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ORIGINAL ARTICLE

Evaluation of Metabolic Disorders in Pediatric Department at Zagazig University Hospital

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ABSTRACT

Background: The inborn errors of Metabolism (IEM) are significantly interrelated with genetic abnormalities from carrier parents to their children. Early diagnosis, genetic analysis of newborns, screening of future parents and nutritional treatment may help in reducing the chance to develop clinical symptoms of IEM. The present study was aimed to evaluate the early detection, diagnosis, and intervention to improve outcome and emphasizing the importance of expanded early neonatal screening.

Methods: This cross-sectional study was included 65 cases with suspected IEM and done in Pediatrics Department, Zagazig University Hospitals. 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. All the studied cases were subjected to full history, clinical examination and Laboratory investigations include routine investigations and specific metabolic screen in the blood.

Results: In our study cases in PKU group were almost normal while the most common manifestation at the time of presentation in diagnosed non PKU group was sepsis-like manifestations (poor suckling) as well as disturbed conscious level each found in 5 cases (45.45%) followed by hepatosplenomegaly as well as delayed motor milestones in 4 cases (36.36%).

Conclusions: Inborn errors of metabolism (IEMs) are rare diseases worldwide and usually presented with poor suckling and lethargyand diagnosed during infancy period. Early diagnosis of IEMs with its proper treatment improve outcomes.

Keywords: Inborn errors of metabolism; Neonates; Hepatosplenomegaly; Poor Suckling.

INTRODUCTION

Inborn errors of metabolism (IEM) cause hereditary metabolic diseases (HMD) and classically they result from the lack of activity of one or more specific enzymes or defects in the transportation of proteins**[1]**. Recently, the estimated incidence rates are one in 800–2500 live births **[2]**. Individual disorders are more frequently diagnosed today, but such diseases are still uncommon and vary in different countries and regions **[3]**.Genetic variants with uncertain significance may induce incidental findings outside IEMs **[4]**. The majority of HMD are inherited autosomal recessive traits with recurrence risk of 25% for each gestation of heterozygous parents as Phenylketonurea and galactosemia **[5]**. None validated genetic variances caused by variable penetrance or random X-chromosome activation affect subsequent adaptation of gene assays for IEM diagnosis **[6]**.

In Egypt, the national neonatal screening program currently includes screening for 2 disorders: congenital hypothyroidism and phenylketonuria (PKU) **[7]**. IEMs involved within complex molecules such as peroxisomal diseases are associated with dysmorphologies, seizures, severe hypotonia and cholestatic liver disease while lysosomal disorders represent a group that involve abnormal accumulation of metabolites in various organs and tissues resulting in multi-system dysfunction: dwarfism, hepatosplenomegaly, recurrent infections, skeletal dysplasias and neurocognitive impairment **[8]**.

In fact, what is more important than the exact tests for the IEM diagnosis is the clinical judgement capable of leading towards a probably safe diagnosis via identifying the group that the disease

belongs to. A lot of information can be gained from the history, physical examination, and more commonly treatment to be started as soon as possible and type of tests and it is generally accomplished in a progressive way, according to the results that are to be obtained **[9]**. It is imperative to keep a high index of suspicion in differential diagnosis for prompt IEM identification as the institution of appropriate therapy, preventive measures and compliance helps avoid severe morbidity or even mortality in some cases **[10].**

Therefore, this study was aimed to evaluate of present status of inborn errors of metabolism in Zagazig University Hospitals.

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 consent was obtained from all participants' parents and the study was approved by the research ethical committee of Faculty of Medicine, Zagazig University. The study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

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 criteria:

Includes 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.

Exclusion criteria:

Includes 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.

The mean age of included neonates was 39.2±43.8 month, 30 male and 35 female. 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 were included 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 Investigations :

Blood sample were collected from all studied cases from venous blood for CBC, 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. Urine samples were collected to estimate ketones in urine using urine test strip.

