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Frequency of Inborn Errors of Metabolism among Infants with Non-Apparent Causes of Failure to Thrive in Zagazig University Hospitals

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ABSTRACT

Background: Inborn errors of metabolism (IEM) are disorders in which there is a block at some point in the normal metabolic pathway caused by a genetic defect of a specific enzyme. Diagnosis is important not only for treatment and prognostication but also for genetic counseling and antenatal diagnosis in subsequent pregnancies.

Objective: The present study aimed to find out the relative frequency of inborn errors of metabolism among infants with unapparent cause of failure to thrive (FTT).

Patients and Methods: This study was cross-sectional prospective study, which was conducted during the period from 2017 to August 2019. It included 58 cases with non-apparent cause of failure to thrive admitted at Pediatric Department, Faculty of Medicine, Zagazig University. All studied cases were subjected to: EMS (extended metabolic screen) using filter paper by Tandem Mass Spectrometry. Urinary organic acids analysis was performed.

Results: In this study, frequency of inborn errors of metabolism (IEM) among the studied unapparent causes of FTT cases was 8.6%. Types of IEM diseases among the studied cases were one case for each of biotinidase enzyme deficiency (1.7%), methyl malonic acidemia (1.7%), mitochondrial disease (1.7%), organic acidemia (1.7%) and phenylketonuria (1.7%). There was statistically significant increase in complains of vomiting and diarrhea among cases with inborn errors of metabolism than those without inborn errors of metabolism.

Conclusion: There was high frequency of inborn errors of metabolism (IEM) among FTT without apparent cause. Frequency of hypoglycemia, positive ketone in urine, high anion gap and high serum ammonia were significantly more frequent among cases with inborn errors of metabolism than those without inborn errors of metabolism.

Keywords: Inborn errors of metabolism, Unapparent cause of failure to thrive, Frequency.

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)].

Specific and effective treatments are available for many IEM, and early therapeutic intervention can prevent the worsening of disease. Even if therapy is unavailable, an accurate diagnosis is crucial for genetic counseling [(2)].

Failure to thrive (FTT) in a child is defined as 'lack of expected normal physical growth', 'failure to gain weight' or 'lack of growth' [(3)].

This affects not only somatic development but also psychosocial and motor maturation, subsequent cognitive performance, immune function, and defenses against infection. Because of the multiple ways in which childhood development is impaired, early correction is needed [(4)].

The study aimed to find out the relative frequency of inborn errors of metabolism among infants with unapparent cause of failure to thrive.

PATIENTS AND METHODS

Design of the study:

This cross-sectional prospective study was conducted during the period from 2017 to August 2019. It included 58 cases with non-apparent cause of failure to thrive. This study was conducted at Pediatric Department, Faculty of Medicine, Zagazig University.

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.

Sample size:

Assuming that the total population size, of failure to thrive infant in Pediatric Department is 72 cases. The Positive Predictive Value (PPV) of extended metabolic screen is 76.6%. The sample size is 58 cases using OPEN-EPI with CI 95% and Power 80%.

Inclusion criteria:

- Age from 1 month to 2 years
- Patients with non-apparent cause of failure to thrive
- Weight: less than 3rd percentile for age and sex [(5)].

Exclusion criteria:

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- Patients presenting by failure to thrive due to other known causes
- Patients refused screening test
- Patients outside age (below 1 month or above 2 years)

All studied cases were subjected to:

- Complete history taking with specific emphasis on age, sex and gestational age (GA):
- Detailed nutritional history including type of feeding (Breast milk or artificial), frequency, signs of satisfaction, time of start of weaning.
- Developmental history including motor, mental milestones.
- Natal history and post-natal history.
- Family history including consanguineous marriage among the patient's parents, previous similar condition in the family.
- Detailed clinical examination with special emphasis on:
- Dysmorphic features, skins and signs of dehydration
- Neurological examination especially hypotonic or spastic patients
- Pelvi-abdominal examination especially organomegaly
- Chest examination
- Cardiac examination including evidence of congenital heart disease or cardiomyopathy
- Skeletal examination including any skeletal deformity
- Weight measurement
- Basic initial investigations:
- Complete blood count (CBC)
- C- reactive protein (CRP)
- Liver function
- Kidney function
- Electrolytes
- Investigations specific for IEM:
- Plasma ammonia and lactate.
- Blood gas and serum anion gap detection
- Blood glucose level and Ketones in urine
- Other specific investigations for IEM as needed.
- EMS (extended metabolic screen):

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) and provide a comprehensive assessment from a single blood spot specimen. **[6];**

- Urine organic acid analysis was performed using gas chromatography–mass spectrometry in all patients.

