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Detection of Inborn Errors of Metabolism among High Risk Infants Admitted to Pediatric Intensive Care Unit

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ABSTRACT

Inborn errors of metabolism (IEM) are a group of disorders that may be inherited or may occur as the result of spontaneous mutation. IEM are relatively common disorders in the Middle East and Arabic populations. This study aimed to detect of IEM among high risk infants admitted to pediatric intensive care unit (PICU). Patients and Methods: This was a cross-sectional study was carried out at NICU in Pediatric Department at Zagazig University Children Hospital during the period study 2021. This study involved 60 neonates and children who were subjected to full medical history, thorough clinical examination, and laboratory investigations:serum levels of electrolytes, plasma ammonia, and lactate, urine organic acid analysis, extended metabolic screening, blood gas, and serum anion gap and blood glucose level. Results:The mean age and weight distribution among confirmed IEM cases were 1.7±0.45 and 6.65±3.45. All confirmed IEM cases delivered by CS, had a positive consangioys parents had negative family history of neither previous abortion nor previous genetic or metabolic diseases. Furthermore, 33.3% of studied confirmed cases had positive family history of previous abortion. The main complain were vomiting, encephalopathy and pallor. All cases showed positive CRP while procalcitonin was positive in 66.7% of cases. About 66.7% of confirmed IEM cases had metabolic acidosis. The hyperammonemia was detected in 66.7% of the confirmed IEM cases. The frequency of Hypoglycemia was detected in 33.3% of the confirmed IEM cases. About 66.7% of confirmed IEM cases had positive blood culture.Conclusion: Extended metabolic screen is helpful in diagnosis of a significant group of treatable IEM. So, early detection and early intervention to the neonates at risk of IEMs before the onset of symptoms can prevent or reduce serious neurological and developmental squeal.

Keywords: Inborn Errors of Metabolism, Metabolic AcidosisHigh Risk Infants

INTRODUCTION

Inborn errors of metabolism (IEM) are a complex, heterogeneous group of genetic diseases. Most of them have severe neonatal onset and are a primary cause of death in newborns and infants. Unfortunately, newborns have a limited variety of responses to illness, and early signs and symptoms of IEM are similar to the features of other, more common neonatal illnesses**(1).** IEM are individually rare but collectively common accounting for about 20% of deaths from genetic disorders and nearly more than one-third of inherited neurological conditions **(2)**. Good intensive care supportive management and specific metabolic crisis treatment by the pediatric intensive care unit (PICU) play a crucial role in optimizing the outcomes **(3)**.

Tandem mass spectrometry (MS/MS) is a powerful new technology for the screening and diagnosis of IEMs. It permits the simultaneous detection of several amino-acidopathies/urea cycle disorders, organic acidemias, and fatty acid oxidation defects in a single dried blood spot in a single analytical run **(4).**Through (MS/MS) technology, one can detect more than 30 different types of IEM. Thus it has helped in screening, diagnosis, and treatment, and to analyze proteins and

substrates in dried blood spots (DBS) has facilitated and expanded the diseases detected in newborn screening programs **(5)**.

Specific and effective treatments are available for many IEM, and early therapeutic intervention can prevent the worsening of the disease. Even if therapy is unavailable, an accurate diagnosis is crucial for genetic counseling [(7).]

This study aimed to early detection of inborn errors of metabolism (IEM) among high risk infants admitted to pediatric intensive care unit (PICU) Zagazig University Children Hospital in order to provide early treatment of treatable and transient disorders of IEM.

PATIENTS AND METHODS

This cross-sectional prospective study was conducted during the period from 2019 to 2020. It included 30 cases admitted to Pediatric Intensive Care Unit (PICU) aged from 28 days to 14 years. This study was conducted at Pediatric Department, Faculty of Medicine, at Zagazig University.

Inclusion criteria:

1) Age from 28 days to 14 years, both male and female
2) Infants with symptoms suspicious for IEM including:

- Lethargy, poor feeding, persistent vomiting, intractable seizures, rapid deep breathing, unexplained neurological signs in a previously well infant. Children with unexplained developmental delay, recurrent unexplained encephalopathy, skin and hair changes, or ophthalmic abnormalities.
- Abnormal investigations like persistent/recurrent hypoglycemia, intractable metabolic acidosis with increased anion gap, hyperammonemia, leucopenia and thrombocytopenia.

Exclusion criteria:

1) Patient outside age (below 28 days or above 14 years).
2) Infants with brain trauma, toxicology, tumors and chromosome anomalies.
3) Parents refuse to share in the study.

