European Journal of Molecular & Clinical Medicine

ISSN 2515-8260 Volume 08, Issue 03, 2021

Evaluation of Inborn Errors of Metabolism in Neonates and Children

Mohamed R. Beshir, Ahmed Emam,Wesam A. Mokhtar and Esraa H. Elsayyad
Pediatric Department, Faculty of Medicine, Zagazig University, Egypt.
Corresponding author:**Esraa Hassan Elsayyad,** Email:
esraa.hassan.elsayyad@gmail.com

Abstract

Background: Inborn errors of metabolism (IEMs) make up a large group of rare disorders caused by an inherited deficiency or absence of proteins that have enzymatic, carrier, receptor, or structural roles. This study is aimed to early detection, diagnosis, and intervention to improve outcome.

Patients and methods: This cross-sectional study was done in Pediatrics Department, Zagazig University Hospitals. It included 65 cases with suspected inborn errors of metabolism. All the studied cases were subjected to full history taking, clinical examination and Laboratory investigations.

Results: The age of neonates, infant and children were 35 (54.6%), 22 (34.37%), 8 (10.93%) cases respectively, 34 cases were females and 30 males. The most common complaint was poor suckling in 14 cases (21.8%) then lethargy as well as fever in 6 cases (9.37%). Disturbed consciousness and hepatosplenomegaly were present in 11 cases (17.18%). Metabolic disorders including metabolic acidosis (25%), hypoglycemia (3.12%), raise lactate level (4.68%), hyperammonemia (14) and presence of ketonuria in (4.68%) of cases, respectively. The different disease types of the studied cases after routine and specific laboratory finding, our results showed that, 18 cases Suspected IEM (not diagnosed), 11 cases Diagnosed metabolic (non PKU), 36 cases Diagnosed Phenylketonuria (PKU).

Conclusion: Early diagnosis of inborn errors of metabolism (IEMs) during neonatal period or infancy for starting its proper treatment will improve outcomes, control complications of metabolic diseases and decrease the mortality rates.

Keywords: Metabolic Acidosis, Disturbed Consciousness, Neonates, Poor Suckling.

Introduction

Inborn errors of metabolism (IEM) are a heterogeneous group of disorders that may be inherited or may occur as the result of spontaneous mutation. These diseases involve failure of the metabolic. Although any given inborn error of metabolism is very rare, taken as a group, inborn errors occur in 1/2500 births, making them quite common **(1)**.IEM cause hereditary metabolic diseases (HMD) and classically they result from the lack of activity of one or more specific enzyme or defects in the transportation of proteins. The consequences can usually be deficiency of critical intermediary or the final products or excess of products of alternative metabolic pathways **(2).**

The molecular basis of biochemical disorders in HMD are genetic mutations in enzymatic loci that affect activator proteins or co-factors for enzymes, protein transportation, carrier systems or recognition markers **(3).**Traditionally IEM are categorized as disorders of carbohydrate metabolism, amino acid metabolism, organic acid metabolism, or lysosomal storage diseases. However, diagnostically these metabolic disorders can be divided into five groups as: (a) energy metabolism disorders: disorders of respiratory chain, pyruvate dehydrogenase; (b) intoxication syndromes: urea-cycle defects, homocystinurias; (c) lipid-storage disorders: lysosomal storage disorders; (d) metal (such as iron, copper) storage diseases; and (e) neurotransmitter metabolism defects **(4).**

Within a few days or weeks after birth, a previously healthy neonate may begin to show signs of an underlying metabolic disorder. Infants with metabolic disorders typically present with lethargy, decreased feeding, vomiting, tachypnea, decreased perfusion, and seizures. As the metabolic illness progresses, there may be increasing stupor or coma associated with progressive hypotonia or hypertonia, fisting or opisthotonos posture, and abnormal movements (tongue-thrusting, lip-smacking, myoclonic jerks), and with sleep apnea **(5).** Therefore, the aim of the present study was to early detection and diagnosis of infants with inborn errors of metabolism and intervention to improve outcomes.

Patients and methods

This cross-sectional study was conducted in Pediatric Department, Faculty of Medicine, Zagazig University Hospital in the period from May 2019 to January 2020. Written informed consents were taken from the parents before sample collection.

This study included 65 cases who were classified into 3 groups: group diagnosed with phenylketonuria diagnosed by neonatal screening program, group diagnosed with metabolic diseases other than PKU, group suspected not diagnosed either died or lost follow up.

