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Original article

Metabolic derangements in IUGR neonates detected at birth using UPLC-MS

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ABSTRACT

Background: Intrauterine growth restriction (IUGR) is associated with short- and long-term metabolic consequences which are possibly dictated by in utero programming together with environmental and dietetic manipulation after birth. Early detection of metabolic derangements in these babies through metabolomics approach will help recognition of cases in need for further follow-up and can help future development of therapeutic and preventive strategies for the late consequences.
Objective: To compare amino acids and acyl carnitine levels in neonates with IUGR to normal birth weight controls; as a part of metabolic profiling.
Methods: Cord blood samples were collected at birth from 40 small-for-gestational-age (SGA) neonates and 20 normal birth weight gestational age-matched neonates, for quantification of amino acids and acyl-carnitines using Ultra Performance Liquid Chromatography-Mass Spectrometry (UPLC-MS).
Results: Significantly elevated acylcarnitine levels especially C18-OH and C16-OH were found in IUGR neonates vs. controls ($p < 0.001$). Specific amino acids that were significantly elevated in IUGR neonates included Histidine, Methionine, Arginine, Aspartic, Valine, Alanine, Leucine, Isoleucine, Glutamic acid, Tyrosine, Ornithine, Phenylalanine, and lastly citrulline. These derangements were recognized to be similar to those found in different disorders.
Conclusion: We conclude that IUGR neonates have unique metabolic derangements detectable by UPLC-MS at birth with similarities to derangements found in certain disorders. These babies should be closely followed up for early detection of the metabolic consequences of IUGR.

1. Introduction

Intrauterine growth restriction (IUGR) or small-for-gestational-age (SGA) is defined as birth weight or birth crown-heel length of less than 10th percentile for gestational age. Both terms are used interchangeably [1].

Prevalence of IUGR in the general population worldwide was estimated to be 7–15%, while in developing countries – including Egypt – it reaches up to 30% and constitutes 50–60% of low birth weight neonates (with birth weight of less than 2500 g) [2,3].

There is growing evidence that IUGR is strongly associated with several short- and long-term complications including, for instance, cognitive and psycho-physical developmental disorders during infancy and the metabolic syndrome during adulthood [4,5]. These consequences are probably related to "Perinatal Programming" and strongly correlated to postnatal dietetic rehabilitation and fast catch-up growth [5,6].

Biomarkers in medicine, particularly in Neonatology, are crucial for defining diagnosis and predicting prognosis of many diseases [7].

Certain biomarkers were previously identified and speculated as being correlated with IUGR such as maternal levels of endothelin-1 and leptin during pregnancy and urinary protein

Abbreviations: AGA, appropriate-for-gestational age; IUGR, intrauterine growth restriction; MS, mass spectrometry; ^{1}H NMR, nuclear magnetic resonance spectroscopy; PCA, principal components analysis; PLS-DA, Partial Least Squares-Discriminate Analysis; SGA, small-for-gestational age; UPLC, Ultra Performance Liquid Chromatography.

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S100B in the newborn [8,9]. Furthermore, some of these markers were useful as early predictors for later development of insulin resistance and type 2 diabetes mellitus [10].

However, through the last 2 decades, a new generation of biomarkers has been extensively studied; the metabolites comprising the metabolome, using the metabolomics approach.

Metabolomics is based on full analysis of metabolites in a biological sample using either mass spectrometry (MS) or nuclear magnetic resonance (^{1}H NMR) spectroscopy [11,12].

Being dynamic and highly sensitive to different environmental, dietetic and disease stimuli, the metabolome is a perfect target for diagnostic and prognostic approaches [13]. Identifying the metabolic derangements that occur at the level of metabolome very early in life will help detection of subsequent derangements through regular follow-up. This should help future development of therapeutic interventions or preventive strategies [14].

