European Journal of Molecular & Clinical Medicine

ISSN 2515-8260 Volume 08, Issue 04, 2021

Early Detection of Inborn Errors of Metabolism among Neonates Admitted to Neonatal Intensive Care Unit

MervatAbdallahHesham, Shams Sami Abdo,Wesam A.Mokhtar,

Pediatrics Department, Faculty of Medicine,Zagazig University, Egypt.

Corresponding author:**Shams Sami Abdo**, Email: Shamssami81190@gmail.com

ABSTRACT

Background:Early diagnosis and treatment are very important to reduce the rates of morbidity and mortality related to Inborn errors of metabolism .The present study aimedto detect the inborn errors of metabolism early among neonates.This was a cross sectional study was carried out at neonatal intensive care unit in pediatric department at Zagazig university children hospital. This study involved 114 neonates who were subjected to full medical history, thorough clinical examination and laboratory investigations which included Complete blood count, Coagulation profile ,C-reactive protein ,procalcitonin, Liver and renal function tests , Serum levels of electrolytes, Plasma ammonia and lactate, Urine organic acid analysis, Extended metabolic screening, Blood gas and serum anion gab and Blood glucose level. Results:About 53.5% of the studied groups were males and 46.5% were females. As regards mode of delivery 74.6% were by CS and 25.4% by NVD. Also, 30.7% had positive consanguinity, 12.3% had sibling death, and 3.5% have similar condition. History of abortion was found in 22.8% and genetic disease was in 2.6% of the studied group. The main clinical presentations among the studied group were RD, Encephalopathy and hypotonia. Only 6.1% of the studied group had positive culture metabolic acidosis was detected only in 9.6% of the studied group. About 90.4% of the studied group was alive and 9.6% were died. Conclusion: IEM disorders are not rare disease in high-risk neonates with attentions to consanguinity which is a common tradition in our country. The manifestations of metabolic disorders are common, and many physicians misdiagnose them as they are unaware about these disorders.

Keywords: Inborn errors of metabolism; Neonates; Intensive Care Unit

INTRODUCTION

Inborn errors of metabolism (IEM) are a highly heterogenous group of genetic disorders and represent a cause of morbidity and mortality in the pediatric population. Inborn errors of metabolism which are individually rare but collectively numerous are well-cognitive entities of the genetic rare diseases. Since, the first descriptions by Garrod at the beginning of the 20th century, many hundred new disorders have been defined, as new biochemical and molecular diagnostic tools become available **(1)**.

The field of IEM is currently experiencing new opportunities with regard to both novel therapeutic options and technology for early disease diagnosis**(2)**.

Typically, an IEM is suspected as a result of a suggestive combination of acute clinical nonspecific symptoms without prior warning. However sometimes IEM can be present in the non-specific clues like unexplained neonatal death, or presence of a previously affected child**(3)**.

Patients with such disorders can have acute nonspecific symptoms such as lethargy, hypotonia, tachypenia, convulsion, vomiting, or may present with developmental delay or intellectual disability and could die of unkown causes despite the fact that a number of such patients could potentially achieve normal growth and development if early detection and intervention were feasible**(4)**.

The early detection of diseases either in pre-symptomatic or early symptomatic phase should, with early treatment result in prevention of severe illness and long term complications**(5,6)**.Therefore, this study aimed to detect the inborn errors of metabolism early among neonates.

PATIENTS AND METHODS

A) Technical design:

Study type and setting: This cross-sectional prospective study was done in neonatal intensive care unit at Pediatric Department, Faculty of medicine, Zagazig University during the period from January 2020 to July 2020. It Included 114 neonates admitted to NICU aged from one day to 28 days.

Sample size: Assuming that the number of newborn admitted to NICU at Zagazig university children hospital is 180 cases in six months, the prevalence of inborn error of metabolism in similar study was 25.8%, the sample size was calculate to be 112 with confidence limits of 5% design effect. But I included all neonates admitted to NICU from Jaunary 2020 till July 2020 which were 114 cases.