Inclusion and exclusion criteria:

Children who aged 1 day to 18 years of both sexes. Fulfilling clinical criteria of inborn error of metabolism including positive family history with affected siblings, persistent unexplained vomiting, metabolic acidemia, convulsions, hypoglycemia, apnea, drowsiness or disturbed consciousness level and poor oral intake and dehydration. While, patients more than 18 years and patients with associated congenital malformation not related to IEM. Birth anoxia or trauma and neonates with intracranial hemorrhage were excluded.

All cases subjected to history taking about suckling, weak crying, convulsions, persistent vomiting. Family history for previous sibling deaths, similar conditions and abortion were taken.

Clinical Examination: this includes:

Vital signs for temperature, blood pressure, respiratory rate and heart rate. Skin examination for: Pallor, cyanosis, rashes, petechiae, mottling, and Jaundice.

Neurological exanimation for neonatal reflexes, tone, level of consciousness. Cardio-respiratory examination for: respiratory rate, sign of respiratory distress, apnea, poor capillary refill time, bradycardia, tachycardia and hypotension. Abdominal examination for abdominal distension, hepatomegaly, splenomegaly, ascites and dilated veins.

Laboratory Methods:

Sample was collected from venous blood for CBC and serum samples were obtained for the following parameters: C-Reactive Protein (CRP), Urea and Creatinine., total bilirubin, direct bilirubin, Total protein, Albumin, ALT and AST , ammonia, serum lactate and electrolytes. Random blood sugar was estimated by Glucose meter.

Statistical analysis

Data analyzed SPSS version 20.0. According to the type of data qualitative represent as number and percentage, quantitative continues group represent by mean ± SD, the following tests were used to test differences for significancedifference and association of qualitative variable by Chi square test (X2). Differences between quantitative independent groups by t test or Mann Whitney, P value was set at <0.05 for significant results &<0.001 for high significant result.

Results

Our results showed that inborn errors of metabolism was more common in neonates than infant and children. The age of neonates, infant and children were 35 (54.6%), 22 (34.37%), 8 (10.93%) cases respectively, 34 cases were females and 30 cases were males. **(Table 1)**. About 70.3% had positive consanguinity, 34.38% were 1st kid, 29.68% had similar condition, 35.9% had abortion in their family and 26.56% had sibling mortality **(Table 2)**.

The highest distributed complaint was infants who not doing well and poor suckling in 14 cases (21.8%) then lethargy (9.3 7%) as well as fever in 6 cases (9.37 %) **(Table 3)**.

The most common finding in examination is disturbed consciousness and hepatosplenomegaly were present in 11 cases (17.18%). Metabolic disorders including metabolic acidosis (25%), hypoglycemia (3.12%), raise lactate level (4.68%), hyperammonemia (14) and presence of ketoneuria in (4.68%) of cases, respectively**(Table 4)**.

Regarding laboratory investigations, our results showed that CBC, liver function test and kidney function test are within normal ranges but CRP (25.03 mg /L) was higher than normal range. There was a significant increase in ammonia, lactate and RBS levels which were 306.72 µg/dL , 10.65 mmol/L and 129.95 mg/dl, respectively while electrolytes are nearly in normal levels **(Table 5)**.

Concerning the different disease types of the studied cases after routine and specific laboratory finding, our results showed that, 18 cases Suspected IEM (not

diagnosed), 11 cases Diagnosed metabolic (non PKU), 36 cases Diagnosed Phenylketonuria (PKU) **(Table 6)**.

Table (1): Age and sex distribution among studied group

Age		Age/ Months	
	Mean± SD	39.2±43.8	
		N	%
	Neonate (1st month)	35	54.6
	Infant (1m. – 2y.)	22	34.37
	Child (>2 y.)	8	10.93
	Total	65	100
		N	%
Sex	Male	30	46.87
	Female	35	54.68
	Total	65	100.0

Table (2). Medical and family history distribution among studied group:

		N	%
Consanguinity	+VE	45	70.3
	-ve	20	29.7
First kid	+VE	22	34.38
	-ve	43	65.62
Family history			
Similar condition	+VE	19	29.68
	-ve	46	70.32
Abortion in family	+VE	23	35.9
	-ve	42	64.1
Sibling mortality	+VE	17	26.56
	-ve	48	73.44

Table (3): Complaint distribution among studied group:

		N	%
Complaint	Not doing well &poor suckling	14	21.8
	Lethargy	6	9.37
	Difficult breathing	5	7.81
	Erythema and patchy skin lesion	4	6.24
	Failure to gain weight	4	6.24
	Jaundice	3	4.68
	Fever	6	9.37
	Recurrent admission with sepsis like manif	2	3.14
	Delayed motor milestones	4	6.24