This study was designed to assess the metabolic fingerprints of IUGR at birth in comparison to normal birth weight neonates, so that we may share our results with the world-wide metabolomic mapping system. Babies with recognized metabolic derangements will be followed-up to detect onset of subsequent derangements known to be associated with IUGR.

2. Patients and methods

This case-control study was conducted in the Maternity Hospital; Ain Shams University, Cairo, Egypt, over a period of 13 months from August 1, 2014 to August 31, 2015.

All SGA neonates, either term or preterm, born during the study period were eligible. Samples from neonates with perinatal asphyxia, intracranial hemorrhage, congenital malformations, or congenital infections were discarded. Informed verbal consents were obtained from parents or caregivers after explanation of the study purpose and planning future visits.

Cord blood samples were collected in the delivery room, immediately after cord clamping, from 40 SGA neonates and 20 gestational age-matched healthy, appropriate-for-gestational age (AGA) neonates; as control. From each sample, three drops of blood were put on a filter paper which was immediately analyzed or stored at −80 °C till analysis using Ultra Performance Liquid Chromatography-Mass Spectrometry (UPLC-MS) [ACQUITY UPLC M-Class System, Waters Corporation (NYSE:WAT), Milford, Massachusetts, USA].

Data management and Statistical analysis were done using SPSS 21 and MetaboAnalyst 2.0.

Data processing started with data integrity check, then missing or zero values treatment, and data filtering. Data normalization was done with the generalized log transformation. Data analysis included Univariate analysis (T-test fold change) for preliminary overview of potentially significant features, Correlation analysis, and most importantly, Multivariate analysis including Principal Components Analysis (PCA) and Partial Least Squares-Discriminate Analysis (PLS-DA). Metabolite Set Enrichment Analysis (MSEA) was used to identify meaningful patterns of compounds combination, if any. Pathway analysis was based on KEGG metabolic pathways as the backend knowledgebase.

In this study, we divided the several variables of metabolomic profile into compounds for data reduction using PCA; this aimed at summarization of data into much fewer variables called scores which represent a weighted average of the original variables. The weighting profiles are generally called loadings.

Loadings for any variable in PCA mean the importance of this variable in that component (the higher the loading, the higher is the importance of that variable to explain variability in data).

Then the components were subsequently compared with components contained in the metabolite set library (KEGG).

3. Results

The mean ± SD (min–max) gestational age of SGA neonates was 34 ± 2.4 (30–39) weeks. Their mean birth weight was 1320 ± 300 (800–2400) g, mean crown-heel length was 40 ± 2.6 (35–45) cm, and mean head circumference was 28 ± 1.9 (25–32) cm. They were 18 (45%) males and 22 (55%) females. Eighty percent of them (32/40) were delivered by Cesarean section and 75% (30/40) of their mothers had preeclampsia.

Control group included 20 neonates with mean gestational age of 35 ± 1.4 (32–38) weeks, mean birth weight of 3100 ± 400 (2100–3800) g, mean crown-heel length of 48.5 ± 2.4 (45–51) cm, and mean head circumference of 34.4 ± 1.2 (33–36) cm. They were 12 (60%) males and 8 (40%) females. They were all AGA and 18/20 (90%) of them were delivered vaginally.

The two groups were non-significantly different as regards gestational age and sex distribution ($p > 0.05$), but cases had significantly less birth weight, length and head circumference than controls ($p < 0.001$).

Distinct metabolic profiles were identified for SGA neonates that are different from AGA neonates. Important features identified by t-tests are shown in Table 1. On the basis of individual metabolites, PCA and PLS-DA revealed very high concentrations of acylcarnitines, especially C18-OH and C16-OH acylcarnitines, in cases versus controls as well as significantly different levels – between the two groups – of Histidine, Methionine, Arginine, Aspartic, Valine, Alanine, Leucine, Isoleucine, Glutamic acid, Tyrosine, Ornithine, Phenylalanine, and lastly citrulline.