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.

Inclusion criteria:

- The study was done for all symptomatic neonates admitted to NICU of Zagazig university children hospital aged {0 – 28} days.
- Prematures more than 32 weeks and full term.
- By normal vaginal delivery and CS
- Both males and females

Exclusion criteria:

- Parents refusal to share in the study
- Aged more than 28 days on admission.

B) Operational design:

All neonates were subjected to the following:

I- Full history was taken from parents with special emphasis on:

- Prenatal, natal and postnatal history.
- Family History including consanguineous marriage among the patient's parents, previous similar condition in the family, previous neonatal death, genetic diseases in the family.

- Age of the onset of the symptoms.
- Relation of symptoms to feeding.

II- Full examination of neonates:

1) Assessment of gestational age using anthropometric measurements.
2) General examination (Weight measurement, vital signs).
3) Cardiac examination including evidence of congenital heart disease or cardiomyopathy.
4) Abdominal examination for organomegaly.
5) Neurological examination including evidence of muscle tone change, convulsion or encephalopathy.
6) Chest examination.

III - Basic initial investigations:

All neonates were subjected to routine laboratory investigations according to local NICU protocol according to the cause of admission as:

- Complete blood count
- Coagulation profile (PTT , PT , INR)
- C-reactive protein (CRP) and procalcitonin (PCT)
- Liver and renal function tests
- Serum levels of electrolytes (Na, K, Mg, Cl , Ca)
- Imaging when indicated
- Plasma ammonia and lactate levels were done in biochemsity central lab, biochemistry and microbiology department, Zagazig University.

- **Precaution for plasma ammonia sampling:**

1) A free-flowing venous (or arterial) 2 ml of blood sample was collected into EDTA or heparin tubes, separated immediately within 15 minute of collection and the plasma kept on ice until analysis. Once separated, plasma [ammonia] is stable for 4 h at 4 °C and 24 h at -20 °C.
2) Ideally, the patient should be nonstressed, as difficult venepuncture can cause a spurious increase in ammonia level.
3) Avoid sampling collected collected via indwelling catheters and capillary samples.

Also, avoid using tourniquet as any significant haemolysis of the sample will cause a spuriously elevated (ammonia).

Percuation of plasma lactate sampling:

1) Samples was withdrawn from arterial sample (but allowed from venous sample) on Na Fluoride tube.
2) Avoid using tourniquet, avoid stress or crying
3) Air was immediately removed from sample, cap tightly, mix gentle without inversion.
4) Samples were transported in ice to lab until analysis.

Extended metabolic screening: Dried blood spots were collected from all patients using Gutherie card made of Whatman 903 filter paper purchased from (GE Healthcare ,NJ and USA).Then blood spots were dried for 4 hours on dry, horizontal and nonabsorbent surface at ambient temperature**(Figure 1)**.

Other confirmatory tests were done for highly suspected cases as urinary organic acid analysis if it is highly indicated.