Statistical analysis

The data were coded, entered and processed on computer using statistical package for the social sciences (SPSS) (version 24). The results were represented in tabular and diagrammatic forms then interpreted. Mean, standard deviation, range, frequency, and percentage were used as descriptive statistics. Chi-Square test (X^2) was used to test the association of variables for categorical data. Fisher's exact (FE) test was used when the expected numbers were small.

Student's t-test was used to assess the statistical significance of the difference between two population means in a study involving independent samples. The accepted level of significance in this work was stated at 0.05 ($P < 0.05$ was considered significant).

RESULTS

Table 1 showed that, frequency of inborn errors of metabolism among the studied cases was 8.6%.

Table (1): Frequency of inborn errors of metabolism among the studied Cases

		n=58	%
Inborn errors of metabolism	**Yes**	5	8.6
	No	53	91.4

Frequency of IEM among the studied 58 case was one case for each one of the inborn errors (Table 2).

Table (2): Type and frequency of inborn errors of metabolism among the studied cases

		n=5	%
Types of IEM diseases	Biotinidase **enzyme deficiency**	**1**	**1.7**
	Methyl Malonic Acidemia	**1**	**1.7**
	Mitochondrial disease	**1**	**1.7**
	Organic Acidemia	**1**	**1.7**
	Phenylketonuria	**1**	**1.7**

There was no statistically significant difference between cases with and cases without inborn errors of metabolism regarding age, gestational age and sex (Table 3).

Table (3): Comparison between cases with and cases without inborn errors of metabolism regarding age, gestational age (GA) **and sex**

			with inborn errors of metabolism (n= 5)	without inborn errors of metabolism (n=53)	T test	P. value
Age (months)	**Rang**		9 - 21	9 - 21	0.556	0.581
	Mean ± SD		14.60 ± 4.83	15.68 ± 4.09		
GA (weeks)	**Rang**		37 - 38	37 - 39	0.812	0.420
	Mean ± SD		37.60 ± 0.548	37.81 ± 0.557		
Sex	**Male**	**No.**	4	30	X^2 1.031	0.310
		%	80.0%	56.6%		
	Female	**No.**	1	23		
		%	20.0%	43.4%		

This table showed that there was statistically significant higher frequency of vomiting and diarrhea among cases with inborn errors of metabolism than those without inborn errors of metabolism (Table 4).

Table (4): Comparison between cases with and cases without inborn errors of metabolism regarding GIT presentations

			with inborn errors of metabolism (n= 5)	without inborn errors of metabolism (n=53)	Fisher exact test	P. value
Vomiting	**Yes**	**n.**	4	10	9.32	0.002
		%	80.0%	18.9%		
	No	**n.**	1	43		
		%	20.0%	81.1%		
Diarrhea	**Yes**	**n.**	2	4	5.18	0.022
		%	40.0%	7.5%		
	No	**n.**	3	49		
		%	60.0%	92.5%		
constipation	**Yes**	**n.**	0	5	0.516	0.472
		%	0.0%	9.4%		
	No	**n.**	5	48		
		%	100.0%	90.6%		

Mean value of pH, HCO_3, and CO_2 were significantly lower in cases with inborn errors of metabolism than those without inborn errors of metabolism (Table 5).

Table (5): Comparison between cases with and cases without inborn errors of metabolism regarding ABG.

		with inborn errors of metabolism (n= 5)	without inborn errors of metabolism (n=53)	T test	P. value
pH	**Mean ± SD**	7.26 ± 0.21	7.386 ± 0.02	4.449	0.001
HCO_3 (mmol/L)	**Mean ± SD**	14.68 ± 3.25	22.18 ± 1.16	6.476	0.001
CO_2 (mmHg)	**Mean ± SD**	27.24 ± 3.72	37.32 ± 2.40	6.953	0.001

Hypoglycemia, ketone in urine, high anion gap, and high serum ammonia were significantly more frequent among cases with inborn errors of metabolism than those without inborn errors of metabolism (Table 6).

Table (6): Comparison between cases with and cases without inborn errors of metabolism regarding serum blood glucose level, ketones in urine, anion gap, plasma ammonia and plasma lactate

			with inborn errors of metabolism (n= 5)	without inborn errors of metabolism (n=53)	Fisher exact test	P. value
Serum blood glucose Level	Normal	n.	3	53	21.96	0.001
		%	60.0%	100.0%		
	Hypoglycemic	n.	2	0		
		%	40.0%	0.0%		
Ketones in urine	Positive	n.	2	4	5.18	0.022
		%	40.0%	7.5%		
	Negative	n.	3	49		
		%	60.0%	92.5%		
Anion gap	Normal	n.	2	53	33.53	0.001
		%	40.0%	100.0%		
	High	n.	3	0		
		%	60.0%	0.0%		
Plasma ammonia level	Normal	n.	2	45	5.99	0.014
		%	40.0%	84.9%		
	High	n.	3	8		
		%	60.0%	15.1%		
Plasma lactate	Normal	n.	2	17	0.130	0.718
		%	40.0%	32.1%		
	High	n.	3	36		
		%	60.0%	67.9%		

