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Yield of Extended Metabolic Screen in Infants and Children Presenting with Encephalopathy

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Abstract:

Background: Inborn errors of metabolism (IEMs) are significant causes of illness and mortality, particularly in pediatric populations. Although each IEM is rare, their collective incidence is high. These genetic disorders often result in damage to the developing brain, leading to encephalopathy and other severe neurological symptoms.

Aim: This study aimed to determine the incidence of IEMs in infants and children presenting with acute encephalopathy, developmental delay, psychomotor regression, or intractable seizures, using extended metabolic screening techniques.

Patients and Methods: This prospective cohort observational study included 277 infants and children aged one month to fifteen years, presenting with the specified conditions. Patients were recruited from the inpatient wards, pediatric intensive care unit, and pediatric neurology outpatient clinic at Aswan University Hospital. Comprehensive clinical data were collected, and metabolic screening was performed using tandem mass spectrometry (MS/MS) and gas chromatography-mass spectrometry (GC/MS). Additional investigations included serum ammonia, lactate, random blood glucose, arterial blood gases, and neuroimaging studies.

Results: Among the 277 patients, the mean age was 3.8 ± 3.42 years, with a slight male predominance (54.2%). Encephalopathy with or without developmental delay was the most common presentation (52.7%), followed by developmental delay (47.3%). Extended metabolic screening revealed abnormal results in 18.8% of patients. The most common metabolic disorders identified were glutaric acidemia (4.3%), fatty acid oxidation defects (3.2%), phenylketonuria (2.9%), and methylmalonic acidemia (2.5%). The metabolic group had higher rates of disturbed conscious levels (73.08%), hypotonia (34.62%), and hyporeflexia (26.92%). Elevated serum ammonia and lactate levels were significantly more common in the metabolic group. The study identified a statistically significant higher mortality rate in patients with abnormal metabolic screening results (13.46%) compared to those with normal results (1.78%).

Conclusion: The study underscores the importance of comprehensive metabolic screening in pediatric patients presenting with encephalopathy, developmental delay, or intractable seizures. Early identification and appropriate management of IEMs are crucial for improving outcomes and preventing irreversible damage. The integration of advanced screening techniques such as MS/MS and GC/MS in routine clinical practice is essential for timely diagnosis and treatment.

Keywords:Inborn errors of metabolism, encephalopathy, developmental delay, tandem mass spectrometry, gas chromatography-mass spectrometry, pediatric neurology, metabolic screening.

1. Introduction

Inborn errors of metabolism (IEMs) are a significant cause of illness and death, particularly in pediatric populations. Despite being individually rare, their collective incidence is relatively high, ranging from approximately 1 in 5,000 to 1 in 800 live births [1]. These genetic disorders can result in damage to virtually any tissue, but the most severe and characteristic consequence, when left untreated or in severe cases, is harm to the developing brain. This neurological impairment often manifests as encephalopathy, an abnormal condition characterized by dysfunction and structural abnormalities in the brain, caused by the toxic buildup of otherwise normal metabolites [2].

Several groups of inherited metabolic disorders, notably organic acidemias, urea cycle defects, and certain amino acid metabolism disorders, typically present with acute, life-threatening symptoms of encephalopathy. These symptoms, such as lethargy, poor feeding, seizures, and abnormal muscle tone, are the result of the toxic effects of accumulated metabolites on the central nervous system (CNS) [3]. In some cases, cerebral edema and intracranial hemorrhage may occur. Importantly, many individuals previously diagnosed with conditions like cerebral palsy, psychiatric disorders, or other medical diseases may actually have an undiagnosed IEM [3].

Since the year 2000, the inclusion of tests for several IEMs has been driven by the tandem mass spectrometry (MS/MS) technology. This powerful analytical tool can rapidly identify and quantify a large number of different analytes from a single sample by separating ions based on their molecular mass-to-charge ratio and measuring their intensities. MS/MS can detect metabolic disorders categorized into four groups: amino acid disorders, urea cycle disorders, organic acid disorders, and disorders of fatty acid oxidation, enabling the detection of around 40 different IEMs with varying severities [4].

Egypt and other countries in the Middle East and Northern Africa region have a high birth rate and a high rate of consanguinity (25-70%) and first-cousin marriages [5, 6]. This genetic homogeneity, coupled with the autosomal recessive nature of many IEMs, contributes to a high incidence of these diseases in the region. Previous studies in Egypt and Iran have reported IEM prevalence rates of 8.56% and 14%, respectively, in children with symptoms suggestive of these disorders [7].

The main objective of this work is to determine the incidence of inborn errors of metabolism in infants and children presenting with acute encephalopathy, developmental delay, psychomotor regression or intractable seizures.

Patients and Method

STUDY DESIGN AND SETTING

This was a prospective cohort observational study conducted at the inpatient wards, pediatric intensive care unit, and pediatric neurology outpatient clinic of the Pediatric Department at Aswan University Hospital.

STUDY POPULATION

Infants and children aged between one month and fifteen years presenting with one or more of the following conditions were included: acute encephalopathy, chronic static unexplained encephalopathy, developmental delay, psychomotor regression, or unexplained intractable

seizures. Neonates and patients whose encephalopathy could be otherwise explained (e.g., traumatic brain injury, toxic ingestion, renal or hypertensive encephalopathy, and diabetic ketoacidosis) were excluded.

CLINICAL DATA COLLECTION

A comprehensive medical history was obtained from all included cases, focusing on age at presentation, sex, residency, chief complaint, family history, and prenatal, natal, and postnatal history. A thorough clinical examination was performed, with emphasis on anthropometric measurements (weight, height, and head circumference), presence of dysmorphic features, neurological examination, congenital anomalies, and organomegaly (hepatosplenomegaly).