Coefficients or VIP scores showed details of the variables which were significantly higher or lower in IUGR compared to AGA neonates. C18-OH, C16-OH acylcarnitines, for example, were of highest concentration in patients not controls, while Histidine and Methionine were lower in patients than controls; Fig. 1.

Enrichment analysis showed disorders with highly significant metabolomic similarity to IUGR profiles. Examples are some of urea cycle defects such as Ornithine Transcarbamylase Deficiency (OTC), *N*-acetylglutamate synthetase deficiency and Argininosuccinic Aciduria, Lysinuric Protein Intolerance, Hyperornithinemia-Hyperammonemia-Homocitrullinuria (HHH-Syndrome), tyrosinemia type I, autism, and diabetes mellitus (MODY); Table 2 and Fig. 2.

Detailed results from pathway analysis are presented in Table 3. It shows that the most significantly altered metabolic pathway in IUGR neonates is the purine metabolism followed by thiamine metabolism, primary bile acid biosynthesis, lysine degradation, pyrimidine metabolism, and lastly glutathione metabolism, among others.

4. Discussion

Metabolomics provide a "snapshot" of metabolic status of a cell, tissue, or organism in relation to genetic variations or external stimuli [14]. During the last decade, many studies in neonates focused on metabolic profiling in different disease states; in order to establish maps for metabolic derangements in different disorders.

In this study, we used UPLC-MS for measurement of amino acids and acyl carnitine profiles in a group of SGA neonates in comparison to a matched group of AGA controls.

UPLC-MS provides significantly more resolution while reducing run times; so it is rapid, simple, and improves sensitivity for the analyses of many compounds [15].

Table 1
Important features identified by *t*-tests.

	p value	P value	log(p value)
C18-OH	3.55E−19	<0.001	18.45
Methionine	3.14E−12	<0.001	11.503
Met:Phe	3.93E−11	<0.001	10.406
Aspartic	5.02E−11	<0.001	10.299
Histidine	1.04E−10	<0.001	9.9834
C14-OH	1.24E−08	<0.001	7.9071
C18:1	1.12E−07	<0.001	6.9508
C4-Carnitine	1.44E−07	<0.001	6.8413
C16-OH	2.34E−07	<0.001	6.6317
C5-Carnitine	2.66E−07	<0.001	6.575
C14:1	8.43E−07	<0.001	6.0743
Phe: Tyr	2.54E−06	<0.001	5.5955
C16:1	3.03E−06	<0.001	5.5191
Valine	3.44E−06	<0.001	5.4629
C4-DC (C5-OH)	5.82E−06	<0.001	5.2353
Arginine	7.16E−06	<0.001	5.1452
C18:1-OH	7.93E−06	<0.001	5.1009
C14-Carnitine	2.78E−05	<0.001	4.556
C6-Carnitine	3.90E−05	<0.001	4.409
Glutamic acid	4.07E−05	<0.001	4.3907
C10-1	0.000102	<0.001	3.9922
Tyrosine	0.000103	<0.001	3.9889
C12-Carnitine	0.000159	<0.001	3.7989
C4-OH (C3-DC)	0.000444	<0.001	3.353
C5-DC	0.000537	<0.001	3.27
C16-Carnitine	0.000776	<0.001	3.1104
C2-Carntine	0.000825	<0.001	3.0834
C10-Carnitine	0.000936	<0.001	3.0286
Leu-lle	0.001625	0.001	2.7892
C0-Carinitine	0.001705	0.001	2.7684
C18-Carnitine	0.002041	0.002	2.6902
C14:2	0.002059	0.002	2.6863
C8:1	0.002133	0.002	2.6709
C8-Carnitine	0.038071	0.038	1.4194
Alanine	0.040699	0.040	1.3904
C3 carnitine	0.043659	0.043	1.3599

Met = Methionine, Phe = Phenylalanine, Tyr = Tyrosine, Leu = Leucine, Ile = Isoleucine.

