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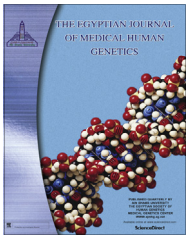

ORIGINAL ARTICLE

Selective screening in neonates suspected to have inborn errors of metabolism

Rabah M. Shawky *, **Heba Salah Abd-Elkhalek**, **Samah Elyamani Elakhdar**

Pediatric Department, Genetics Unit, Ain Shams University, Egypt

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KEYWORDS

Newborn screening;
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Abstract *Background:* Inborn errors of metabolism (IEM) have a high morbidity and mortality in neonates. Unfortunately, there is no nationwide neonatal screen in Egypt, so several cases may be missed.

Objective: The aim of this work was to detect the prevalence of IEM among neonates with suspected IEM, and to diagnose IEM as early as possible in order to minimize morbidity and mortality in high risk neonates.

Subjects and methods: This prospective study included 40 neonates admitted to the Elmahalla General Governmental Hospital Neonatal Intensive Care Unit (NICU) with sepsis like symptoms (lethargy, hypoactivity, poor suckling, and poor crying), convulsions, persistent metabolic acidosis, persistent vomiting, or previous sib death of unidentified cause (neonates with suspected IEM). All included patients were subjected to detailed full history, through clinical examination, laboratory investigations, and metabolic screening by tandem mass spectrometry (MS/MS). Other investigations for IEM including lactate, ammonia, and galactose 1 phosphate levels in the blood, as well as organic acids in urine were done according to each case.

Results: 13 patients (32.5%) were diagnosed as having IEM, 7 of them (53.8%) had urea cycle defect, 2 (15.4%) had maple syrup urine disease, while methylmalonic acidemia, fatty acid oxidation defect, mitochondrial disease, and galactosemia were diagnosed in one patient each (7.7%). Out of these patients, 12 patients (30%) were discharged from NICU after therapy, and one patient (2.5%) died (the one who had mitochondrial disease). Two patients were diagnosed as diseases other than IEM, one had hyperinsulinism and another one had congenital myopathy, while 2 patients were proved to be normal. Five patients (12.5%) were suspected to have IEM (tyrosinemia, mitochondrial

* Corresponding author.

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disease, organic acidemia) 4 of them died before final diagnosis, and one transferred to another NICU. There was a significant difference between diagnosed and undiagnosed patients as regards history of sibling death ($p = 0.012$), plasma ammonia level ($p = 0.002$), and discharge from NICU ($p = 0.000$).

Conclusion: IEM represent a high percent (32.5%) of neonates who had sepsis like symptoms, and when diagnosed, patients showed marked improvement after therapy. IEM should be considered in differential diagnosis of the sick neonates, and investigations, and management should be started rapidly to decrease morbidity, and mortality till nationwide screen for IEM is applied in Egypt.

1. Introduction

Inborn errors of metabolism (IEM) are a highly heterogeneous group of genetic conditions and represent a relevant cause of morbidity and mortality in the pediatric population. IEM, which are individually rare but collectively numerous, are well-recognized entities of the generic class of ''rare'' diseases. Since the first descriptions by Garrod at the beginning of the 20th century, several hundred new disorders have been defined, as new biochemical and molecular diagnostic tools became available [1].

The early diagnosis of IEM by laboratory-based mass screening is a type of preventive medicine. However, several factors restrict the range of IEM that can be screened for, and the number of people to whom it can be made available. Ideally, extension of mass screening of neonates for a clinically significant IEM is a desirable strategy. Tandem mass spectrometry (TMS) is a powerful and effective diagnostic technique and has been proposed as a means to realize this aim. Its main advantages are improved accuracy, sensitivity and specificity over existing methods, and its suitability for cost-effective multidisease IEM mass screening [2].

The aim of this work was to detect the prevalence of IEM among neonates with suspected IEM, and to diagnose IEM as early as possible in order to minimize morbidity and mortality in high risk neonates.

2. Subjects and methods

This study included 40 neonates (31 males and 9 females) admitted to the Elmahalla General Governmental Hospital Neonatal Intensive Care Unit (NICU) with sepsis like symptoms (lethargy, hypoactivity, poor suckling, and poor crying), as well as convulsions, persistent metabolic acidosis, persistent vomiting, or history of previous sib death of unidentified cause, or clinical deterioration in a previously healthy neonate. The study was conducted at the Genetics Unit, Children's Hospital, Ain Shams University, Cairo, Egypt.