METABOLIC SCREENING

Amino acids and acylcarnitines analysis was performed on dried blood samples (DBS) collected on Guthrie paper by tandem mass spectrometry (MS/MS). Three blood spots were obtained from each patient via finger or heel prick, dried at room temperature, and stored in dried plastic bags until analysis within 24 hours or frozen until analysis.

Sample preparation involved punching out a 5mm disk from each DBS and extracting it with a solvent in a microtiter plate. The resulting extracts were then introduced into the MS/MS instrument for ionization and analysis based on mass-to-charge (m/z) ratios. Individual amino acids, amino acid ratios, acylcarnitine profiles (short, medium, long, and very long-chain fatty acids, free or carnitine esters), free carnitine, carnitine esters, dicarboxylic acids, and free fatty acids were quantified and analyzed.

COMPLEMENTARY INVESTIGATIONS

Depending on the clinical presentation and metabolic screening results, additional investigations were performed as needed, including serum ammonia, serum lactic acid, random blood glucose, arterial blood gases, urinary organic acid analysis by GC/MS, MRI brain, electroencephalography, cerebrospinal fluid analysis, TORCH screening, targeted enzyme assays, karyotyping, and whole-exome sequencing.

ETHICAL CONSIDERATIONS

The Research Ethics Committee of Aswan Faculty of Medicine approved the study protocol, and verbal consent was obtained from guardians of participants.

STATISTICAL ANALYSIS

Data were analyzed using SPSS version 26. Categorical variables were described as frequencies and percentages, and group differences were assessed using the Chi-square test. Continuous variables were expressed as minimum, maximum, mean ± standard deviation, or median (first quartile - third quartile), and group differences were detected using the Mann-Whitney test for non-parametric data. A two-tailed p-value < 0.05 was considered statistically significant.

Results

Table 1 provides an overview of the basic demographic data for the 277 patients included in the study. The gender distribution was roughly equal, with 54.2% males and 45.8% females. The

mean age was 3.8 ± 3.42 years, ranging from 0.13 to 15 years. The majority (79.4%) resided in urban areas, primarily the cities of Aswan (42.2%) and Luxor (37.2%), while 20.6% were from rural areas like Idfu and Kom Ombo. The main presenting features were developmental delay (47.3%) and encephalopathy with or without developmental delay (52.7%), with a smaller proportion (5.1%) exhibiting developmental regression. Associated disorders included attention deficit hyperactivity disorder (7.9%), autism spectrum disorder (7.2%), and seizures (39.7%). Consanguinity was reported in 55.6% of cases, and 28.2% had a positive family history suggestive of an underlying condition. A history of sibling death due to a neurological condition and previous abortions were noted in 10.1% and 7.2% of cases, respectively. The majority of patients (92.8%) were born full-term, with only 7.2% being preterm. Maternal illnesses during pregnancy, such as preeclamptic toxemia (1.8%) and gestational diabetes mellitus (2.5%), were infrequent. The mode of delivery was evenly split between cesarean section (49.5%) and vaginal delivery (50.5%). Nearly a quarter (23.8%) of the patients required admission to the neonatal intensive care unit, primarily for respiratory distress (10.5%), encephalopathy (6.9%), neonatal jaundice (3.6%), and neonatal sepsis (2.5%). Regarding anthropometric measures, most patients had normal weight (78.7%) and height (94.6%) within the -2SD to +2SD range. However, 21.3% were underweight (<-2SD), and 5.4% were stunted (<-2SD height). Microcephaly (<-2SD head circumference) was observed in 14.1% of patients, while 4% had macrocephaly (>+2SD head circumference).

The clinical and investigation data of the studied group. Regarding dysmorphic features, 12.6% of patients exhibited some form of dysmorphism, including fair color, coarse features, abnormal pigmentation, or abnormal facial features. On neurological examination, 52.3% of patients had a disturbed conscious level at presentation, and the vast majority exhibited underdeveloped speech (84.1%) and cognitive delay (85.9%). Movement disorders, such as dystonia, chorioathetosis, and ataxia, were observed in 8.9% of cases. Muscle bulk was wasted in 31.8% of patients, while muscle tone was abnormal, with 22% exhibiting hypotonia and 27.8% exhibiting hypertonia. Tendon reflexes were also abnormal, with 15.5% showing hyporeflexia and 28.2% showing hyperreflexia.

Congenital anomalies were present in 5.1% of patients, including cataracts, congenital heart disease, and sensory neural hearing loss. Hepatosplenomegaly was noted in 4.7% of cases. Electroencephalography (EEG) findings revealed generalized epileptic activity in 68% of cases and focal epileptic activity in 14%, while 18% had normal EEG results. Magnetic resonance imaging (MRI) of the brain was abnormal in 48.7% of patients, with the most common findings being atrophy (37.9%), periventricular leukomalacia (9.7%), white matter disease (4.7%), and cerebral cortex malformations (2.9%). Other less frequent abnormalities included calcifications, bat wing sign, corpus callosum agenesis, cerebellar atrophy, Dandy Walker malformation, encephalomalacia, hydrocephalus, infarction, Joubert's syndrome, subdural hemorrhage, and Van Der Knaap disease.

Cerebrospinal fluid (CSF) examination revealed central nervous system infection (CNSI) in 10.4% of the cases tested. Laboratory data findings included a mean serum ammonia level of 63.52 ± 61.47 μmol/L, a mean lactate level of 17.21 ± 6.62 mg/dL, and a mean random blood sugar level of 92.03 ± 20.66 mg/dL. Metabolic acidosis was detected on arterial blood gas analysis in 10.1% of patients (Table 2).

