Female N=95		p-values
	ρ	p-values	Median (μmol/L)	Range	Median (μmol/L)	Range	
5-Oxo Pro	-0,364	0.000	39.88	20.30;103.51	26.76	19.09;90.46	0.137
Arg	0.619	0.000	22.99	14.99;37.55	23.36	15.94;46.42	0.676
Gly	-0.613	0.000	473.46	325.25;629.45	505.17	384.91;632.76	0.324
Ile	-0.196	0.005	57.28	53.07;62.04	58.61	50.11;67.07	0.233
Leu	-0.411	0.000	144.02	114.61;172.50	146.67	125.56;183.24	0.407
Met	-0.153	0.032	26.32	20.32;53.62	32.26	22.90;62.16	0.035
Phe	-0.514	0.000	54.16	43.70;62.82	55.80	45.10;67.10	0.262
Pro	-0.402	0.000	148.43	115.95;175.46	150.76	122.32;171.50	0.544
Tyr	-0.598	0.000	83.81	56.57;120.23	89.03	61.95;140.54	0.058
Val	0.053	0.459	124.03	104.00;145.08	125.82	106.94;155.84	0.326

Significant differences between groups of children with suspected female and male IEM were found only in the concentration of methionine in dried blood spots (Table 4). The highest values were determined in female group.

Table 4. Statistical analysis according to body weigh (Spearman's correlation) in group A.

Analyte	5-Oxo Pro	Arg	Gly	Ile	Leu	Met	Phe	Pro	Tyr	Val
ρ	0.463	-0.011	0.129	0.075	0.068	-0.181	0.066	0.118	0.008	0.236
p-values	0.000	0.813	0.075	0.301	0.389	0.009	0.405	0.078	0.857	0.000

The effect of body weight on the concentration of essential and conditionally essential amino acids in dried blood spots of children with suspected IEM was assessed (Table 4). There were no significant correlations between amino acid concentrations and body weight in groups B and C. In group A (newborns), significant weak positive correlations were noted between body weight and the concentration of hydroxyproline and valine and a weak negative correlation for the concentration of methionine.

The influence of factors such as age, gender, and body weight on the concentration of metabolites, including amino acids, in the blood of children was reported by Manta-Vogli et al. (2020), Sarker et al. (2019), Dietzen et al. (2016), Yu et al. (2018), Uaariyapanichkul et al. (2018). In a study by Manta-Vogli et al. (2020) found an association between a number of amino acids, including essential and conditionally essential phenylalanine, leucine, tyrosine and glycine, in breastfed full-term infants and their birth weight. On the contrary, they found no relationship between birth weight and blood concentrations of the amino acids valine, methionine, citrulline and arginine (Manta-Vogli et al., 2020). However, in our study, no relationship was found between the levels of glycine, leucine, tyrosine and phenylalanine and body weight, but the concentration of hydroxyproline, methionine and valine in dried blood spots was found to be related to birth weight.

Conclusion

The results of this study may be important in determining thresholds for newborn screening and in selective screening for IEM in different age groups of the pediatric population.

Conflicts of Interest

The authors declare no conflict of interest.

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Scientific Ethics Declaration

The authors declare that the scientific ethical and legal responsibility of this article published in EPHELS Journal belongs to the authors.

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