Ethical Approval:

This study was ethically approved from Institutional Reviewer Board (IRB) in Faculty of Medicine, Zagazig University and a parental consent from every case caregiver that participates in this research was taken.

Operational Design:

1- All studied cases were subjected to full history taking and clinical examination.

2- **Routine laboratory investigation:** All children were subjected to routine laboratory investigation according local PICU protocol according to cause of admission.

3- **Specific investigation for IEM:** All children included in the study were further investigated by tandem mass spectrometry (MS/MS). MS/MS technology expands the metabolic disorder screening panel (i.e., the number of disorders that can be detected) by incorporating an acylcarnitine profile, which enables detection of fatty acid oxidation disorders (e.g. medium-chain acyl-CoA dehydrogenase deficiency) and other organic acid disorders. MS/MS can reliably analyze ~20 metabolites in one short-duration run (i.e., ~2 minutes).

Plasma ammonia and lactate

Time of the sample collection: On admission in critical ill children.If there was no feeding in previous 24 hr, Confirmatory sample taken 24 hr after full enteral feeding or after TPN administration.

A. **Plasma ammonia measurement**:

They were measured by colormetric method (Cobas Integra Auto analyzer, Germany)[8].Values of 50- 80 µg/dl as normal ranges of plasma ammonia and the values above 150 µg/dl as hyperammonemia were defined.Plasma ammonia was done in biochemistry central lab, Biochemistry and Microbiology Department, Zagazig University.

A free flowing arterial blood sample was collected into EDTA separated immediately within 15 minute of collection and the plasma kept on ice until analysis. Once separated, plasma [ammonia] is stored at 4 °C and processed in the same day. Some percausions must be taken as the patient should be non-stressed, as difficult venipuncture can cause a spurious increase in ammonia level.Avoid sampling collected via indwelling catheters and capillary samples.Also, avoid using tourniquet as any significant hemolysis lead to elevated ammonia.

B. Plasma Lactate measurement:

It measured by colormetric method (Cobas Integra Auto analyzer, Germany) including: Samples was withdrawn from arterial sample on Na Fluoride tube.Avoid using tourniquet, avoid stress or crying زAir was immediately removed from sample, cap tightly, mix gentle without inversion.Samples were transported in ice to lab until analysis.

C. Extended metabolic screening:

The blood spots were collected from all the patients using Gutherie card made of Whatman 903 filter paper purchased from (GE Healthcare, NJ, and USA) . Then the blood spots were dried for 4 hr on the dry, horizontal and non-absorbent surface at ambient temperature.

1. Samples were analyzed by tandem mass spectrometry (MS/MS) which is an analytical system composed of two mass spectrometers (MS-1 & MS-2) placed in tandem, which allows rapid identification and measurement of many individual analytes in a sample without the need for prior separation**.**
2. Eight amino acids were analyzed including [alanine, glycine, arginine, citrulline, methionine, ornithine, proline, valine, phenylalanine, tyrosine] and 20 acylcarnitine were analyzed.Samples were analyzed at Central Laboratory Department, Ministry of Health, Cairo-Egypt.
3. Blood gas and serum anion gab detection by (Bayer 248 blood gas analyzer).
4. Blood glucose level by (Cobas Integra 6000 Roche, Germany) and Ketones in urine was measured with dipsticks (Multistix) read by Clinitek 50 (Bayer)
5. Other specific tests were done for highly suspected cases as urinary organic acid analysis. Urine organic acid analysis was performed using gas chromatography–mass spectrometry in highly suscpected patients.

STATISTICAL ANALYSIS

The data were processed on computer using statistical package for the social sciences (SPSS) (Version 24). Mean, standard deviation ± SD, range, frequency, and percentage (%) were used as

descriptive statistics. The accepted level of significance in this work was stated at 0.05 ($P < 0.05$ was considered significant).

RESULTS

The present study showed the mean age and weight distribution among confirmed IEM cases were 1.7±0.45 and 6.65±3.45. All confirmed IEM cases delivered by CS, had a positive consangioys parents had negative family history of neither previous abortion nor previous genetic or metabolic diseases. Furthermore, 33.3% of studied confirmed cases had positive family history of previous abortion**(Table 1)**.

The main complain were vomiting, encephalopathy and pallor**(Table 2)**.

Mean distribution of basic laboratory investigations. All cases showed positive CRP while procalcitonin was positive in 66.7% of cases**(Table 3)**.Mean distribution of PH, PaCO2 and HCO3 were 7.10±0208, 42.85±2.41 and 17.5±3.37**(Table 4)**.