The metabolic screening tests performed on the study group. The extended metabolic screen by tandem mass spectrometry (MS/MS) and urine organic acid analysis by gas chromatography-mass

spectrometry (GC/MS) revealed abnormal results in 18.8% of the patients. Among the abnormal findings, the most common disorder detected was glutaric acidemia, identified in 4.3% of patients through both MS/MS and GC/MS. Other disorders identified by MS/MS included fatty acid oxidation and very long-chain fatty acid (VLCFA) disorders (3.2%), phenylketonuria (2.9%), methylmalonic acidemia (2.5%), citrullinemia (1.4%), maple syrup urine disease (1.4%), isovaleric acidemia (0.7%), non-ketotic hyperglycinemia (0.7%), tyrosinemia (0.7%), and Canavan disease (0.7%). Urine organic acid analysis by GC/MS also detected cases of glutaric acidemia (4.3%), methylmalonic acidemia (2.5%), phenylketonuria (2.9%), and isovaleric acidemia (0.7%). It is worth noting that while 18.8% of patients had abnormal metabolic screening results, the remaining 81.2% had normal findings on the extended metabolic screen and urine organic acid analysis (Table 3).

Among the 52 cases with abnormal metabolic screening results, the most prevalent disorder diagnosed was glutaric acidemia, accounting for 23.08% (12 cases) of the metabolic cases. Phenylketonuria (PKU) was the next most common, identified in 15.38% (8 cases), followed by methylmalonic acidemia (MMA) in 13.46% (7 cases). Fatty acid oxidation defects (FAOD) were found in 9.62% (5 cases), comprising adrenoleukodystrophy (ALD) in 1.92% (1 case), AR peroxisomal acyl-CoA oxidase deficiency in 1.92% (1 case), and other peroxisomal disorders in 3.85% (2 cases). Citrullinemia and maple syrup urine disease (MSUD) were each diagnosed in 7.69% (4 cases). The remaining diagnoses included Canavan disease, isovaleric acidemia (IVA), non-ketotic hyperglycinemia (NKH), and tyrosinemia, each representing 3.85% (2 cases) of the metabolic cases (Figure 1).

The study investigated the presence of TORCH infections (Toxoplasmosis, Other agents, Rubella, Cytomegalovirus, and Herpes simplex) in 53 cases, with 7 (13.2%) testing positive. Specifically, 5 cases (9.4%) were diagnosed with cytomegalovirus (CMV), while 1 case each (1.9%) was positive for rubella and toxoplasmosis, respectively. Several additional diagnostic tools were employed in the study. Cerebrospinal fluid (CSF) analysis for central nervous system (CNS) infection revealed 14 cases of post-meningitic sequelae out of 134 cases tested. Targeted enzyme assays for mucopolysaccharidosis (MPS) identified 4 cases, with 2 cases each of MPS type 1 and MPS type 3. Karyotyping, performed in 12 cases, diagnosed 2 cases of Williams syndrome and 1 case of Turner syndrome. Whole exome sequencing, conducted in 7 cases, uncovered various rare genetic disorders, including 1 case each of AD Weaver syndrome, Aicardi-Goutières syndrome type 1, Allan-Herndon-Dudley syndrome, AR spastic paraplegia type 47, AR Joubert's syndrome, Rett syndrome, and AR peroxisomal acyl-CoA oxidase deficiency. Brain MRI findings were abnormal in 45 out of 277 cases, with 30 cases showing hypoxic-ischemic encephalopathy and 15 cases revealing other diagnoses such as cerebral cortex malformations (7 cases), corpus callosum agenesis (3 cases), cerebellar atrophy and Dandy-Walker malformation (2 cases), Joubert's syndrome (2 cases), and Van Der Knaap disease (1 case). The time lapse between symptom onset and diagnosis varied considerably, ranging from a few days to several years, depending on the diagnostic tool and condition. For example, the mean time to diagnosis was 1.599 ± 2.518 months for extended metabolic screening (n=52), 0.577 ± 0.848 months for CSF analysis for CNS infection and its sequelae (n=14), 5.25 ± 0.957 years for targeted enzyme assays for MPS (n=4), 7 ± 1 year for karyotyping (n=3), 0.216 ± 0.145 months for TORCH screening (n=7), 2.714 ± 2.870 years for whole exome sequencing (n=7), 1.017 ± 0.846 years for MRI diagnosis of hypoxic-ischemic encephalopathy (n=30), and 1.267 ± 1.279 years for MRI diagnosis of other conditions (n=15). Despite these extensive investigations, 146 cases remained undiagnosed. Regarding

disease outcome, 11 patients (4%) died, while the majority, 266 patients (96%), were still living at the time of the study.

The comparison of basic demographic data revealed several notable differences between patients with metabolic diseases and those with other conditions. While factors such as gender distribution, age, residence (urban vs. rural), maternal illness during pregnancy, mode of delivery, and admission to the neonatal intensive care unit (NICU) were comparable between the two groups, distinct patterns emerged in their presenting features, family history, neonatal history, and anthropometric measures. Patients with metabolic diseases had a significantly higher proportion presenting with encephalopathy with or without developmental delay (73.1% vs. 48%, p=0.002), while the non-metabolic group had a higher prevalence of isolated developmental delay (52% vs. 26.9%, p=0.002). Consanguinity (80.8% vs. 49.8%, p<0.001) and positive suggestive family history (59.6% vs. 20.9%, p<0.001) were more common in the metabolic group. Encephalopathy as a reason for NICU admission was also significantly more frequent in the metabolic group (25% vs. 2.7%, p<0.001). Regarding anthropometric measures, underweight (<-2SD weight) was more prevalent (34.6% vs. 18.2%, p=0.009), and macrocephaly (>+2SD head circumference) was more common (11.5% vs. 2.2%, p=0.007) in patients with metabolic diseases (Table 4).