Anemia could be classified into mild moderate and severe according to (de Leeuw et al., 1996) **[11]** as follow:

- Children less than 5 years of age : mild anemia 10-10.9 g/dL , moderate anemia 7-9.9 g/dL, severe anemia lower than 7 g/dL .
- Children 5 - 11 years of age: mild anemia 11-11.4 g/dL , moderate anemia 8-10.9 g/dL, , severe anemia lower than 8 g/dL .
- Children 12 - 14 years of age: mild anemia 11-11.9 g/dL, moderate anemia 8-10.9 g/dL, , severe anemia lower than 8 g/dL

Arterial blood gas (ABG) specimen should be collected in a heparinised blood gas syringe anerobically and analysed within 30 minutes in blood gas appratus ; otherwise, they should be placed on ice. metabolic acidosis considered when ph less than 0.35 , HCO_3 less than 18 , CO_2 less than 35. Anion Gap (AG) = Na – [Cl + HCO_3], anion gap exceeding 24 mmol/l was suggested the presence of metabolic acidosis.

Extended metabolic screen (Mass spectrometry analysis): Whole blood samples were drawn by heel prick or venipuncture from high-risk babies and spotted on Whatman 903 filter paper (Whatman Inc., USA) **[12]**.

STATISTICAL ANALYSIS

Data analyzed using SPSS version 20.0. Qualitative represent as number and percentage, quantitative continues group represent by mean ± SD, the following tests were used to test differences for significance difference and association of qualitative variable by Chi square test (X2). P value was set at <0.05 for significant results & <0.001 for high significant result.

RESULTS

In our study, PKU group diagnosed mainly during neonatal period while other groups presented more during infancy. Consanguility and positive family

history are compared between groups. The number of each group not the total number **(Table 1)**

In our study, cases in PKU group were almost normal while the most common manifestation at the time of presentation in diagnosed non PKU group was sepsis-like manifestations (poor suckling) as well as disturbed conscious level each found in 5 cases (45.45%) followed by hepatosplenomegaly as well as delayed motor milestones in 4 cases (36.36%) , also in suspected metabolic group the most common manifestation was sepsis-like manifestations (poor suckling) in 10 cases (55.5%) followed by hepatosplenomegaly in 7 cases (38.89%) **(Table 2)**.

Regarding lab investigations, routine lab showed no significant difference between 3 groups except for CRP that was significant higher in cases diagnosed metabolic non PKU, also ammonia, lactate and metabolic acidosis were significant higher in diagnosed metabolic non PKU as well as suspected not diagnosed group **(Table 3)**. A mild anemia was showed within the groups without a significant difference **(Table 4)**. Metabolic non PKU cases significantly higher regard CRP **(Table 5)**

Table (1): Relation between basic demographic data inbetween cases

	Suspected not diagnosed N=18	**Diagnosed metabolic N=47**		**Kruskal Walis/ X^2**	**P**
		Diagnosed metabolic (non pku) N=11	**Diagnosed pku by neonatal screening N=36**		
Age					
Neonate (1st month)	3 (16.67%)	3 (27.27%)	29 (80.5%)	1.92	0.75
Infant (1m. – 2y.)	12 (66.67%)	5 (45.45%)	5 (13.8%)		
Child (>2 y.)	3 (11.11%)	3 (27.27%)	2 (5.56%)		
Sex					
Male	8 (44.4%)	5 (45.45%)	17 (47.22%)	0.04	0.98
Female	10(55.5%)	6 (54.54%)	19 (52.77%)		
Consanguinity	15 (83.3%)	7 (63.63%)	23 (63.89%)	2.32	0. 31
First kid	5 (27.78%)	4 (36.36%)	13 (36.11%)	0.41	0.81
Family history					
Similar condition	8 (44.4%)	3 (27.27%)	8 (22.22 %)	2.8	0.23
Abortion	9 (50%)	5 (45.45)	9 (25%)	3.88	0.14
Sibling death	6 (33.3%)	5 (45.45%)	6 (16.66%)	4.21	0.11