About 66.7% of confirmed IEM cases had metabolic acidosis. The hyperammonemia is considered when ammonia is more than 100 mg/dl in critical infant, the hyperammonemia detected in 66.7% of the confirmed IEM cases.hyperlactatemia is considered if lactate is more than 19 mg/dl in serum among confirmed IEM 3 cases, it was detected in all confirmed IEM cases.The frequency of Hypoglycemia was detected in 33.3% of the confirmed IEM cases**(Table 5)**.About 66.7% of confirmed IEM cases had positive blood culture **(Table 6)**. All confirmed IEM cases were died **(Table 7)**.

Table (1): Basic demographic data distribution among confirmed IEM cases

Variable	(n = 13)		
Age (years)	Mean± SD	1.7±0.45	
	Median (Range)	1.2 (0.2-2.5)	
Weight (kg)	Mean± SD	6.65±3.45	
	Median (Range)	6.0 (3.1-12.0)	
		N	%
Sex	Male	2	66.7%
	Female	1	33.3%
Mode of delivery	CS	3	100%
	NVD	0	0.0%
Consanguinity	-VE	0	0.0%
	+VE	3	100%
History of previous Sibling death	-VE	2	66.7%
	+VE	1	33.3%
History of Previous hospitalization	-VE	1	33.3%
	+VE	2	66.7%
Previous Abortion	-VE	3	100%
	+VE	0	0.0%
Genetic or metabolic disease in family	-VE	3	100.0
	+VE	0	0.0%
	Total	3	100.0%.

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Table (2):Initial clinical presentation among confirmed IEM cases

		N	%
Vomiting	-VE	0	0.0
	+VE	3	100.0
Diarrhea	-VE	3	100.0
	+VE	0	0.0
Dehydration	-VE	1	33.3
	+VE	2	66.7
Convulsion	-VE	2	66.7
	+VE	1	33.3
Hypotonia	-VE	2	66.7
	+VE	1	33.3
RD	-VE	1	33.3
	+VE	2	66.7
Apnea	-VE	2	66.7
	+VE	1	33.3
Encephalophagy	-VE	0	0.0
	+VE	3	100.0
Jaundice	-VE	3	100.0
	+VE	0	0.0
Pallor	-VE	0	0.0
	+VE	3	100.0
Developmental	Normal	1	66.7
	Delay	2	33.3
Skin manifestation	-VE	3	100.0
	+VE	0	0.0
Bleeding tendency	-VE	3	100.0
	+VE	0	0.0
Liver dysfunction	-VE	1	33.3
	+VE	2	66.7
Cardiac dysfunction	-VE	2	66.7
	+VE	1	33.3
	Total	3	100.0

Table (3):Lab parameters distribution among confirmed IEM cases

HB (gm/dl)	Mean± SD		10.92±1.36
	Median (Range)		11.0 (9-13)
10^3×WBCs	Mean± SD		17.14±7.35
	Median (Range)		13.0 (10-30)
10^3×PLT	Mean± SD		205.85±126
	Median (Range)		211.0 (55-411)
ALT (U/dl)	Mean± SD		111.0±56.4
	Median (Range)		113.0 (31-212)
AST (U/dl)	Mean± SD		95.85±44.9
	Median (Range)		98.0 (34-141)
BUN (mg/dl)	Mean± SD		40.57±8.07
	Median (Range)		39.0 (31-51)
Cr (mg/dl)	Mean± SD		0.44±0.15
	Median (Range)		0.50 (0.2-0.6)
PT (sec)	Mean± SD		13.38±1.26
	Median (Range)		14.0 (11.5-15)
PTT (sec)	Mean± SD		40.14±5.8
	Median (Range)		41.0 (34-51)
INR	Mean± SD		1.24±0.21
	Median (Range)		1.2 (1.1-1.7)
Na^+ (mEq/dl)	Mean± SD		135.42±5.12
	Median (Range)		133.0 (129-142)
K^+ (mEq/dl)	Mean± SD		3.57±0.44
	Median (Range)		3.6 (2.9-4.1)
Ca^+ (mg/dl)	Mean± SD		9.24±0.41
	Median (Range)		9.2 (8.7-9.8)
Mg^+	Mean± SD		2.30±0.30
	Median (Range)		2.4 (1.9-2.7)
Cl^+	Mean± SD		6.08±0.64
	Median (Range)		6.0 (5.2-7)
		N	%
CRP (mg/dl)	-VE	0	0.0%
	+VE	3	100.0%
PCT (ng/ml)	-VE	1	33.3%
	+VE	2	66.7%

HB: heamoglobin; **WBCs**: white-blood-cells; **PLT**: platelets; **ALT**: alanine-aminotransferase; **AST**: aspartate-aminotransferase; **BUN**: blood urea nitrogen; **Cr**: creatinine; **PTT**: partial thromboplastin time; **PT**: prothromin time; **INR**: international normalized ratio; **Na**: sodium; **K**: potassium;**Ca**: calcium; **Mg**: magnesium; **Cl** :chloride; **CRP**: C-reactive protein; **PCT**: procalcitonin.