The clinical and investigation data of the studied group, as detailed in Table 5, reveal significant differences between patients with metabolic conditions (n=52) and those with other conditions (n=225). Dysmorphic features were slightly more common in the metabolic group (17.3%) compared to the other conditions group (11.6%), although this difference was not statistically significant (P=0.261). Notably, a fair complexion was significantly more prevalent among the metabolic group (13.46%) than the other group (0.44%) (P<0.001). Neurological examination showed a higher incidence of disturbed conscious level at presentation in the metabolic group (73.08%) versus the other group (47.56%) (P=0.001), and a higher rate of cognitive delay (76.92% vs. 88%, P=0.038). Muscle tone abnormalities, specifically hypotonia, were significantly more frequent in the metabolic group (34.62%) compared to the other conditions group (19.11%) (P=0.025). Hyporeflexia was also more common in the metabolic group (26.92%) compared to the other group (12.89%) (P=0.021). EEG results showed normal findings in 30.6% of the metabolic group compared to 14% of the other group (P=0.044), while MRI revealed a higher incidence of brain atrophy in the metabolic group (50%) versus the other group (35.11%) (P=0.046), and a significant presence of periventricular leukomalacia in the other conditions group (12%) (P=0.009). Furthermore, the metabolic group showed higher serum ammonia and lactate levels, with mean values of 158.35±86.8 µmol/L and 26.9±7.38 mg/dL, respectively, compared to 41.61±19.26 µmol/L and 14.97±3.83 mg/dL in the other group (both P<0.001). Arterial blood gases indicated a significant occurrence of metabolic acidosis in the metabolic group (50%) versus the other group (0.89%) (P<0.001) (Table 4).

This figure two shows highly statistically significant (p-value < 0.001) increased percentage of death in patients with abnormal metabolic screen (7 patients, 13.46%) when compared with patients of normal metabolic screen (4 patients, 1.78%). The 7 cases that died among the metabolic cases were 3 cases with glutaric acidemia and 4 cases with methylmalonic acidemia. They died at ages ranging from 1.2 to 7 years with mean age of death of 2.81 years. The causes of death were mainly sepsis, severe dehydration and hypovolemia on top of severe failure to thrive and progressive severe encephalopathy.

Tables

Table (1): Basic demographic data of the studied group

Variables	Patients (n=277)	
	No.	%
Personal data distribution		
Gender		
Male	150	54.2
Female	127	45.8
Age (years)		
Min.-Max.	0.13 - 15	
Mean±SD	3.8±3.42	
Residence		
Urban	220	79.4
City of Aswan	117	42.2
City of Luxor	103	37.2
Rural	57	20.6
Idfu	6	2.2
Kom Ombo	51	18.4
Distribution of presenting features		
Main presenting features		
Developmental delay	131	47.3
Encephalopathy with or without Developmental delay	146	52.7
Developmental regression	14	5.1
Other associated disorders		
Attention deficit hyperactivity disorder	22	7.9
Autism spectrum disorder	20	7.2
Seizures	110	39.7
Family history distribution		
Consanguinity		
No	123	44.4
Yes	154	55.6
Positive suggestive family history		
No	199	71.8
Yes	78	28.2
Sibling death due to neurological condition		
No	249	89.9
Yes	28	10.1
Previous abortions		
No	257	92.8
Yes	20	7.2
Antenatal and postnatal history		
Gestational age		
Full term	257	92.8

Preterm	20	7.2
Maternal illness		
No	265	95.7
Preeclamptic toxemia	5	1.8
Gestational diabetes mellites	7	2.5
Mode of delivery		
Caesarian section	137	49.5
Vaginal delivery	140	50.5
Neonatal Intensive Care Unit admission		
No	211	76.2
Yes	66	23.8
Infant of diabetic mother	1	0.4
Neonatal jaundice	10	3.6
Neonatal sepsis	7	2.5
Respiratory destress	29	10.5
Encephalopathy	19	6.9
Anthropometric measures		
Weight		
Less than -2SD	59	21.3
Min.-Max.	(-2.326) - (-2.051)	
Mean±SD	-2.151±0.131	
Normal (between -2SD and +2SD)	218	78.7
Min.-Max.	(-1.881) - 1.555	
Mean±SD	-0.183±0.884	
Height		
Less than -2SD	15	5.4
Min.-Max.	(-2.362) - (-2.054)	
Mean±SD	-2.201±0.143	
Normal (between -2SD and +2SD)	262	94.6
Min.-Max.	(-1.881) - 1.645	
Mean±SD	-0.157±0.725	
Head circumference		
Less than -2SD (Microcephaly)	39	14.1
Min.-Max.	(-2.326) - (-2.054)	
Mean±SD	-2.159±0.134	
Normal (between -2SD and +2SD)	227	81.9
Min.-Max.	(-1.881) - 1.881	
Mean±SD	-0.329±0.779	
More than +2SD (Macrocephaly)	11	4
Min.-Max.	2.054 - 2.326	
Mean±SD	2.153±0.137	