Table (2): Relation between clinical data in between cases

	Suspected not diagnosed N=18	**Diagnosed metabolic N=47**		**Kruskal Walis/ X2**	**P**
		metabolic (non PKU) N=11	**PKU by neonatal screening N=36**		
Sepsis like (poor suckling or not doing well)	10 (55.5%)	5 (45.45%)	0	19.74	0.00**
Coarse features	1 (5.56%)	2 (18.18%)	0	3.03	0.22
Disturbed consciousness	6 (33.3%)	5 (45.45%)	0	13.06	0.001**
Convulsion	3 (16.6%)	2 (18.18%)	0	3.51	0.17
Respiratory distress	5 (27.78%)	2 (18.18%)	0	7.18	0.02*
Delayed motor milestones	3 (16.67%)	4 (36.36)	2 (5.55%)	6.87	0.03*
chest crepitations	5 (27.78%)	2 (18.18%)	0	7.18	0.02*
Cardiomyopathy & Heart failure	1 (5.55%)	1 (9.09%)	0	0.42	0.81
Hepato-slenomegaly	7 (38.89%)	4 (36.36%)	0	12.62	0.001**

	Suspected not diagnosed N=18	Diagnosed metabolic N=47		Kruskal Walis/ X2	P
Erythema $ patchy skin lesion	2 (11.11%)	2 (18.18%)	0	2.61	0.25
Skeletal manif	1 (5.55%)	2 (18.18%)	0	3.02	0.22
Wide Anion gap	2 (11.11%)	1 (9.09%)	0	1.41	0.49
Ketones in urine	1 (5.55%)	2 (18.18%)	0	3.02	0.22

Table (3): Lab parameters comparison in between groups

	Suspected not diagnosed N=18	Diagnosed metabolic N=47		F/X^2	P
		metabolic (non PKU) N=11	**PKU by neonatal screening N=36**		
HB (g/dL)	10.16±3.12	10.23±2.94	10.86±2.38	1.214	0.398
WBCs (X10 3/µL)	8.88±2.66	11.26±3.7	10.53±2.54	2.232	0.073
PLT (X10 3/µL)	281.92±91..3	242.18±71.3	276±87.64	2.414	0.062
Cr (mg/dL)	0.50±0.18	0.42±0.14	0.38±0.07	1.923	0.089
BUN (mg/dL)	9.76±3.38	13.34±4.51*	11.76±5.65	3.441	0.031*
Bilirubin (mg/dL)	1.13±0.41	2.62±0.72*	0.89±0.38	4.666	0.004*
T protein (g/dL)	5.73±0.65	5.58±0.8	5.98±0.74	0.958	0.487
Albumin (g/dL)	3.73±0.51	3.69±0.32	4.23±0.42	0.741	0.512
ALT (u/l)	41.6±14.6	38.48±13.66	20.63±10.86*	0.391	0.697
AST (u/l)	63.39±21.6	60.59±20.11	18.58±12.65	0.162	0.872
Ammonia (µg/dL)	470.5±156.6*	172.68±54.6		11.998	0.00**
Lactate (mmol/L)	2.81±0.91	27.65±9.58		-2.521	0.006*
RBS (mg/dl)	127.77±41.52	133.86±38.63	90.3±20.2*	-3.299	0.038*
CRP(mg/L)	16.87±27.9 14 (0.15-155)	39.3±41.32* 35 (2.6-176)	8.43±18.54 7 (0.85-168)	15.621	0.00**

Table (4): Anemia comparison between groups

	Suspected not diagnosed N=18	Diagnosed metabolic N=47		F/X^2	P
		metabolic (nonPKU) N=11	**PKU by neonatal screening (N=36)**		
HB	10.16±3.12	10.23±2.94	10.86±2.38	1.214	0.398
No anemia	3 (16.7%)	0	9 (25.0%)	4.21	0.26
Mild anemia	7 (38.8%)	6 (54.5%)	**17 (47.2%)**		
Moderate anemia	5 (27.7%)	4 (36.3%)	**10 (27.8%)**		
Severe anemia	3 (16.7%)	1 (9.0%)	**0**		