The patients' age ranged from 3 to 25 days. All included patients were subjected to detailed full history with special emphasis on age, sex, gestational age, antenatal and perinatal history, symptoms of the patient, age of onset of symptoms, relation of symptoms to feeding, similar cases in the family, parental consanguinity, and previous neonatal death. Through clinical examination, laboratory investigations including complete blood count (CBC), C reactive protein (CRP), electrolytes (Na, K, Ca), blood gases, pH, and metabolic screening by tandem mass spectrometry (MS/MS) were done to detect aminoacid and acyl carnitine profile. Other investigations for IEM including plasma lactate, ammonia level, and organic acids in urine were done according to each case. Galactose 1 phosphate level estimation was done in one patient.

2.1. Statistical methodology

Analysis of data was performed using standard computer program statistical package for social sciences (SPSS) 13.0 for windows (SPSS Incorporation, USA). $P < 0.05$ was considered significant.

3. Results

Thirty-one neonates were males (77.5%). Family history of paternal consanguinity and sibling health of the patients is presented in (Table 1). The weight of the patients ranged from 1.2 to 3.8 kg, with a mean of 2.65 kg ± 0.61 kg. All patients were normal at birth with no complications during delivery, then they started to develop symptoms at an age ranged from 1 to 10 days with a mean of 3.35 ± 2.155 days. The main presenting symptoms were sepsis like symptoms in 25 patients (62.5%) (Table 2). Neurological examination was normal in 12 patients (30%).

Aminoacid and acyl carnitine profile (metabolic screen) by tandem mass spectrometry was abnormal in 13 patients (32.5%), while organic acids in urine showed methyl malonic acidemia in 1 patient (2.5%). The investigations done are shown in Table 3.

Thirteen patients 13/40 (32.5%) were diagnosed as having IEM, out of them 12/13 (92.3%) patients were discharged from NICU after therapy. Urea cycle defect was the commonest IEM diagnosed in 7/13 (53.8%), followed by MSUD in 2/13 (15.4%). 18/40 patients (45%) were not diagnosed as 12/18 (66.7%) of them died and 6/18 (33.3%) of them discharged from NICU before diagnosis. Data are shown in Table 4.

There was no significant difference between diagnosed and undiagnosed patients as regards sex of the patient, age of onset of symptoms, consanguinity, and type of the presenting symptom. There was a statistically significant difference between diagnosed and undiagnosed patients as regards family history of sib death ($p = 0.012$), plasma ammonia level ($p = 0.002$), metabolic screen (aminoacid and acyl carnitine profile) ($p = 0.045$), and fate of the patients ($p = 0.000$).

Seven patients (53.8%) (out of 13 who diagnosed as IEM) had a urea cycle defect. They were full term, and their weight ranged from 1.700 to 3.1 kg. All were normal at birth, and then they started to develop hypoactivity, poor suckling, and poor crying at age ranged between 2 and 7 days. Two of them developed convulsions. Consanguinity of the parents

Table 1 Family history of the patients.

		Studied patients (n = 40)
Consanguinity	Positive	17 (42.5%)
	Negative	23 (57.5%)
Sibling health	No sib death	24 (60%)
	Sib death	15 (37.5%)
	Sib death (diagnosed with IEM)	1 (2.5%)

IEM: inborn errors of metabolism, n: number.

was positive in 3 patients (42.9%). Clinical examination showed hypoactivity, hypotonia, and hyporeflexia. Laboratory investigations showed that serum ammonia was significantly high in all cases (ranged from 200 to 330 mcg/dL), with no acidosis, and normal extended metabolic screening test. Management was started and all were discharged from NICU for follow up.

Two patients (15.4%) had maple syrup urine disease (MSUD). They were full term males. Their ages were 8, and 15 days old. Their weights were 2.760 and 3.160 kg respectively. Both were of consanguineous parents. They presented with poor suckling, poor activity and spasticity at age of 2 days. Clinical examination showed poor moro reflex, opisthotonus position, fair chest air entry and mild intercostal retraction. Laboratory finding showed acidosis with high anion gap. The extended metabolic screening test showed high leucine, isoleucine, valine, leucine:phenylalanine ratio and leucine:alanine ratio which are diagnostic for MSUD. Specific management was started which led to improvement of the patients who were discharged from NICU for follow up.