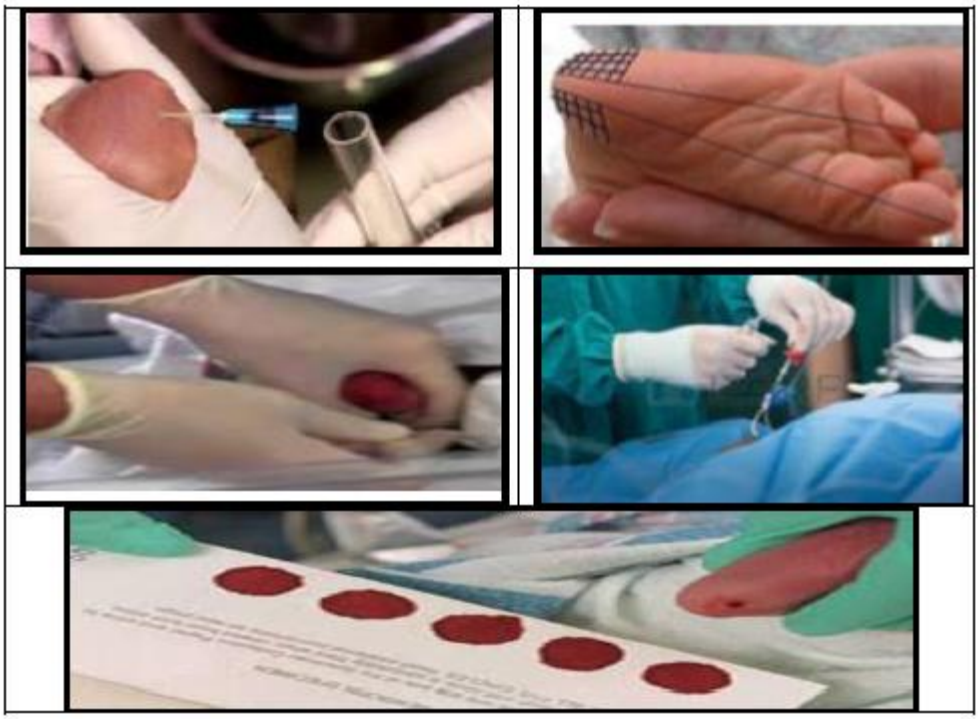

Figure (1): Samples collection for diagnosis of IEM in neonates

Statistical Analysis:

Data collected throughout history, basic clinical examination, laboratory investigations and outcome measures coded, entered and analyzed using Microsoft Excel software. Data were then imported into Statistical Package for the Social Sciences (SPSS version 20.0) **(**Statistical Package for the Social Sciences) software for analysis. According to the type of data qualitative represent as number and percentage, quantitative continues group represent by mean ± SD.Data were collected and submitted to statistical analysis.

RESULTS

The present study showed that 53.5% of the studied group were males and 46.5% were females. As regards mode of delivery 74.6% were by CS and 25.4% by NVD. Also, 30.7% had positive consanguinity, 12.3% had sibling death, 3.5% have similar condition. History of abortion was found in 22.8% and genetic disease was in 2.6% of the studied group **(Table 1).**

The main clinical presentations among the studied group were RD, cyanosis and hypotonia**Table (2)**. Leukocytosis in CBC with normal Hb and platelets, elevated CRP, normal coagulation parameters, electrolytes levels and liver and renal functions of the studied group (**Table 3)**. Only 6.1% of the studied group had positive blood culture. Hypoglycemia was detected only in 5.26% of the studied group. Hyperammonemia was detected only in 6.14% of the studied group. Lactic acidosis

was detected only in 26.31% of the studied group **(Table 4).** Metabolic acidosis was detected only in 9.6% of the studied group **(Figure 2)**. Random blood glucose among studied group shows mean (80.19 ± 28.8). Plasma ammonia level among the studied group shows mean (117.87±87.73). Also the plasma lactate level shows mean (7.53±6.87) **Table (5)**. About 90.4% of the studied group was survived and 9.6% were died **(Figure 3)**.

Table (1): Demographic data of the studied group:

Gestational age (weeks)	**Mean± SD**	36.50±1.64	
	Median (Range)	37.0 (32-39)	
Weight (Kg)	**Mean± SD**	3.04±0.87	
	Median (Range)	3.0 (1.15-6.0)	
		N (114)	**%**
Sex	**Male**	61	53.5
	Female	53	46.5
Mode of delivery	**CS**	85	74.6
	NVD	29	25.4
Consanguinity	**-VE**	79	69.3
	+VE	35	30.7
Previous sibling death	**-VE**	100	87.7
	+VE	14	12.3
Previous similar conditions	**-VE**	110	96.5
	+VE	4	3.5
History of Abortion	**-VE**	88	77.2
	+VE	26	22.8
Genetic or metabolic disease in family	**-VE**	111	97.4
	+VE	3	2.6
Total		114	100.0

CS: cesarian section. / NVD: normal vaginal delivery.