Table (4). Examination data distribution among studied group

	N	%
Coarse features	3	4.68
Disturbed consciousness	11	17.18
Convulsion	5	7.81
Respiratory distress	7	10.93
Delayed motor milestones	7	10.93
chest crepitations	7	10.93
Cardiomyopathy & Heart failure	2	3.12
Hepatosplenomegaly	11	17.18
Erythema & patchy skin lesion	4	6.25

Table (5): Lab parameters distribution among studied group

	Mean ±SD
HB (g/dL)	10.63±2.34
WBCs (X10 3/µL)	9.74±3.87
PLT (X10 3/µL)	260.2±88.6
CRP (mg/L)	25.03±42.05
Cr (mg/dL)	0.47±0.16
BUN (mg/dL)	11.06±3.23
T bilirubin (mg/dL)	1.51±1.95
T protein (g/dl)	5.68±0.71
Albumin (g/dl)	3.71±0.45
ALT(u/l)	40.47±18.6
AST(u/l)	62.37±21.8
Na (mEq/L)	139.5±4.56
K (mEq/L)	4.19±0.79
Ca (mEq/L)	9.18±1.0
Phosphorous (mg/dL)	4.67±1.09
Ammonia (µg/dL)	306.72±576.6
Lactate (mmol/L)	10.65±25.6
RBS (mg/dl)	129.95±42.6

Tables (6): The different disease types of the studied cases after routine and specific laboratory finding

Suspected IEM (not diagnosed) N=18	Diagnosed metabolic (non pku) N=11	Diagnosed Phenylketonurea N=36
1. Suspected organic academia 4 (22.2%) : a- malonic acidemia	1. Maple syrup urine disease (MSUD) 2 (18.18%)	diagnosed by routine neonatal screening and

2cases **b-citrullinemia 1 case** **c-propionic acidemia 1 case** **2. Suspected Mitochondrial disease 1 (5.5%)** **3. suspected panthonate kinase deficiency 1(5.5%)** **4. lost follow up 12 (66.5%)**	**2.Galactosemia 2 (27.27%)** **3. Organic academia 2 (18.18%)** **4.Nonketotic Hyperglycinemia 1 (9 %)** **5.Biotidinases deficiency 2 (18.18%)** **6.Mucopolysaccaraidosis 2 (18.18)**	**follow up with our outpatient clinic**

Discussion:

Inborn errors of metabolism (IEM)can be controlled with early diagnoses and treatment. Early diagnosis and treatment are very important to reduce the rates of morbidity and mortality related to IEMs. The first step is suspicion, followed by performing routine and specific laboratory analysis as soon as possible. Early neonatal screening is important especially in countries with high rates of consanguinity because early diagnosis and treatment are likely to result in better neurodevelopment outcomes and lower mortality rates **(6)**. Therefore, the aim of our study is to determine the present status of infants with inborn errors of metabolism in Zagazig University Hospitals.

Our study showed that females (54.6%) were slightly higher than males (46.87%), this was in agreement with **Hoell et al. (7)** who reported that 44.8% of cases were males and others were females and not in agreement with **Khalaf et al. (8)** and **Dogan et al., (9)** who reported that males were higher (60% and 63.64% respectively) among cases of their studies.

Our study showed that consanguinity was positive in 45 patients (70.3%). It was higher than that reported in a study conducted by **Shawky et al. (10)** at Ain Shams University, Egypt, in which 17 patients (43.5%) had consanguineous parents. Also, our results were higher than a study carried out in Iraq by**Arifetal.(11)**, in which 174 (9.9%) patients had positive consanguineous marriage.

Our study showed that 19 cases (29.6%) had history of presence of similar conditions in their family , positive history of abortion was present in 23 cases (35.9%), also positive history of sibling death was present in 17 cases (26.6%), that was in agreement with **Gündüzet al.(12)** who reported that 33.3% of cases had sibling history and higher than a study reported 132 (7.5%) of their patients had positive family history of either metabolic disorders or sudden unexplained death of siblings carried out by **Arifet al.(11)**.

In this study, the most common complaint was poor suckling in 14 cases (21.8%) then lethargy as well as fever in 6 cases (9.37%), the most common presentation was disturbed consciousness and hepatosplenomegaly in 11 cases (17.18%). Our results were in agreement with **Shawky et al. (10)** and **Clarke (13)** who reported that sepsis-like symptoms were the most common presentation (26.5% and 15%), respectively. Also, **Lunda et al.(14)** who reported that the predominant symptoms in patients suggesting the possibilty of metabolic disorders were convulsions and lethargy.