Another patient (2.5%) aged 18 days, was diagnosed as lactic acidosis (probably due to mitochondrial disorder). He was a full term male, 2nd in order of birth of non consanguineous

Table 2 The presenting symptoms of the patients.

Main presentation	Associated symptoms	Studied patients (n = 40)
Sepsis like symptoms	–	15 (37.5%)
	Convulsions	3 (7.5%)
	Vomiting	3 (7.5%)
	Previous sib death (? IEM)	2 (5%)
	Metabolic acidosis	1 (2.5%)
	Acidosis, previous sib death (? IEM) and vomiting	1 (2.5%)
		25 (62.5%)
Convulsions	–	6 (15%)
	Vomiting	1 (2.5%)
	Persistent metabolic acidosis	1 (2.5%)
		8 (20%)
Previous sib death (? IEM)		3 (7.5%)
Persistent vomiting		2 (5%)
Persist metabolic acidosis	–	1 (2.5%)
	Vomiting	1 (2.5%)
		2 (5%)

Table 3 Investigations of inborn errors of metabolism of the studied patients.

Investigation	Result	n	%
Metabolic screen	Normal	27	67.5
	Specific finding	13	32.5
Ammonia	Normal	3	7.5
	Border line elevation	5	12.5
	High	13	32.5
	Not done	19	47.5
Lactate	High	35	87.5
	Not done	5	12.5
ABG with anion gap	Normal	20	50
	Acidosis with high anion gap	6	15
	Acidosis, anion gap not done	14	35
Organic acids in urine	Specific findings	1	2.5
	Normal	4	10
	Not done	35	87.5

n: number; ABG: arterial blood gas.

Table 4 Final diagnosis and fate of the patients.

Final diagnosis		*n*	Percent	Fate			
				Died	%	Discharged	%
IEM	UCD	7	53.8	0		7	
	MSUD	2	15.4	0		2	
	Mitochondrial	1	7.7	1	100	0	
	MMA	1	7.7	0		1	
	Galactosemia	1	7.7	0		1	
	FAOD	1	7.7	0		1	
		13	**32.5**	**1**	**7.7**	**12**	92.3
Other diagnosis	Hyperinsulinism	1	50	0		1	
	Congenital myopathy	1	50	0		1	
		2	**5**	**0**		**2**	
Normal		**2**	**5**	**0**		**2**	
Suspected IEM	Organic acidemia	3	60	2	66.6	1	33.4
	Tyrosinemia	1	20	1	100	0	
	Mitochondrial	1	20	1	100	0	
		5	**12.5**	**4**	**80**	**1**	20
Undiagnosed*		**18**	**45**	**12**	**66.7**	**6**	33.3
Total		**40**		**17**	**42.5**	**23**	**57.5**

IEM: inborn errors of metabolism, *n*: number, UCD: urea cycle defect, MSUD: maple syrup urine disease, MMA: methylmalonic acidemia, FAOD: fatty acid oxidation defect.
The bold numbers indicate the total number of each final diagnosis.
* Discharged on parent request.

parents. The mother had gestational diabetes. His weight was 2.9 kg at 18 day. He had persistent metabolic acidosis which started at the age of 5 days. There was no family history of the same condition. Clinical examination showed poor activity, and hepatomegaly. Laboratory findings showed impaired liver functions tests, high lactate (78.3 mg/dL) repeatedly, and persistent metabolic acidosis with high anion gap. Extended metabolic screening showed high free carnitine. Magnetic resonance spectroscopy (MRS) on the brain was arranged but unfortunately the patient died.

There was also one patient (2.5%) diagnosed with methyl malonic acidemia at 25 days. He was a full term male, 2nd in order birth of 1st cousin consanguineous parents. His weight was 3 kg. He had persistent vomiting and acidosis which started at the age of 5 days. There was a history of sib death at the neonatal period without diagnosis. Clinical examination showed hypotonia. Laboratory investigations showed high ammonia and metabolic acidosis. Extended metabolic screen showed high propionyl carnitine (C3), and C3:C2 ratio. Organic acids in urine showed high methyl malonic acid which is consistent with the diagnosis of methyl malonic acidemia. Specific management was started and the patient improved and discharged from NICU for follow up.