Table (2): Initial clinical presentation among the studied group:

	N (114) %	
Vomiting	3	2.6
Diarrhea	3	2.6
Dehydration	3	2.6
Convulsion	12	10.5
Hypotonia	13	11.4
Respiratory Distress (RD)	II 58	50.9
	III 45	39.5
	IV 11	9.6
Apnea	2	2.7
Encephalopathy	14	12.3
Jaundice	2	1.8
Pallor	6	5.3
Bleeding tendency	10	8.8
Hepatomegaly	2	1.8
Cyanosis	24	21.1

ISSN 2515-8260 Volume 08, Issue 04, 2021

Table (3): Laboratory parameters of the studied group:

HB (gm)	**Mean± SD**	14.02±3.02
	Median (Range)	13.6 (5.1-20.0)
WBCs x10 ^{3}	**Mean± SD**	15.44±6.79
	Median (Range)	13.25 (4.1-39.9)
PLT x10 ^{3}	**Mean± SD**	309.85±135.02
	Median (Range)	291.0 (32.0-699.0)
CRP (mg/dl)	**Mean± SD**	18.66±30.12
	Median (Range)	5.8 (0.13-141.0)
PCT (ng/dl)	**Mean± SD**	0.54±0.84
	Median (Range)	0.10 (0.01-4.8)
Albumin (mg/dl)	**Mean± SD**	3.82±0.91
	Median (Range)	3.8 (1.25-6.4)
Total bilibrubin (mg/dl)	**Mean± SD**	3.61±3.06
	Median (Range)	2.9 (0.2-11.3)
ALT (U/dl)	**Mean± SD**	20.24±14.74
	Median (Range)	17.0 (3.4-81.0)
AST (U/dl)	**Mean± SD**	54.35±44.32
	Median (Range)	40.0 (16.6-253.0)
BUN (mg/dl)	**Mean± SD**	15.85±13.73
	Median (Range)	12.2 (2-90)
Cr (mg/dl)	**Mean± SD**	0.53±0.37
	Median (Range)	0.45 (0.1-4.7)
PT (sec)	**Mean± SD**	12.68±2.19
	Median (Range)	12.1 (9.9-23.0)
PTT (sec)	**Mean± SD**	40.02±13.62
	Median (Range)	39.0 (0.4-90.5)
INR	**Mean± SD**	1.0±0.19
	Median (Range)	0.98 (0.8-1.9)
Na (mEq/dl)	**Mean± SD**	141.44±4.59
	Median (Range)	140.0 (131-157)
K (mEq/dl)	**Mean± SD**	5.20±0.83
	Median (Range)	5.2 (2.9-6.7)
Ca (mEq/dl)	**Mean± SD**	9.13±1.18
	Median (Range)	9.2 (3.3-11.4)
Cl (mEq/dl)	**Mean± SD**	6.04±1.46
	Median (Range)	6.1 (2.1-9.5)
Mg (mEq/dl)	**Mean± SD**	2.23±0.23
	Median (Range)	2.2 (1.7-2.9)

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

Table (4): Blood culture, Frequency of hypoglycemia, hyperammonemia and lactic acidosis among the studied group:

		N	%
Blood Culture	Sterile	107	93.9
	+VE	7	6.1
	Total	114	100.0
hypoglycemia	-VE	108	94.73
	+VE	6	5.26
	Total	114	100.0
Hyperammonemia	-VE	107	93.85
	+VE	7	6.14
	Total	114	100.0
Lactic acidosis	-VE	84	73.68
	+VE	30	26.31
	Total	114	100.0

hyperammonemia is considered when ammonia is more than 200mg/dl in critical baby.
*lactic acidosis is considered if lactate is more than 19 mg/dl in serum.