Table (4): ABG distribution among confirmed IEM cases

	PH	$PaCO_2$	HCO_3
Mean± SD	7.10±0208	42.85±2.41	17.5±3.37
Median (Range)	7.10 (6.8-7.3)	42.0 (40.0-47.0)	16.0 (14.0-22.0)

Table (5):Metabolic acidosis distribution, Frequency of hyperammonemia, Frequency of hyperlactatemia and Frequency of hypoglycemia among confirmed IEM cases

Variable		N = 13	%
Metabolic Acidosis	-VE	1	33.3
	+VE	2	66.7
	Total	3	100.0
Hyperammonemia	-VE	1	33.3
	+VE	2	66.7
	Total	3	100.0
Hyperlactatemia	-VE	0	0.0
	+VE	3	100.0
	Total	3	100.0
Hypoglycemia	-VE	2	66.7
	+VE	1	33.3
	Total	3	100.0

Table (6): Culture distribution among confirmed IEM cases

Variable		N	%
Culture	Sterile	1	33.3
	+VE	2	66.7
	Total	3	100.0

Table (7): Outcome among confirmed IEM cases

Variable		N	%
Outcome	Survived	0	0.0
	Died	3	100.0
	Total	3	100.0

DISCUSSION

Inborn errors of metabolism (IEM) can present as acute metabolic emergencies resulting in significant morbidity, progressive neurological injury, or death. The optimal outcome for children with IEM depends on recognition of signs and symptoms of the metabolic disease, prompt evaluation, and referral to a center familiar with the evaluation and management of these disorders**(2)**.IEM are relatively common disorders in the Middle East and Arabic populations, mainly because of the high rates of consanguinity in the region (positive consanguinity up to 48.3%) and also the autosomal recessive mode of inheritance of these disorders**(3).**

The lack of newborn screening program and specialized healthcare centers in Egypt must have further contributed to this health problem. The newborn screening program has not been introduced nationally. Only where siblings have a history of an IEM disorder, will the newborn be offered

testing. An accurate diagnosis of IEM relies heavily on a large knowledge on the part of experienced clinicians because of the large number of disorders, a high index of suspicion and access to expert laboratory services. This is critically important for subsequent appropriate treatment of these patients which may differ depending on the underlying enzyme defect **(8).**

This cross sectional study was carried out at NICU in Pediatric Department at Zagazig University Children Hospital during the period study 2021.This study aimed to early detection of IEM among high risk infants admitted to pediatric intensive care unit (PICU) Zagazig University Children Hospital in order to provide early treatment of treatable and transient disorders of IEM and intervention to improve outcome.

As regard basic demographic and clinical data distribution among confirmed case, the present study revealed that the mean age was distributed as 1.7±0.45 years and the mean weight was distributed as 6.65±3.45. Regarding sex distribution male were 66.7% and female 33.3%. Additionally, the mode of delivery 100% were CS and 0% were by NVD, 100% had consanguinity, 33.3% had sibling previous hospitalization (1 case), no previous abortion and genetic disease. This finding in agreement with the study of **El-Desouky et al.** (**9**) found that age distribution was 14.60 ± 4.83 months and regard sex distribution male was 80.0% and female 20%.Also, **Ames et al**. (**10**) study found that males were 84% and females were 16% with confirmed IEM. However, **Sivaraman et al**. (**11**) found that forty percent (6/15) were male. The majority (12/15) was born out of consanguineous marriage.

Consanguineous mating is genetically important as closely related individuals have a higher chance of carrying the same alleles than unrelated individuals; hence the offspring of consanguineous mating are more frequently homozygous for various alleles than those from other unions **(12).** Indeed, a study of IEM in an Omani population of the Arabian Peninsula, **Joshi et al. (13)** found that the parental consanguinity was twice as frequent in the study of patients as in the general population. In contrast, **Carlo et al. (14),Sandersonet al. (15)**revealed patients with IEM had a low rate of consanguinity**.**

Consanguineous marriages are very common in Egypt (35.3%), **Shawky et al.** (**8**) leads to an increase in the risk of metabolic disorders. This was in accordance with other studies done including**Al Riyami et al.(16**)in Oman, **Al-Qaqaet al.(17**) in Jordanand **Al-Obaidy (18**) inLibya. These studies confirmed that there are consistent with the recessive autosomal inheritance of IEMs and reflect the significant contribution of consanguinity in Egypt in this particular health problem.