Should the analytical techniques used in neonatology be simple, safe, and non-invasive, urine samples are preferred, especially in very preterm babies [12,16].

Other biological fluids frequently used for metabolomic studies in neonates include plasma, amniotic fluid, and cord blood, among others [17–20].

We collected cord blood samples immediately after cord clamping and this absolutely does not affect the babies [21].

Several metabolites were identified, in our study, at different concentrations allowing a clear discrimination between profiles of SGA and AGA neonates at birth and supporting previous studies. Certain amino acids and acyl carnitines were significantly increased in cases than controls. Similar results in respect to some amino acids; such as Alanine, Methionine, Ornithine, and Tyrosine, were reported in a recent study in China [22].

Some studies as well using the metabolomic approach have been published and all have shown altered metabolic profiles in IUGR compared to AGA neonates [23,17,24].

Significant differences between the two groups in respect to glucose and amino acid levels were previously identified in cord blood analyzed using liquid chromatography high-resolution mass spectrometry (LC-HRMS). Phenylalanine, tryptophan, and methionine were particularly shown to be significantly different and a cut-off value for the former two amino acids could be calculated for excellent discrimination between IUGR and AGA neonates [25].

Phenylalanine and Tyrosine were also found to be significantly elevated in our SGA compared to AGA neonates similar to several studies, while the opposite was reported by Sanz Cortéz et al. [21,26,27].

Sanz-Cortés et al. used ^{1}H NMR spectroscopy rather than MS and found reduced phenylalanine and tyrosine levels in IUGR cases. They attributed this reduction to an altered placental transport; possibly resulting from a "damaged" placental tissue, together with the inherent hyper-catabolic state in IUGR [21].

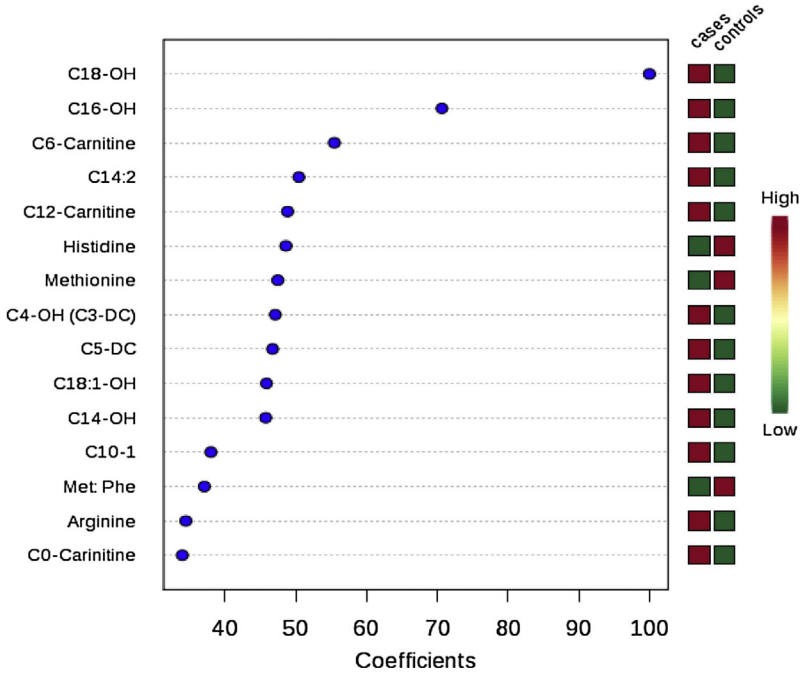

Figure 1. Coefficients (VIP score). Red color = variable is high, green color = variable is low. It shows that C18-OH and C16-OH acylcarnitines were of highest concentration in patients not controls, while Histidine and Methionine were lower in patients than controls.

Table 2
Identified metabolomic disorders with significant similarity to SGA babies.