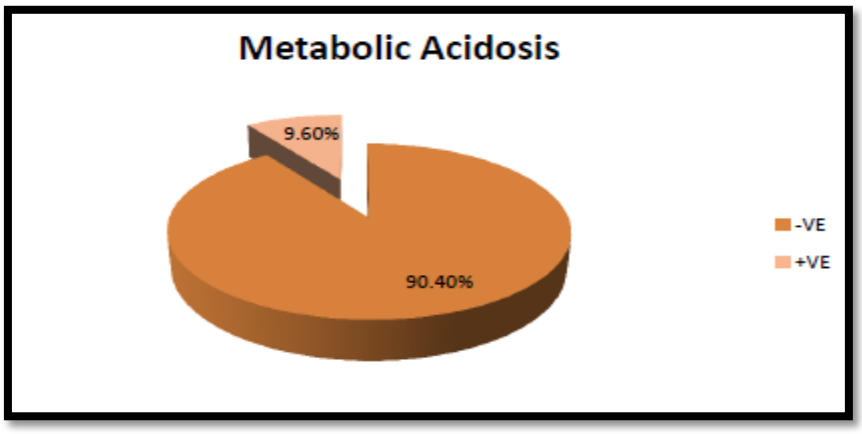

Fig. (2): Frequency of metabolic acidosis among the studied group.

Table (5): Random blood glucose and Plasma ammonia and plasma lactate levels among studied group:

Random blood glucose (mg/dl)		
Mean ±SD	80.19 ± 28.8	
Median (Range)	90.0 (15.1-120)	
Mean± SD	117.87±87.73	7.53±6.87
Median (Range)	95.0 (70-900)	4.5 (0.4-40)

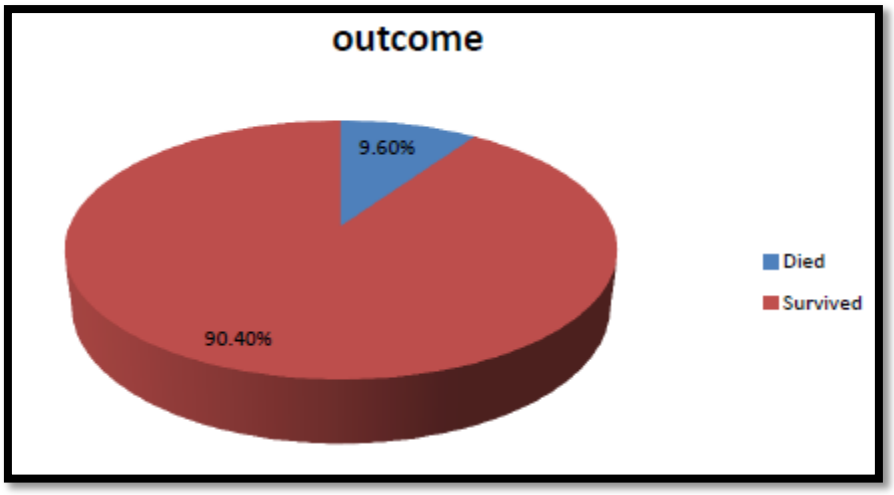

Fig. (3): The outcome of the studied group.

DISCUSSION

Newborn screening has been expanded by new technology, and can now detect more than 50metabolic disorders. The recognition and diagnosis of inborn errors of metabolism were further propelled by advances in chemistry and technology**(7)**.

The present study showed that more than half (53.5%) of the studied group were males and 46.5% were females. As regards mode of delivery 74.6% were by CS and 25.4% by NVD. Also, 30.7% had positive consanguinity, 12.3% had sibling death, and 3.5% have similar condition. History of abortion was found in 22.8% and genetic disease was in 2.6% of the studied group.However, in the study of **Khalaf et al.(8)** revealed that socio-demographic characteristics of the studied cases were 60.6% males and 39.4% females. Their age ranged from 1 to 30 days after birth. The consanguinity was positive in 122 patients (61%) of patients. It was higher than that reported in this study. On the other hand**,** our results were comparable to**Shawky et al.(9)**at Ain Shams University, Egypt, who reported that 17 patients (43.5%) had consanguineous parents.