Table (2): Clinical and investigation data of the studied group

Variables	Patients (n=277)	
	No.	%
Dysmorphic features		
No	242	87.4
Yes	35	12.6
Fair color	8	2.9
Coarse	8	2.9
Abnormal pigmentation	6	2.2
Abnormal features	13	4.7
Neurological examination distribution		
Disturbed conscious level at presentation		
No	132	47.7
Yes	145	52.3
Under-developed speech		
No	44	15.9
Yes	233	84.1
Cognitive delay		
No	39	14.1
Yes	238	85.9
Associated movements disorders		
Normal	250	90.3
Dystonia, Chorioathetosis	10	3.6
Ataxia	12	4.3
Muscle bulk		
Normal	189	68.2
Wasted	88	31.8
Muscle tone		
Normal	139	50.2
Hypotonia	61	22.0
Hypertonia	77	27.8
Tendon reflexes		
Normal	156	56.3
Hyporeflexia	43	15.5
Hyperreflexia	78	28.2
Congenital anomalies		
Normal	263	94.9
Cataracts	2	0.7
Congenital heart disease (CHD)	7	2.5
Sensory neural hearing loss (SNHL)	2	0.7

Others	3	1.1
Hepatosplenomegaly		
No	264	95.3
Yes	13	4.7
Electroencephalography (EEG)		
Normal	27	18
Generalized epileptic activity	102	68
Focal epileptic activity	21	14
Magnetic resonance imaging		
Normal	142	51.3
Abnormal	135	48.7
Atrophy	105	37.9
Periventricular leucomalacia	27	9.7
Cerebral cortex malformation	8	2.9
White matter disease	13	4.7
Calcifications	4	1.4
Bat wing sign	4	1.4
Corpus callosum agenesis	3	1.1
Cerebellar atrophy	1	0.4
Dandy Walker malformation	1	0.4
Encephalomalacia	1	0.4
Hydrocephalus	2	0.7
Infarction	3	1.1
Joubert`s syndrome	2	0.7
Subdural hemorrhage	2	0.7
Van Der Knaap disease	1	0.4
Cerebrospinal fluid examination (CSF)		
Normal	120	89.6
Central nervous system infection (CNSI)	14	10.4
Laboratory data		
Serum ammonia (NH3)		
Min.-Max.	10 - 469	
Mean±SD	63.52±61.47	
Lactate		
Min.-Max.	9 - 50	
Mean±SD	17.21±6.62	
Random blood sugar (RBS)		
Min.-Max.	25 - 145	
Mean±SD	92.03±20.66	
Arterial blood gases (ABG)		
Normal	249	89.9
Metabolic acidosis	28	10.1

Table (3): Result of metabolic screen distribution of the studied group

	No. (n=277)	%
Extended metabolic screen by tandem mass spectrometry (MS/MS) and Urine organic acids (GC/MS)		
Normal	225	81.2
Abnormal	52	18.8
MS/MS findings and GC/MS findings		
Canavan	2	0.7
Citrullinemia	4	1.4
Fatty acid oxidation and VLCFA disorders	9	3.2
Glutaric acidemia	12	4.3
Isovaleric acidemia	2	0.7
Methylmalonic acidemia	7	2.5
Maple syrup urine disease	4	1.4
Non ketotichyperglycenemia	2	0.7
Phenylketonuria	8	2.9
Tyrosinemia	2	0.7
Urine Organic Acids (GC/MS) findings		
Glutaric acidemia	12	4.3
Isovaleric acidemia	2	0.7
Methylmalonic acidemia	7	2.5
Phenylketonuria	8	2.9

Table (4): Comparison of Basic demographic data in patients with or without metabolic disease

Variables	Metabolic (n=52)	Other conditions (n=225)	P. value
Demographic data			
Gender			
Male	29(55.77%)	121(53.78%)	0.795
Female	23(44.23%)	104(46.22%)	
Age (years)			
Min.-Max.	0.13 - 15	0.13 - 13	
Mean±SD	3.9±4.42	3.77±3.16	
Median (Q1-Q3)	1.7(0.75-5.88)	3(0.96-6)	0.326
Residence			

Urban Rural	40(76.92%) 12(23.08%)	180(80%) 45(20%)	0.621
Residence City of Aswan Idfu Kom Ombo City of Luxor	 23(44.23%) 3(5.77%) 9(17.31%) 17(32.69%)	 94(41.78%) 3(1.33%) 42(18.67%) 86(38.22%)	 0.232
Presenting features distribution			
Presenting features Developmental delay Encephalopathy with or without Developmental delay Developmental regression	 14(26.92%) 38(73.08%) 1(1.92%)	 117(52%) 108(48%) 13(5.78%)	 0.002** 0.0019** 0.427
Other associated disorders Attention deficit hyperactivity disorder Autism spectrum disorder Seizures	 7(13.46%) 4(7.69%) 24(46.15%)	 15(6.67%) 16(7.11%) 86(38.22%)	 0.178 0.880 0.370
Family history			
Consanguinity No Yes	 10(19.23%) 42(80.77%)	 113(50.22%) 112(49.78%)	 <0.001**
Positive suggestive family history No Yes	 21(40.38%) 31(59.62%)	 178(79.11%) 47(20.89%)	 <0.001**
Sibling death due to neurological condition No Yes	 43(82.69%) 9(17.31%)	 206(91.56%) 19(8.44%)	 0.056
Previous abortions No Yes	 50(96.15%) 2(3.85%)	 207(92%) 18(8%)	 0.297
Antenatal and postnatal history			
Gestational age Full term Preterm	 49(94.23%) 3(5.77%)	 208(92.44%) 17(7.56%)	 0.654
Maternal illness No Preeclamptic toxemia Gestational diabetes mellites	 50(96.15%) 0(0%) 2(3.85%)	 215(95.56%) 5(2.22%) 5(2.22%)	 0.850 0.613 0.853
Mode of delivery			