DISCUSSION

In this study, frequency of inborn errors of metabolism (IEM) among the studied unapparent causes of FTT cases was 8.6%. Frequency of types of IEM diseases among the studied cases was one case for each of biotinidase enzyme deficiency (1.7%), methyl malonic acidemia (1.7%), mitochondrial disease (1.7%), organic acidemia (1.7%) and phenylketonuria (1.7%).

Isabel *et al.* [(1)] found the prevalence of IEM in their group was 1 in 184 newborns. **Abdel Maksoud *et al.*** [(7)] estimated the frequency of inborn errors of metabolism (IEMs) in patients (1 month to 5 years) presenting with acute encephalopathy-like picture at an emergency department (ED). Their study was a prospective observational study conducted on 30 patients admitted to the Pediatric ED with unexplained acute encephalopathy. All were screened for suspected IEMs. Ten (33.3%) of them were positive in the initial screening test.

In our study in FTT of unknown origin the prevalence of IEM was (8.6%) more than the rates reported in Bahrain where **Golbahar *et al.*** [(8)] found prevalence of (1:79) of inborn errors of amino acids in suspected children referred for screening in a newly established Princess Al-Jawhara Centre for Genetic Diagnosis and Research in the Kingdom of Bahrain. Out of 1986 newborns screened, 25 infants were diagnosed and confirmed. The prevalence (8.6%) in our study was less than the rates in Oman (1:4) [(9)].

The explanation of high frequency of inborn errors of metabolism (IEM) among the studied cases may be due to target population in our study which were infants with unapparent cause of failure to thrive.

The variation in detection rates of IEM in different countries, as mentioned before, is not surprising, considering the different screening criteria for IEM used in different countries, sample size and consanguinity rate in the country.

In the current study, there was statistically significant increase in complaints of vomiting and diarrhea, encephalopathy, metabolic acidosis, dehydration, and neurological manifestations among cases with inborn errors of metabolism than those without inborn errors of metabolism. This is in agreement with **Isabel *et al.*** [(1)].

In this study, mean value of Hb (gm/dl) was significantly lower among cases with inborn errors of metabolism and without inborn errors of metabolism (8.1 gm/dl and 12.7 gm/dl respectively) p <0.001.

This is in agreement with **Tavil *et al.*** [(10)] who aimed to evaluate the frequency and types of hematological abnormalities in children with various inherited metabolic disorders. Their study suggested that anemias should be kept in mind as a coexisting hematological diseases in young patients with inborn errors of metabolism and nutritional anemias are the most prevalent anemias seen in patients with inborn errors of metabolism. So early detection of the disease, early administration of specific diet, and close monitoring of the patients are very important factors to prevent the development of hematological complications in patients with inborn errors of metabolism.

This study showed that, mean value of pH, HCO_3, CO_2, was significantly lower in cases with inborn errors of metabolism than those without inborn errors of metabolism. This agreed with **Christopher and Sankaran [11].**

This study showed that, frequency of hypoglycemia was significantly higher in cases with inborn errors of metabolism than those without inborn errors of metabolism, which is in agreement with **Agana *et al.* [12]** who reported that, hypoglycemia was commonly seen in IEM cases

In this study, positive ketone in urine was significantly more frequent among cases with inborn errors of metabolism than those without inborn errors of metabolism. This is in agreement with **Hori *et al.*, [13].**

Frequency of high anion gap was significantly higher among cases with inborn errors of metabolism than those without inborn errors of metabolism. This agrees with **Alfadhel and Babiker, [14]** who reported that patients with IEM had high anion gap, and ketonuria. Frequency of high serum ammonia and serum lactate were significantly higher among our cases with inborn errors of metabolism than those without inborn errors of metabolism.

This agrees with **Shawky *et al.* [15]** who aimed 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. Their 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). They found 13 patients (32.5%) 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%). They found high serum ammonia and serum lactate were significantly higher among cases with inborn errors of metabolism than those without inborn errors of metabolism.

CONCLUSION

- There was high frequency of inborn errors of metabolism (IEM) among FTT without apparent cause.
- There was statistically significant increase in complains of vomiting and diarrhea, among cases with inborn errors of metabolism than those without inborn errors of metabolism.
- Frequency of hypoglycemia, positive ketone in urine, high anion gap and high serum ammonia were significantly more frequent among cases with inborn errors of metabolism than those without inborn errors of metabolism.

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