The current study showed that the main clinical presentations among the studied group were RD, Encephalopathy and hypotonia. The most common presentations among the cases of IEM were RD, convulsion and Encephalopathy (100%, 80%, 80% respectively).In the study of **Khalaf et al.(8)** reported the most common manifestation at the time of presentation was sepsis-like manifestations (poor suckling, found in 122 out of 200 cases (61%), followed by respiratory distress in 114 out of 200 cases (57%), then convulsions in 108 out of 200 cases (54%), and vomiting in 104 out of 200 cases (52%).

In the study of**Benninga et al.(10)** revealed that neurological symptoms were the most frequent event in all newborns, followed by abnormalities in biochemical blood markers.

Inborn errors of metabolism (IEMs) are a large group of monogenic diseases resulting in death and abnormalities of physical and neurological development at almost all stages of life. Nowadays, the introduction of tandem mass spectrometry (TMS) allows screening for more than 50 IEMs using dried blood spot in the neonatal period. For the neonates screened to have IEMs, some serious clinical consequence could be prevented, including mild to severe irreversible mental retardation, lifelong disability, physical handicaps, coma, and early death, if early diagnosis and treatment were implemented**(11).**

In this study, 90.4% of the studied group was alive and 9.6% were died.In **Shawky et al.(9)** study, there were also 5 patients (12.5%) who were suspected to have IEM but 4 of them (80%) died and one (20%) discharged from NICU as requested by the parents before completing their confirmatory investigations.

Based on Our Findings, we recommend for further studies on larger sample and on large geographical scale to emphasize our conclusion.

CONCLUSION

We concluded that IEM disorders are not rare disease in high-risk neonates with attentions to consanguinity which is a common tradition in our country. The manifestations of metabolic disorders are common, and many physicians misdiagnose them as they are unaware about these disorders.

No Conflict of interest.

REFERENCES:

1) **Deodato F, Boenzi S, Rizzo C, Abeni D, Picca S, Bartuli A, et al**. Inborn errors of metabolism: an update on epidemiology and on neonatal-onset hyperammonemia. ActapadediatrSuppl 2004; 93(445):18-21.
2) **Harms E, Roscher A, Jakobs C, Sylvia S**. Early diagnosis of inherted metabolic diseases: towards improving outcome. Proceeding of an international symposium. EurJ Pediatr 2003; 162: S1-76.
3) **Chakrapani A, Cleary MA, Wraith JE.** Detection of inborn error of metabolism in the newborn. Arch Dis Child Fetal Neonatal Ed 2001;84:F205-10.
4) **Fu X, Iga M, Yamaguchi S**. Simplified screening for organic academia using GC/MS and urine filter paper: a study on neonatal mass screening. Early Hum Dev 2000;58:41-55.
5) **Walter JH.** Arguments for early screening: a clinician perspective. Eur J Pediatr 2003;162:S2-S4.
6) **William ZR, Hurley PE, Altiparmak UE, Feldon SE, Arnold GL, Mejico LJ, et al**. Late onset optic neurology in methylmalonic and propionic academia. Am J Ophthalmol 2009;147:929-33.

7) Sahai I, Marsden D. Newborn Screening. Critical Reviews in Clinical Laboratory Sciences 2009; 46(2): 55–82.

8) **Khalaf SM, El-Tellawy MM, Refat NH, Abd El-Aal AM.** Detection of some metabolic disorders in suspected neonates admitted at Assiut University Children Hospital. EgyJ Med Hum Genet 2019; 20(1):1-7.

9) **Shawky RM, Abd-El Khalek HS, Elakhdar SE .**Selective screening in neonates suspected to have inborn errors of metabolism. Egyp J Med Hum Genet 2015;16(2):165–17.

10) **Benninga MA, Nurko S, Faure C, Hyman PE, Roberts ISJ, Schechter NL, et al.** Childhood functional gastrointestinal disorders: neonate/toddler. Gastroenterology 2016; 150(6):1443-55.

11) **Therrell BL, Padilla CD, Loeber JG, Kneisser I, Saadallah A, Borrajo GJ, et al.** Current status of newborn screening worldwide: 2015. Semin. Perinatol 2015; 39:171–87.