Caesarian section Vaginal delivery	26(50%) 26(50%)	111(49.33%) 114(50.67%)	0.931
Neonatal Intensive Care Unit admission No Yes	35(67.31%)	176(78.22%)	0.138
Infant of diabetic mother	1(1.92%)	0(0%)	0.425
Neonatal jaundice	0(0%)	10(4.44%)	0.256
Neonatal sepsis	0(0%)	7(3.11%)	0.425
Respiratory destress	3(5.77%)	26(11.56%)	0.328
Encephalopathy	13(25%)	6(2.67%)	<0.001**
Anthropometric measures			
Weight Less than -2SD Normal (between -2SD and +2SD)	18(34.6%) 34(65.4%)	41(18.2%) 184(81.8%)	0.009**
Height Less than -2SD Normal (between -2SD and +2SD)	2(3.8%) 50(96.2%)	13(5.8%) 212(94.2%)	0.579
Head circumference Less than -2SD (Microcephaly) Normal (between -2SD and +2SD) More than +2SD (Macrocephaly)	7(13.5%) 39(75%) 6(11.5%)	32(14.2%) 188(83.6%) 5(2.2%)	0.928 0.210 0.007**

Data represent as Mean ± SD, Median (minimal-maximum) or number (percentage).

SD: Standard deviation,

p: p value for comparing between the two studied groups. *: Statistically significant at $p \leq 0.05$

Table (5): Clinical and investigation data of the studied group according to metabolic screen methods

	Metabolic (n=52)	Other conditions (n=225)	P. value
Dysmorphic features			
No Yes	43(82.7%) 9(17.3%)	199(88.4%) 26(11.6%)	0.261
Fair color	7(13.46%)	1(0.44%)	<0.001**
Coarse	1(1.92%)	7(3.11%)	0.998
Abnormal pigmentation	0(0%)	6(2.67%)	0.507
Abnormal features	1(1.9%)	12(5.3%)	0.496
Neurological examination			
Disturbed conscious level at presentation No Yes	14(26.92%) 38(73.08%)	118(52.44%) 107(47.56%)	0.001**

Under-developed speech			
No	12(23.08%)	32(14.22%)	0.115
Yes	40(76.92%)	193(85.78%)	
Cognitive delay			
No	12(23.08%)	27(12%)	0.038*
Yes	40(76.92%)	198(88%)	
Associated movements disorders			
Normal	47(90.38%)	208(92.44%)	0.833
Dystonia, Chorioathetosis	3(5.77%)	7(3.11%)	0.607
Ataxia	2(3.85%)	10(4.44%)	0.850
Muscle bulk			
Normal	33(63.46%)	156(69.33%)	0.412
Wasted	19(36.54%)	69(30.67%)	
Muscle tone			
Normal	21(40.38%)	118(52.44%)	0.157
Hypotonia	18(34.62%)	43(19.11%)	0.025*
Hypertonia	13(25%)	64(28.44%)	0.743
Tendon reflexes			
Normal	25(48.08%)	131(58.22%)	0.241
Hyporeflexia	14(26.92%)	29(12.89%)	0.021*
Hyperreflexia	13(25%)	65(28.89%)	0.696
Congenital anomalies			
Congenital anomalies			
Normal	52(100%)	211(93.78%)	0.135
Cataracts	0(0%)	2(0.89%)	0.822
Congenital heart disease (CHD)	0(0%)	7(3.11%)	0.425
Sensory neural hearing loss (SNHL)	0(0%)	2(0.89%)	0.822
Others	0(0%)	3(1.33%)	0.927
Hepatosplenomegaly (HSM)			
No	51(98.08%)	213(94.67%)	0.295
Yes	1(1.92%)	12(5.33%)	
Electroencephalography (EEG)			
Normal	11(30.6%)	16(14%)	0.044*
Generalized epileptic activity	24(66.7%)	78(68.4%)	0.989
Focal epileptic activity	1(2.8%)	20(17.5%)	0.052
Magnetic resonance imaging			
Normal	22(42.31%)	120(53.33%)	0.152
Abnormal	30(57.69%)	105(46.67%)	

Atrophy	26(50%)	79(35.11%)	0.046*
Periventricular leucomalacia	0(0%)	27(12%)	0.009**
Cerebral cortex malformation	1(1.92%)	7(3.11%)	0.645
White matter disease	5(9.62%)	8(3.56%)	0.134
Calcifications	0(0%)	4(1.78%)	0.333
Bat wing sign	4(7.69%)	0(0%)	<0.001**
Corpus callosum agenesis	0(0%)	3(1.33%)	0.927
Cerebellar atrophy	0(0%)	1(0.44%)	0.418
Dandy Walker malformation	0(0%)	1(0.44%)	0.418
Encephalomalacia	0(0%)	1(0.44%)	0.418
Hydrocephalus	0(0%)	2(0.89%)	0.822
Infarction	0(0%)	3(1.33%)	0.927
Joubert`s S	0(0%)	2(0.89%)	0.822
Subdural hemorrhage	2(3.85%)	0(0%)	0.041*
Van Der Knaap diseas	0(0%)	1(0.44%)	0.418
Cerebrospinal fluid examination (CSF)			
Normal Central nervous system infection	38(100%) 0(0%)	82(85.4%) 14(14.6%)	0.013*
Laboratory data			
Serum ammonia (NH3) Min.-Max. Mean±SD	 47 - 469 158.35±86.8	 10 - 210 41.61±19.26	 <0.001**
Lactate Min.-Max. Mean±SD	 9 - 50 26.9±7.38	 9 - 36 14.97±3.83	 <0.001**
Random blood sugar (RBS) Min.-Max. Mean±SD	 36 - 128 73.83±23.57	 25 - 145 96.23±17.47	 <0.001**
Arterial blood gases (ABG)			
Arterial blood gases (ABG) Normal Metabolic acidosis	 26(50%) 26(50%)	 223(99.11%) 2(0.89%)	 <0.001**

Data represent as Mean ± SD, Median (minimal-maximum) or number (percentage).