	Total	Hits	Raw p	Holm p
Ornithine Transcarbamylase Deficiency (OTC)	10	7	4.89E−12	4.31E−10
Glycine N-Methyltransferase Deficiency/Homocystinuria-Megaloblastic Anemia Due To Defect In Cobalamin Metabolism, Cblg Complementation Type	1	1	5.86E−09	4.86E−07
Homocystinuria Due To Defect Of N(5,10)-Methylene Thf Deficiency/Homocystinuria (CBLE)	2	1	5.86E−09	4.86E−07
Methionine Adenosyl Transferase Deficiency/Methylmalonic Aciduria And Homocystinuria, Cblc Type/Methylmalonic Aciduria And Homocystinuria, Cbld Type	2	1	5.86E−09	4.86E−07
Histidinemia	2	1	1.13E−07	8.56E−06
Dengue fever	3	2	1.32E−07	9.92E−06
Sotos Syndrome	2	2	2.17E−06	0.000161
Argininosuccinic Aciduria (ASL)	6	3	2.59E−06	0.000189
Short Bowel Syndrome (Under Arginine-Free Diet)	4	3	5.36E−06	0.000381
Short-Bowel Syndrome (Permanent Intestinal Failure)	2	2	1.49E−05	0.001028
Delta-Pyrrolidine-5-Carboxylate Synthase Deficiency	5	4	4.21E−05	0.002649
3-Phosphoglycerate Dehydrogenase Deficiency	2	1	0.000136	0.008451
D-Glyceric Acidura/Hyperglycinemia, Non-Ketotic	1	1	0.000136	0.008451
Phosphoserine aminotransferase deficiency – new disorder?	2	1	0.000136	0.008451
Hypervalinemia	1	1	0.00024	0.012473
Congenital Glutamine Deficiency	1	1	0.000711	0.034825
Hyperinsulinism-Hyperammonemia Syndrome	2	1	0.000711	0.034825
Tyrosinemia II/Tyrosinemia III/Transient Tyrosinemia of Newborn	1	1	0.001806	0.084882
Carbamoyl Phosphate Synthetase Deficiency (CPS)	3	2	0.002188	0.094336
Lysinuric Protein Intolerance (LPI)	4	2	0.002753	0.11561
Hyperornithinemia With Gyrate Atrophy (HOGA)	4	2	0.002848	0.11677
Hyperornithinemia-Hyperammonemia-Homocitrullinuria [HHH-S]	3	2	0.002848	0.11677
Ethylmalonic Encephalopathy (EPEMA)	2	1	0.00463	0.17595
Lethal Infantile Cardiomyopathy: X-Linked Cardioskeletal Myopathy (Barth Syndrome)	1	1	0.00463	0.17595
Mamel (Methylmalonic Aciduria Mitochondrial Encephelopathy Leigh-Like)	2	1	0.00463	0.17595
Inflammatory Diseases	2	2	0.004854	0.17595
Myocardial Infarction	4	2	0.004854	0.17595
N-acetylglutamate synthetase deficiency. NAGS deficiency	5	3	0.006804	0.17595
Citrullinemia Type I	3	2	0.008398	0.17595
Citrullinemia Type II, Adult-Onset	2	1	0.17018	1
Narp Syndrome	1	1	0.17018	1
Hyperphenylalaniemia Due To Guanosine Triphosphate Cyclohydrolase Deficiency/Hyperphenylalaninemia Due To 6-Pyruvoyltetrahydropterin Synthase Deficiency (Ptps)/Hyperphenylalaninemia Due To Dhpr-Deficiency/ Hyperphenylalaninemia Due To Pterin-4a-Carbinolamine Dehydratase/Phenylketonuria, Mother (MPKU)	1	1	0.47635	1
Dicarboxylic Aminoaciduria. Glutamate-Aspartate Transport Defect	2	1	0.65581	1
Hyperprolinemia, Type I	1	1	0.65581	1
Hyperprolinemia, Type II	2	2	0.68806	1

Total: total number of compounds in the pathway; Hits: the actually matched number from uploaded data; Raw p: original p value calculated from enrichment analysis; Holm p: p value adjusted by Holm-Bonferroni method.