According to the initial clinical presentation among three cases were confirmed by IEM. In the present study, as regards clinical picture and organ affection distribution among confirmed cases, our finding revealed that the main complaint was vomiting, encephalopathy and pallor. Our results were supported by the study of **El-Desouky et al.** (**9**)showed that there was higher frequency of vomiting among cases with inborn errors of metabolism. This also was in agreement with the study of **Isabel et al. (3).**

In the present study, as regard Lab parameters distribution among confirmed IEM three cases, our study found that HB was distributed 10.92±1.36, WBCs and PLT and was distributed as 17.14±7.35 and 205.85±126, also showing the distribution of liver enzyme and BUN and also creatinine (40.57±8.07 and 0.44±0.15 respectively), CRP and PCT were positive at 100% 66.7% and ABG distribution among confirmed cases was PH, $PaCO_2$ and HCO_3 was distributed as 7.10±0208,

42.85±2.41 and 17.5±3.37 respectively. These findings were in agreement with **El-Desouky et al**. (**9**) found that the mean value of Hb (gm/dl) was lower among cases with inborn errors of metabolism. Our results are agree also with the study of **El-Desouky et al**. (**9**) showed that the mean value of pH, HCO_3, and $PaCO_2$ were lower in cases with IEM.

The present study shows that the hyperammonemia is considered when ammonia is more than 100 mg/dl in critical infant. However, the hyperlactatemia is considered if lactate is more than 19 mg/dl in serum. The frequency of hyperammonemia among IEM three cases indicated that hyperammonemia and hyperlactatemia was detected in 66.7% and 100% respectively. This agrees with **El-Desouky et al. (9)** found that plasma ammonia and plasma lactate levels were high in 60.0% of infants with IEM and high serum ammonia were significantly more frequent among cases with IEM. Similarly, **Alfadhel and Babiker, (19)** reported that patients with IEM had high anion gap, and ketonuria. Frequencies of high serum ammonia and serum lactate were higher among cases with IEM.Also, **Shawky et al. (20)** found that, high serum ammonia and serum lactate were higher among cases with inborn IEM.In addition to the high prevalence, there are several major challenges that must be considered as risk factors for the outcome of hyperammonemic individuals in the Middle East (**19**).

In the current study, as regard frequency of hypoglycemia among confirmed IEM three cases, the hypoglycemia was detected only in 33.3% of the studied group. In agreement with our study, **El-Desouky et al. (9)** demonstrated that the distribution of hypoglycemia among infants with inborn errors of metabolism was 40.0% and hypoglycemia was significantly more frequent among cases with inborn errors of metabolism. Also, **Agana et al. (2)** reported that, hypoglycemia was commonly seen in IEM cases.

Critically, the study shows that 2/3 cases (66.7%) confirmed IEM cases had positive blood culture. As regard outcome among confirmed cases, we found that that 100% (3 cases) died. The mortality rate in the study of **Tu et al.** (**21)** waslower than our results as the mortality for patients with IEM was 4/8 (50%). This difference can be explained by different sample size and delay in diagnosis in numbers of patients, which may be due to unawareness of IEM diseases, and poor socio economic conditions of some patients in isolated areas which prevent the parents to consult early and may be the severity of clinical condition in our patients.

In contrast,**Sivaraman et al. (11)** found that 33% of children died either during first or subsequent crisis admission despite adequate medical management during the ICU stay. **Khalafet al. (22)** found that the outcome of the cases with IEM shows that 36% of them were discharged on treatment and continue follow-up at genetic unit and the rest of the cases (64%) died due to complications.

The high rates of IEM diseases can be attributed to several factors including high rate of traditional consanguineous marriages, which increases the frequency of autosomal recessive diseases; large family sizes, which may increase the number of affected children in families with autosomal recessive conditions; the shortage of genetic services and inadequate health care prior to and during pregnancy **(23).**

Therefore, an implement strategies such as the training of individuals and recruitment of international experts to ultimately develop high-quality clinical practice guidelines.

Conclusion:

Extended metabolic screen is helpful in diagnosis of a significant group of treatable IEM. so early detection and early intervention to the neonates at risk of IEMs before the onset of symptoms can prevent or, at least, reduce serious neurological and developmental squeal.

No Conflict of interest.

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