SD: Standard deviation,

p: p value for comparing between the two studied groups. *: Statistically significant at $p \leq 0.05$

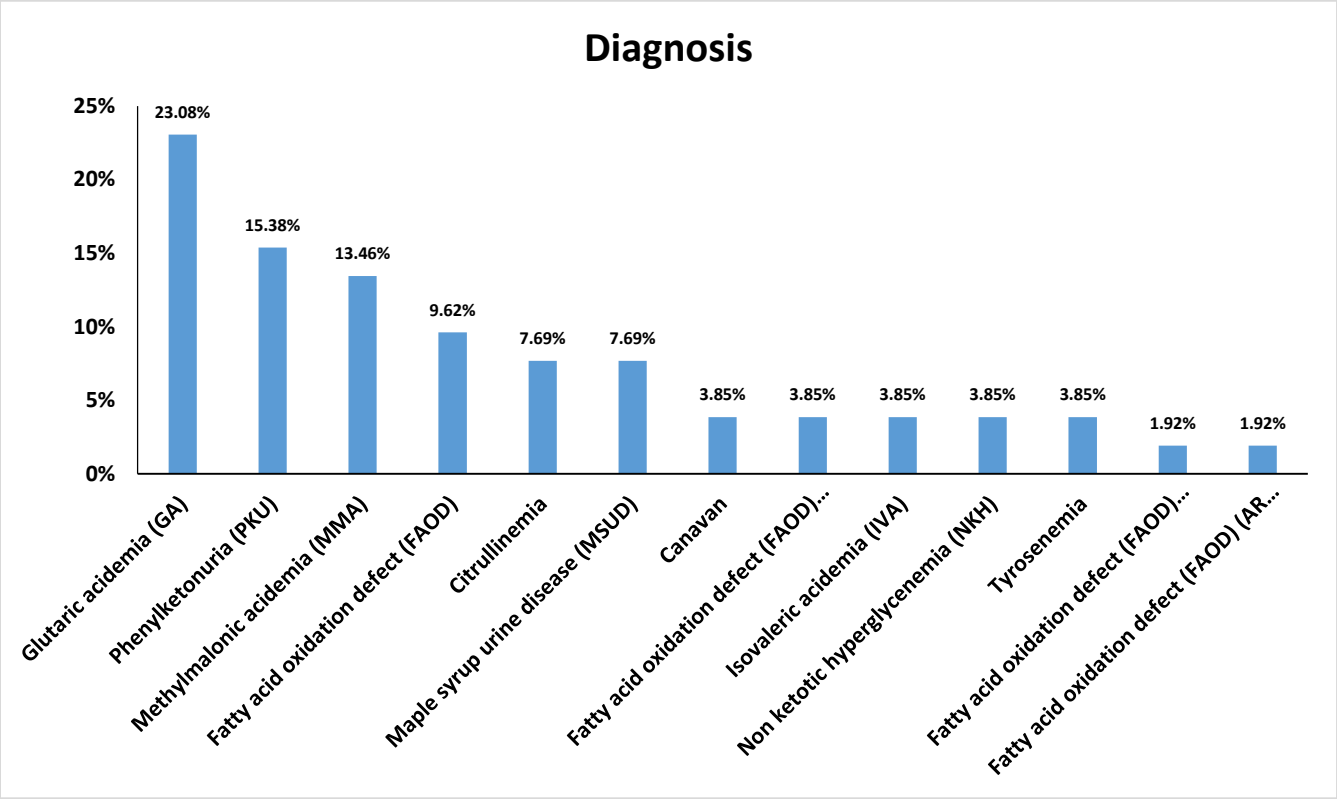

Fig. (1): Diagnosis distribution among metabolic cases.