Reduced phenylalanine and tyrosine levels in these cases would be associated with adverse neurological outcome; being neurotransmitter precursors and this deserves further investigation [28].

Horgan et al. analyzed placenta villous explants from nine SGA neonates using UPLC-MS and found that 574 metabolites were significantly different from AGA controls. Changes in phospholipids and essential amino acids (tryptophan, methionine, and phenylalanine) concentrations were, again, the most prominent [29].

Leucine and Valine were significantly elevated in our SGA neonates. Theoretically, these amino acids are reduced during chronic malnutrition and some research work on IUGR showed reduced placental transport of leucine in these fetuses [30]. However, glucocorticoids; which increase during stressful situations, reduce the specific catabolic enzymes of these amino acids leading to stationary or even increased levels [31].

Interestingly, studies in adults could discriminate a population who were extremely low birth weight (ELBW) infants from a control population of adults born at term with normal birth weight, based on alterations in arginine and proline metabolism, in purine and pyrimidine metabolism, in histidine beta-alanine metabolism, and in the urea cycle [12].

Clear differences among the urinary metabolic profiles of AGA, IUGR, and large-for-gestational-age (LGA) neonates; analyzed by ^{1}H NMR spectroscopy, were also reported. The main metabolites responsible for these differences were identified as myo-inositol, creatinine, creatine, citrate, urea, and glycine. In particular, among these metabolites, myo-inositol was proposed as a potential biomarker of an altered glucose metabolism during fetal development both in IUGR and LGA neonates [32].

Similar results regarding myo-inositol in urine and plasma of IUGR neonates were reported in other studies using either ^{1}H NMR or gas chromatography-mass spectrometry (GC–MS) [17,24,33].

So, increased myoinositol concentration in plasma and urine, which has been associated with glucose intolerance and insulin resistance, can be also considered as a valid marker of altered glucose metabolism during fetal development in IUGR [34].

Glutamine levels in our study were significantly elevated in SGA babies; a finding that was previously recorded [21,35].

Fetal glutamine is next to glucose as one of the main sources of cellular energy during fetal life. It also plays a key role in fetal neurodevelopment being a precursor of alpha amino butyric acid; a neurotransmission inhibitor [36].

Increased glutamine levels in severe IUGR could be explained by the inherent hypercatabolic status of IUGR in association to decreased glucose levels. This lack of energy substrates may convey to increase glutamine supply to the fetus through different mechanisms; not only transfer from maternal blood, but also placental synthesis [35].

As for Acyl carnitine abnormalities found in our study, similar abnormalities were previously described and attributed to either chronic hypoxia or under-nutrition [37,38]. This seems to be con-