Another patient (2.5%) had fatty acid oxidation defect. He was a full term male aged 10 days, 4th in order of birth of non consanguineous parents. His weight was 2.6 kg, and he had hypoactivity at the age of 2 days. Family history showed previous 3 sibs death. The 1st was a female died at birth due to suspected obstructed labor, the 2nd was a female who had hypo activity, poor suckling, metabolic acidosis and high ammonia which started at 2 days old, and she died at 17 days, and the 3rd was a male who had persistent metabolic acidosis which started at 2 days old, and he died at 7 days old. In our patient laboratory findings showed persistent hypoglycemia, border line elevation of ammonia, no acidosis and extended metabolic screen showed high C6,C8,C10 consistent with the diagnosis of medium chain acyl CO-A dehydrogenise deficiency (MCAD). He started management and discharged from NICU for follow up.

Another patient (2.5%) had galactosemia. She was a full term female aged 23 days, 5th in order birth of 1st cousin consanguineous parents. Her weight was 3 kg. She was admitted to NICU at birth for respiratory distress and she was on mechanical ventilator. After improvement she was weaned from ventilator and started normal feeding, but she deteriorated, and started to develop jaundice, and hematemesis. Family history showed that her 1st sib was a healthy female, the 2nd sib was a premature male with imperforate anus who died soon after birth, the 3rd sib was a female who developed jaundice & hematemesis then died without diagnosis at 14 days, and the 4th sib was a female who developed epilepsy at the age of 11 months and now she is on depakine, otherwise she is normal. Clinical examination showed jaundice. Laboratory findings showed high liver function tests, direct hyperbilirubinemia, and high alpha-fetoprotein. There was no acidosis. Extended metabolic screen showed high citrulline and methionine for correlation with clinical picture. Non glucose reducing substance in urine was detected, and galactose 1 phosphate level was high which is consistent with the diagnosis of galactosemia. Management was started and she was discharged from NICU for follow up.

In our 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. Three patients of them (7.5%) were suspected to have organic acide-

mia. The 1st patient was a full term male, 1st in order of birth of 1st cousin consanguineous parents. His weight was 3 kg. He presented with poor activity, poor suckling, and convulsions at the age of 3 days. Laboratory investigations showed persistent metabolic acidosis, and extended metabolic screen showed High C16-Carnitine (6.35 μmol/L), C6-Carnitine (0.41 μmol/L), C5-DC (0.5 μmol/L), C4-OH (C3-DC) (1.78 μmol/L), and high C3 DC. Organic acidemia was suspected and organic acids determination in urine was recommended, however the patient died before completing the investigations.

The 2nd patient was a preterm female, 1st in order of birth aged 11 days, of non consanguineous parents. Her weight was 1.48 kg, and she had poor activity at the age of 3 days. Her twin died at the age of 5 days old by the same presentation. Clinical examination showed hypotonia, hypoactivity and dehydration. Laboratory investigations showed persistent metabolic acidosis with high anion gap. Extended metabolic screen showed high free carnitine (540 μmol/L), C4-Carnitine (0.840 μmol/L), C6-Carinitine (0.290 μmol/L), for correlation with clinical picture. Organic acids in urine and lactate were recommended, however the patient died before completing the investigations.

The 3rd patient was a preterm male aged 5 days, 1st in order of birth, of non consanguineous parents. His weight was 2.200 kg. He presented with poor activity at the age of 1 day. Clinical examination showed hypotonia. Laboratory findings included high ammonia, metabolic acidosis with high anion gap, and extended metabolic screen showed high C6, C4. Organic acids in urine and lactate were recommended, but the patient discharged from NICU as requested by the parents, and lost follow up.