In our study amino acid disorder (AA) was accounted as the most common disorder detected, and this was in accordance with **Selim et al. (15)**. Regarding the AA disorders, phenylketonuria (PKU) was the most common type in our study, detected in 36/65 (56.2%) of diagnosed cases, with female predominance in 19/36 case (52.7%). This was in agreement with a study of **Hassan et al.,(16)**whorevealed that PKU was the most common single IEM detected in high-risk cases (116/235 (49.3%).

Conclusion:

Early diagnosis of inborn errors of metabolism (IEMs) during neonatal period or infancy for starting its proper treatment will improve outcomes, control complications of metabolic diseases and decrease the mortality rates.It could be recommended that, increase awareness of primary care providers to know how to recognize IEM disorders, manage them in the interim while awaiting definitive diagnosis and refer them to the appropriate metabolic specialist for collaborative management of these patients.

No conflict of interest.

References:

1.**Dionisi-Vici, C., Rizzo, C. and Burlina, A.B., et al. (2008).** Inborn errors of metabolism in the Italian pediatric population: a national retrospective survey. J. Pediatr. Mar; 140(3): 321-7.

2. **Waber, L. (2006).** Inborn errors of metabolism. Ped Ann 2018; 19(2): 105-17.

3. **Wappner, R.S. (2011).** Biochemical diagnosis of genetic diseases. Ped Ann; 22(5): 282-97.

4. **Sedel, F. (2013).** Inborn errors of metabolism in adult neurology. Rev Neurol (Paris); 169 A (Suppl 1): S63–9.

5. Clarke, J.T. (2017). A Clinical Guide to Inherited Metabolic Diseases. 2nd ed. New York: Cambridge University Press.

6. **Cloherty J.P., Eichenwald E.C. and Stark A.R. (2008).** Manual of neonatal care. 15 Lippincott Williams & Wilkins p.119–135.

7.**Hoell, J. I., Warfsmann, J., Distelmaier, F., Borkhardt, A., Janßen, G., &Kuhlen, M. (2018).** Challenges of palliative care in children with inborn metabolic diseases. Orphanet journal of rare diseases, 13(1), 1-7.

8. **Khalaf, S. M., El-Tellawy, M. M., Refat, N. H., &Abd El-Aal, A. M. (2019).** Detection of some metabolic disorders in suspected neonates admitted at Assiut University Children Hospital. Egyptian Journal of Medical Human Genetics, 20(1), 1-7.

9.**Dogan, E., Uysal, S., Ozturk, Y., Arslan, N., & Coker, C. (2017)**. Selective screening for inborn errors of metabolism: A report of six years experience. Iranian Journal of Pediatrics, 27(5).

10. **Shawky R.M., Abd-El Khalek H.S. and Elakhdar S.E. (2015).** Selective screening in neonates suspected to have inborn errors of metabolism. Egyptian Journal of Medical Human Genetics. 16(2): 165–171.

11. **Arif A., Thejeal R.F. and Farhan A. (2016).** Inborn errors of metabolism status in Iraq. IOSR J. Pharm Biol Sci. 11:58–62.

12.**Gündüz, M., Ünal, S., Okur, İ., Ayranci-Sucakli, I., Güzel, F., &Koç, N. (2015).** Neonates with inborn errors of metabolism: spectrum and short-term outcomes at a tertiary care hospital. The Turkish journal of pediatrics, 57(1), 45.

13. **Clarke S. (2002).** Tandem mass spectrometry: the tool of choice for diagnosing inborn errors of metabolism. British journal of biomedical science. 59(1): 42–46.

14. **Lunda A., Christensen E. and Skovby F. (2002)**. Diagnosis and acute treatment of inborn metabolic diseases in infants. Ugeskrift for Laeger. 164(48): 5613–5619.

15. **Selim L.A., Hassan S.A.H. and Salem F. et al. (2014)**. Selective screening for inborn errors of metabolism by tandem mass spectrometry in Egyptian children: a 5 year report. Clinical biochemistry. 47(9): 823–828.

16.**Hassan, F. A., El-Mougy, F., Sharaf, S. A., Mandour, I., Morgan, M. F., Selim, L. A., et al. (2016)**. Inborn errors of metabolism detectable by tandem mass spectrometry in Egypt: the first newborn screening pilot study. J. Med. Screen. 23, 124–129.