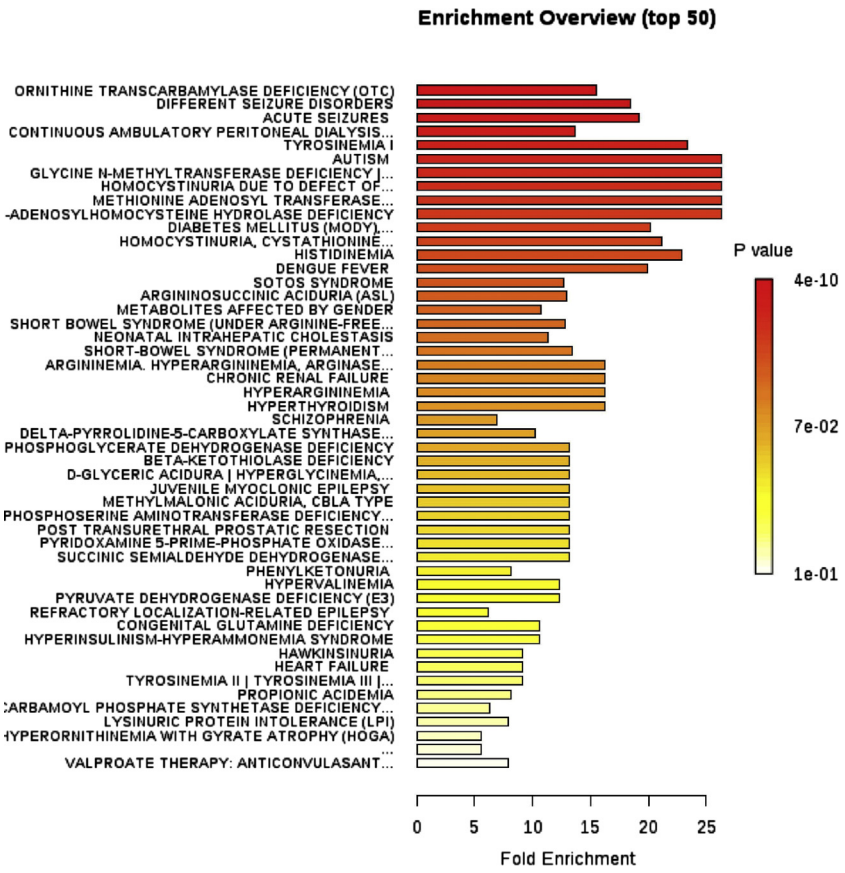

Figure 2. Enrichment analysis showing disorders with high metabolomic similarity to IUGR profiles.

Table 3
Detailed results from pathway analysis.

	Total	Hits	Raw p	Log (p)	Holm adjust	FDR p	Impact
Aminoacyl-tRNA biosynthesis	75	9	5.49E−17	37.441	1.54E−15	1.54E−15	0
Alanine, aspartate and glutamate metabolism	24	2	7.59E−13	27.907	2.05E−11	1.06E−11	0.22982
Glycerophospholipid metabolism	39	1	9.76E−12	25.353	2.54E−10	9.11E−11	0.00317
Nitrogen metabolism	39	5	4.54E−10	21.514	1.13E−08	3.18E−09	0
Cysteine and methionine metabolism	56	1	5.86E−09	18.956	1.41E−07	3.28E−08	0.03806
Histidine metabolism	44	1	1.13E−07	16	2.59E−06	4.50E−07	0.13988
Beta-Alanine metabolism	28	1	1.13E−07	16	2.59E−06	4.50E−07	0
Arginine and proline metabolism	77	5	8.82E−06	11.639	0.000185	3.09E−05	0.37816
D-Arginine and D-ornithine metabolism	8	2	2.77E−05	10.492	0.000555	8.63E−05	0
Purine metabolism	92	2	6.68E−05	9.6139	0.001269	0.000187	0
Thiamine metabolism	24	2	9.32E−05	9.281	0.001677	0.000237	0
Glycine, serine and threonine metabolism	48	1	0.000136	8.9006	0.002317	0.000239	0.18774
Primary bile acid biosynthesis	47	1	0.000136	8.9006	0.002317	0.000239	0.00822
Lysine degradation	47	1	0.000136	8.9006	0.002317	0.000239	0
Methane metabolism	34	1	0.000136	8.9006	0.002317	0.000239	0
Porphyrin and chlorophyll metabolism	104	1	0.000136	8.9006	0.002317	0.000239	0
Valine, leucine and isoleucine biosynthesis	27	1	0.00024	8.3354	0.002879	0.000336	0.01325
Valine, leucine and isoleucine degradation	40	1	0.00024	8.3354	0.002879	0.000336	0
Propanoate metabolism	35	1	0.00024	8.3354	0.002879	0.000336	0
Pantothenate and CoA biosynthesis	27	1	0.00024	8.3354	0.002879	0.000336	0
D-Glutamine and D-glutamate metabolism	11	1	0.000711	7.2492	0.005686	0.000905	0.02674
Pyrimidine metabolism	60	1	0.000711	7.2492	0.005686	0.000905	0
Tyrosine metabolism	76	1	0.001806	6.3166	0.010836	0.002107	0.04724
Ubiquinone and other terpenoid-quinone biosynthesis	36	1	0.001806	6.3166	0.010836	0.002107	0
Phenylalanine metabolism	45	2	0.004854	5.3279	0.019417	0.005228	0.11906
Phenylalanine, tyrosine and tryptophan biosynthesis	27	2	0.004854	5.3279	0.019417	0.005228	0.008
Glutathione metabolism	38	2	0.019292	3.948	0.038585	0.020007	0
Cyanoamino acid metabolism	16	2	0.063324	2.7595	0.063324	0.063324	0