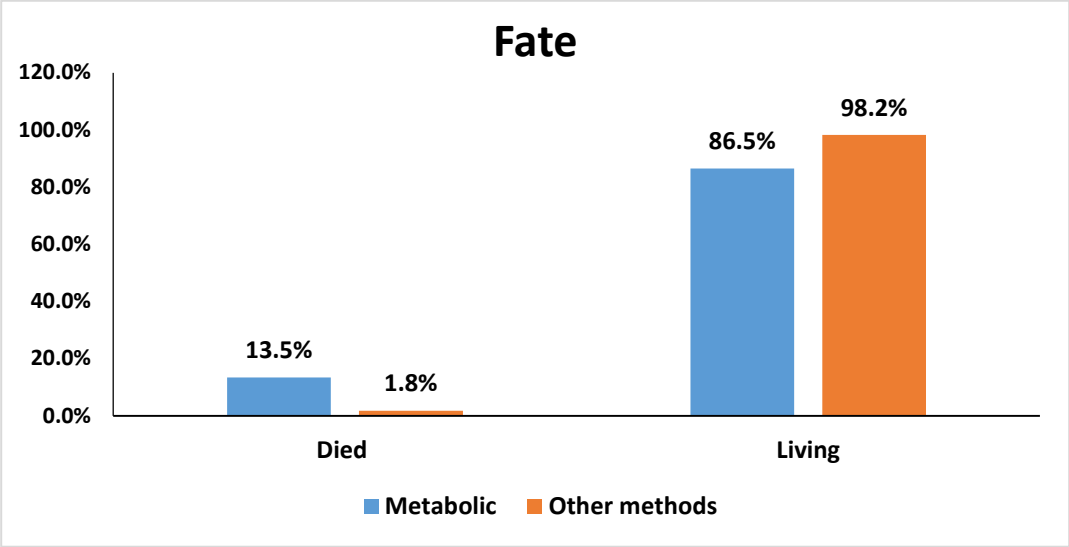

Fig. (2): Comparison of fate distribution between the studied groups

Discussion

Inborn errors of metabolism (IEMs) are a diverse group of disorders, either inherited or resulting from spontaneous mutations, affecting the metabolic pathways responsible for breaking down or storing carbohydrates, fatty acids, and proteins. While individually rare, collectively they occur in about 1 in 2500 births, making them relatively common. These disorders can present at any age, necessitating emergency providers to be knowledgeable about their presentations and evaluation methods [8, 9].

IEMs often present with non-specific symptoms such as respiratory distress, hypotonia, poor sucking reflex, vomiting, diarrhea, dehydration, lethargy, and seizures, which can be mistaken for sepsis or other common conditions [10]. The advent of tandem mass spectrometry (MS/MS) has enhanced newborn screening capabilities over the past few decades [11]. Coupled metabolomics techniques like MS/MS and GC/MS are pivotal for diagnosing IEMs, guiding therapy, follow-up, genetic counseling, and prenatal diagnosis [12].

The diagnosis of IEMs poses challenges due to limited access to specific laboratory tests, a shortage of experts, and inadequate dissemination of knowledge among healthcare providers. Early diagnosis is crucial for effective treatment and prevention of sequelae [13]. This study aimed to determine the incidence of IEMs in infants and children with acute encephalopathy, developmental delay, psychomotor regression, or intractable seizures.

The study involved 277 patients, with a mean age of 3.8 ± 3.42 years (range 0.13 to 15 years), and a slight male predominance (54.2% males). Encephalopathy, with or without developmental delay, was the most common presentation (52.7%), followed by developmental delay (47.3%). Seizures were found in 39.7% of cases, ADHD in 7.9%, and ASD in 7.2%.

These findings are consistent with Wajner et al., [14] who reported neurological abnormalities and psychomotor delay as common presentations in aminoacidopathies and organic acidurias. Selim et al. [15] found developmental delay in 75.9% and neurological abnormalities in 65.5% of cases.

In this study, 55.6% had a family history of consanguinity, 28.2% had a suggestive family history, 10.1% had a history of sibling death due to a neurological condition, and 7.2% had a history of previous abortion. These results align with other studies in Egypt and the Middle East, highlighting the high prevalence of consanguinity [16-18].

The study found that 92.8% of patients were full-term, 50.5% were delivered vaginally, 2.5% of mothers had gestational diabetes mellitus, and 1.8% had preeclamptic toxemia. Additionally, 23.8% of patients required NICU admission. Growth parameters showed 78.7% had normal weight, 94.6% had normal height, and 81.9% had normal head circumference. Dysmorphic features were detected in 12.6% of patients.

Neurological examination revealed that 52.3% had a disturbed conscious level at presentation, 84.1% had delayed speech, 85.9% had cognitive delay, and 3.6% had abnormal movements. Muscle bulk was wasted in 31.8% of patients, with 22% exhibiting hypotonia and 27.8% hypertonia. EEG results showed 18% had normal EEG, 68% had generalized epileptic activity, and 14% had focal epileptic activity.

MRI findings indicated 51.3% of cases had normal MRI. Brain atrophy was the most common abnormality (37.9%), followed by periventricular leukomalacia (9.7%) and white matter disease (4.7%). Serum ammonia levels were elevated in 21.7% of patients, 19.5% had elevated lactate levels, and 6.5% had hypoglycemia. The majority (89.9%) had normal ABG, while 10.1% had metabolic acidosis.

Extended metabolic screening using MS/MS and GC/MS revealed that 18.8% of patients had abnormal results. The most common metabolic disorders identified were glutaric acidemia (4.3%), fatty acid oxidation defects (3.2%), phenylketonuria (2.9%), and methylmalonic acidemia (2.5%). Other less common disorders included maple syrup urine disease and citrullinemia (1.4% each).

This study highlights the significant clinical and biochemical differences between patients with metabolic conditions and those with other conditions, underscoring the importance of comprehensive metabolic screening in pediatric patients presenting with encephalopathy, developmental delay, or intractable seizures. Early identification and appropriate management of IEMs are crucial for improving outcomes and preventing irreversible damage.

In agreement with our findings, several studies reported similar observations. Romão et al. noted that early diagnosis and intervention in IEM cases significantly improve patient outcomes [13]. Similarly, Selim et al. in Egypt found developmental delay as the predominant presentation in their cohort [15]. Khalaf et al. and Shawky et al. also reported high consanguinity rates among their patients, reflecting the genetic predisposition in these populations [16, 17].

In conclusion, this study emphasizes the need for heightened awareness and improved diagnostic capabilities for IEMs in pediatric populations. The integration of advanced screening techniques such as MS/MS and GC/MS in routine practice can facilitate early diagnosis, leading to timely and effective treatment, ultimately enhancing patient outcomes.

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