Another patient (2.5%) was suspected to have tyrosinemia. He was a full term male aged 17 days, 3rd in order of birth, of 1st cousin consanguineous parents. Her weight was 3.6 kg. She presented with poor activity and poor suckling at the age of 4 days. Clinical examination showed high respiratory rate, hypoactivity and hepatomegaly. Laboratory investigations showed low platelet count, high liver function tests, direct hyper bilirubinemia, metabolic acidosis, negative non glucose reducing substance in urine, and extended metabolic screen showed high tyrosine level. Succinyl acetone in urine was recommended as tyrosinemia was suspected. The patient died before doing the test.

There was another patient (2.5%) with suspected mitochondrial disorder. He was full term male aged 9 days, 1st in order of birth, of 1st cousin consanguineous parents. His weight was 2.85 kg. He presented with poor activity, poor suckling and vomiting at the age of 4 days. Clinically he showed hypoactivity. Laboratory investigations showed high ammonia, high lactate, acidosis and normal organic acids in urine. Extended metabolic screening did not show specific findings. CSF lactate or repeat blood lactate, and magnetic resonance spectroscopy (MRS) were recommended, however the patient died before doing the test.

In our study there were also 2 patients (5%) aged 12, and 21 days who presented with sepsis like symptoms, persistent vomiting and persistent metabolic acidosis, but the investigations and metabolic screening did not prove IEM. While other investigations proved other diagnosis. One of the patients was diagnosed as a case of hyperinsulinism. He was a full term male, 1st in order of birth, of non consanguineous parents. His weight was 2.9 kg. He presented with poor suckling and poor activity at the age of 3 days. His twin had the same symptoms and died at the age of 10 days without diagnosis. Laboratory findings showed persistent hypoglycemia. Ammonia showed border line elevation, and no specific findings were detected in the extended metabolic screening. Insulin level was high during hypoglycemia. Management was started and the patient discharged from NICU.

The other patient was diagnosed as a case of congenital myopathy. He was a full term male, 3rd in order of birth, of 1st cousin consanguineous parents, his weight was 3.800 kg. He had poor activity, persistent vomiting, and persistent metabolic acidosis at the age of 2 days. Family history showed a previous sib death at 1 month old by the same symptoms without reaching a definite diagnosis. Clinical examination showed hypoactivity, hypotonia, weak grasping reflex, absent deep tendon reflexes. EMG showed the presence of low amplitude, polyphasic, brief duration potential with voluntary contractions, and normal nerve conduction velocity. He was discharged from NICU for follow up.

In our study there were also 2 neonates admitted to NICU under observation as the parents had previous infant deaths at the neonatal period of unknown cause. They did not develop any manifestations, and their laboratory findings did not show any abnormality and they were discharged. Both of them were normal.

We did not reach a specific diagnosis in 18/40 patients (45%) as 12 patients died early and 6 were discharged from NICU and/or transferred to other NICU as requested by the parents and lost follow up before completing their investigations and their EMS did not show specific findings.

4. Discussion

This study included 40 neonates with suspected diagnosis of inborn errors of metabolism (IEM) depending on symptoms like poor suckling, poor crying, hypoactivity, lethargy, convulsions, persistent metabolic acidosis, persistent vomiting, and previous neonatal deaths in the family without definite diagnosis or with suspected IEM. Investigations including ammonia and lactate in blood, as well as organic acids in urine were done according to the suspected diagnosis. Screening for IEM was done by MS/MS. IEM was proved in 13 patients (32.5%).

The introduction of MS/MS into neonatal screening has enabled the screening of conditions that might otherwise have been missed, and thus believed to be extremely rare [3]. This technique has significantly improved the efficacy of neonatal screening programs, demonstrating the importance of early identification and treatment of infants with disorders that would otherwise go unrecognized, before irreversible clinical damage occurs [4].

In this study we found that IEM was diagnosed in 13/40 (32.5%) of neonates presented with sepsis like symptoms, convulsions, persistent metabolic acidosis, and persistent vomiting, or previous sib deaths. EMS showed specific findings in 12/40 patients (30%).