Total: total number of compounds in the pathway; Hits: actually matched number from uploaded data; Raw p: original p value calculated from enrichment analysis; Holm p: p value adjusted by Holm-Bonferroni method; FDR p: p value adjusted using False Discovery Rate; Impact: pathway impact value calculated from pathway topology analysis.

troversial because another study in Germany has shown reduced, rather than elevated, cord blood levels of acylcarnitines in smaller babies, though the researchers also reported increased levels with hypoxic insults [39].

Important to emphasize is that acylcarnitine analysis is used to investigate common metabolic derangements such as insulin resistance; as long-chain acylcarnitines interfere with insulin signaling directly within the cell membrane [40].

Significant elevation of cord blood levels of lipids; mainly VLDL, were also reported together with elevated creatine and glutamine levels and reduced glucose, choline and phenylalanine in SGA compared to AGA neonates [21].

In a recent review by Dessì and colleagues, they concluded that intermediates of the tri carboxylic acid (TCA) cycle; such as glutamine, alanine, leucine, and aspartate, are the most frequently revealed metabolites in metabolomic studies in IUGR. Considering the fact that insulin helps oxidation of acetyl-CoA and promotes conversion of glucose to pyruvate through TCA cycle, insulin resistance found pre- and post-natal in cases of IUGR may be responsible for these altered TCA intermediates [41].

Enrichment analysis in our study also revealed moderate similarity of our IUGR neonates' metabolic derangements to some disorders like tyrosinemia type I, Neonatal Intrahepatic Cholestasis, propionic acidemia and Maple syrup urine disease (MSUD) and remote similarity to some other disorders as non-insulin dependent diabetes mellitus, autism, and Very-Long-Chain Acyl Co-A Dehydrogenase Deficiency (VLCAD). We speculate that the marked deviation from normal metabolism which is found in IUGR causes diversity of derangements which in turn are, individually, related to a diversity of diseases. And although type II diabetes mellitus, for instance, is a well known long-term morbidity strongly associated to IUGR, the definite metabolic derangements known in this disease had a weak similarity to our studied neonates; denoting that the previously shown similar derangements build up over time and follow-up is thus strongly needed.

Promising treatment modalities are still under research, however, studies focusing on protein metabolism in IUGR neonates suggested that both neonatal and long-term morbidity can be modified by the rate of postnatal growth specifically during the neonatal period [42].

We found that our IUGR neonates had their metabolic derangements best matching those of urea cycle defects. This can be explained by the previously shown impaired urea cycle function in IUGR babies especially with more severe growth restriction, and its postnatal maturation is delayed especially in preterm IUGR ones [43,44]. However, intestinal urea recycling in these infants is increased, which means that their protein usage is more efficient [45].

So, when feeding these babies, protein intake must be balanced; to be low enough to prevent accumulation of ammonia, but high enough to guarantee adequate growth.

5. Conclusion

In Summary, this study sheds light on the unique amino acid and acyl carnitine profile of IUGR neonates at birth and can be used to establish the metabolic map in these babies immediately at birth to help defining cases that need further follow-up.

Conflicts of interest

The authors declare that they have no conflicts of interest or any financial issues to disclose.

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