In Egypt, as there is no nationwide newborn screening, variable percentages of IEM were found in different studies according to the type of selection of patients. In a study done by Shawky et al. (2001) they screened mentally retarded

children by paper chromatography, ferric chloride test, and nitroprusside test for plasma and urine. 51/450 (11.3%) were diagnosed to have IEM [5]. In another extended metabolic screen done in 2004 on 232 cases (44 neonates and 187 children) with symptoms suggestive of IEM abnormal results were detected in 22.73% of neonates [6]. Also IEM were diagnosed in 20/50 infants and children (40%) who were suspected to have IEM [7]. Also in another study the incidence of IEM was 2.3% (11/486) in screening of neonates admitted to NICU for any cause not specifically for IEM in a period of 6 months [8]. IEM were also confirmed in 6% (203/3380) of children suspected to have IEM [9]. The high incidence of IEM in our study compared to other studies is due to that we selected neonates with suspected IEM, not all admitted to NICU.

In Brazil, a study on neonates presenting with hypoglycemia (glucose less than 40 mg/dl), metabolic acidosis (fall of 0.15 in pH and fall of 10 mEq/l in bicarbonate), jaundice, difficulty in gaining weight (weight gain <10 g over four consecutive days, despite a calorific offer >100 cal/kg), diarrhea, vomiting, hepato- and/or splenomegaly, cataracts, apnea, convulsions, and hypo- or hypertonia. They diagnosed 64 (63.3%) patients out of 101. Most of the positivity was due to transitory metabolic alterations of the newborn. Others were mucopolysaccharidoses, tyrosinemia type I, non-ketotic hyperglycinemia, Alpers' Syndrome and pyruvate dehydrogenase complex deficiency [10].

The incidence of IEM was higher in de Oliveira et al. (2001) [10] (63.5%), than in our study (32.5%) which may be related to the wider range of symptoms they included in their study, different methods of investigations used (the cetyltrimethyl ammonium bromide test, utilized for the detection of glycosaminoglycans in urine and the nitrosonaphthol test specific for the detection of tyrosine and an excess of its metabolites in urine) in their study, versus MS/MS in ours, so the detection method will affect the rate and type of IEM detected in the screening method. Also a high number of preterm infants were included in their study, and so their results revealed several cases with transitory neonatal tyrosinemia. Transient neonatal tyrosinemia is believed to be the most common alteration in the metabolism of amino acids in human beings, with an incidence of 10% among full-term newborns and between 30% and 50% among premature newborns [11].

In China, a study was done by Huang et al. 62 IEM patients (0.56%) were diagnosed out of 11,060 symptomatic patients. The age of included patients ranged from 0.04 to 168.2 months, and they presented with metabolic acidosis, jaundice, hepatosplenomegaly, recurrent vomiting, hypoglycemia, hyperammonemia, mental retardation of unknown cause, language retardation, seizures and unconsciousness. Only one patient had consanguineous parents [12]. The main difference between China study and our study was the age of the patients as they included older patients, with wider presenting symptoms, while our study included neonates only. Consanguinity rate was also high among included neonates.

Two studies were done in Korea in 2003, and 2005 respectively to screen for IEM. Blood spots of newborns were collected between 48 and 72 h after birth, and children between 1 month and 18 years of age presented with symptoms of IEM. They diagnosed IEM in 35 (0.079%) out of 44,300 in one study [13], and 20 (0.29%) out of 6795 in the other study [14]. In a Chinese study, which screened 129,415 neonates, revealed 23 (0.02%) neonates having IEM [15]. Also in a German study, among 250,000 neonates revealed 106 (0.04%) neonates with IEM [16]. Also a North Carolina study reported 219 (0.02%) out of 944,078 patients in neonatal screening over 20 years [17].

The variation in detection rates of IEM in different countries is not surprising, considering the different screening criteria for IEM used in different countries, sample size and consanguinity rate in the country. There was a low incidence of IEM in these studies compared to our study as they screened all neonates, also high incidence of consanguineous marriage in our country may be another factor to explain the high incidence of IEM in our study [18].

In our study, out of 13 patients who had IEM, 7 patients (53.8%) had consanguineous parents. This could not be explained only by the high consanguinity rate in Egypt which reaches up to 35.3% [18], but also by the fact that most IEM diagnosed in the patients are autosomal recessive which increase in incidence by consanguineous mating because relatives more often share abnormal genes inherited from a common ancestor and most IEMs are autosomal recessive disorders. Hence a history of parental consanguinity and/or sibling deaths should increase the suspicion of IEM [19].

So the initial step in the evaluation of any sick neonate and clearly the most important one is a thorough clinical assessment including a positive family history of consanguinity or sib death [20].

In our study, 12 males (92.3%) and one female (7.7%) were diagnosed as cases of IEM. The male predominance can be explained by the predominance of urea cycle defects in our patients {7 out of 13(53.8%)}, most probably carbamyl synthase or ornithine transcarbamylase deficiency. The later is inherited as X linked disease which usually manifests in males.

In our study, the most common IEM was urea cycle defect in 7/13 then MSUD in 2/13, followed by MMA, and MCAD in 1/13 each. In contrast to other studies done in Egypt, a general screening program including 2000 infants was done in 2001 from plasma samples. Transient neonatal tyrosinemia was detected in 0.05% and generalized aminoacidemia in 0.05%, and in another selective screening study on children with mental retardation revealed that phenyl ketonuria was the commonest IEM (40/51 cases 40%), followed by generalized aminoaciduria (4/51 cases 7.84%) [5]. In another study organic acidemias were detected in 13.63%, aminoacidopathies in 4.55%, fatty acid oxidation defects in 4.55% of neonates. In children abnormal results were also detected in 8.56% of children, including aminoacidopathies in 5.88%, organic acidemias in 1.07%, cystic fibrosis, congenital adrenal hyperplasia and congenital hypothyroidism in 1.61%, PKU was detected in 6.48% of children with MR, and MSUD in 10% of children with convulsions [6]. PKU was the commonest IEM detected in another study [7]. Aminoacidopathies in 127/203 (62.6%), mainly PKU in 100/203 (49.3%), were the most encountered IEM, followed by organic acidemias in 69/203 (34%) in another study [9]. MSUD was the commonest IEM in 5/11 (45.5%) patients, followed by non ketotic hyperglycinemia in 2/11 (18.2%), then tyrosinemia I in 1/11 (9.1%), MMA in 1/11 (9.1%), glutaric aciduria in 1/11 (9.1%), and isovaleric acidemia in 1/11 (9.1%) in another study [8].

The variation in the commonest cause of IEM in these studies is due to variation in investigations done (ammonia and lactate were added in our study), and age variation of the patients. PKU was not found in our cases, which is expected

as it does not have manifestations in newborn period, and it usually presents later in life with mental retardation.

In China, the most common IEM diagnosed was aminoacidopathy, PKU, followed by maple syrup urine disease (MSUD) [12]. Also in Taiwan in nationwide survey of newborn screening revealed that the most common IEM was a defect in phenylalanine metabolism then MSUD [21]. In North Carolina, the most common IEM was MCAD (medium-chain acyl-CoA dehydrogenase) deficiency, PKU, followed by MMA, then MSUD [17].

The patients who were diagnosed by a specific diagnosis and so specific management for their diseases was initiated has improved and discharged from NICU, while patients who were not diagnosed mostly died. This leads to a highly significant difference in the outcome of patients diagnosed and not diagnosed. So reaching a diagnosis, starting effective specific management is highly critical in improvement of patients.

In our study the most common symptom was sepsis like symptoms (poor feeding, poor activity and poor crying) in 25/40 (26.5%) which was in agreement with Clarke who advised to consider inborn errors of metabolism at the same time as common acquired conditions, such as sepsis [2]. The other common presenting features among our cases included convulsions in 8/40 (15%). This came in agreement with Lund et al. who reported that the predominant symptoms in neonates suggesting the possibility of metabolic disorders were convulsions and lethargy [22].

In our study there was a highly significant frequency of hyperammonemia in 10 patients (66.7%) who were diagnosed with IEM, 7 had urea cycle defect, 2 had MSUD and 1 had MMA. The main presentation of them was lethargy, poor feeding, suckling and crying, then convulsions, persistent vomiting and acidosis. This means that serum ammonia should be done for every neonate presented by these symptoms, or suspected to have IEM.

From this study we conclude that IEM represent a significant cause for sick neonates in NICU, and it should be considered in the differential diagnosis of any sick neonate. Investigations for IEM should be done routinely in NICU for neonates, until nationwide newborn screening can be applied in Egypt, and they should be done collectively not one by one in order to improve survival and decrease mortality and morbidity of patients.

Conflict of interest

The authors declare no conflict of interests.

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