Table (5): ABG and electrolyte comparison

	Suspected not diagnosed N=18	Diagnosed metabolic N=47		F	P
		metabolic (non PKU) N=11	PKU by neonatal screening N=36		
PH	7.36±1.74	7.33±1.07*	7.37±0.42	11.014	0.00**
CO2 (mmHg)	39.1±6.64	58.54±16.99*	38.43±7.43	8.521	0.00**
HCO3 (mEq/L)	19.68±9.33	16.03±8.62*	21.64±4.32	8.410	0.00**
Na (mEq/L)	138.39±4.12	140.43±4.77	139.3±4.32	2.225	0.074
K (mEq/L)	4.12±0.81	4.31±1.37	4.32±0.54	-0.985	0.451
Ca (mEq/L)	9.45±0.99	8.7±0.85*	9.57±0.94	5.548	0.002*
Mg (mEq/L)	2.13±0.45	2.09±0.34	2.15±0.24	0.821	0.416
Ph (mg/dL)	4.71±1.07	4.59±1.14	4.93±1.74	0.413	0.718

DISCUSSIONS

Inborn errors of metabolism (IEM) are a group of inherited genetic metabolic disorders that lead to enzymatic defects in the human metabolism and form a large class of genetic diseases. In most disorders, problems arise from accumulation of substrates which are toxic to tissues and blood. IEM was classified as follows: disorders of amino acid as (maple syrup urine disease, organic acidemias, and urea cycle defects) , disorders of carbohydrate metabolism as (galactosemia and glycogen storage disorders) and disorder of lipid metabolism as (fatty acid oxidation defects [medium chain acyl-CoA dehydrogenase deficiency) **[13]**.

The study aimed to evaluate of the present status of infants with inborn errors of metabolism in Zagazig University Hospitals and emphasizing the importance of expanded early neonatal screening. Our study included 65 cases diagnosed and suspected with inborn errors of metabolism in pediatric department, Zagazig University Hospitals as a tertiary centre in Sharkia Governorate.

In our study by comparing between cases included in the study we found that age presentation in cases of PKU group was more during neonatal period 29 cases (80.5%) while in other two groups age presentation was more during infancy 12 cases (66.67%) and 5 cases (45.45%), as neonatal screening help in early detection and diagnosis of PKU cases while diagnosis of other cases detected mostly during stages of illness and decompensation. This was in agreement with **Hassan et al.[14]** who reported that PKU was the most common single IEM detected in neonates. Also **Essaam et al. [7]** who reported Median age of diagnosis of PKU for screened neonates was 7days only 15 cases were diagnosed as PKU very late with median age was 6 years.

Most of our cases in PKU group, diagnosed non PKU group and suspected metabolic group were present in females (52.77% , 54.54% , 55.5% respectively) slight higher than males (47.22% , 45.45% ,44.4% respectively), this was in agreement with **Hoell et al. [15]** and not in agreement with **Essaam et al. [7]** who reported that cases of PKU Males 39/74 (52.7%) were more than females 35/74 (47.3%).

Consanguility was positive in most cases of 3 groups (63.89 % , 63.63 % , 83.3% respectively) this was in agreement with **Essaam et al. [7]** who reported 49/61 (80.3%) consanguineous marriage in PKU cases . Also positive family history was detected in most cases either history of similar conditions (22.22% , 27.27% , 44.4%), history of abortion (25% , 45.5% , 50%) and history of previous sibling death (16.66% , 45.45% , 33.3 %). This was in agreement with **Essaam et al. [7]** who reported positive family history was 20%.

In our study, cases in PKU group were almost normal while the most common manifestation at the time of presentation in diagnosed non PKU group was sepsis-like manifestations (poor suckling) as well as disturbed conscious level each found in 5 cases (45.45%) followed by hepatosplenomegaly as well as delayed motor milestones in 4 cases (36.36%), also in suspected metabolic group the most common manifestation was sepsis-like manifestations (poor suckling) in 10 cases (55.5%) followed by hepatosplenomegaly in 7 cases (38.89%). Thus there were significant difference among groups regarding sepsis-like manifestations (poor suckling), disturbed conscious level, hepatosplenomegaly, Respiratory distress, Delayed motor milestones, chest crepitations. This was in agreement with **Gu et al. [16]** who reported that many patients diagnosed PKU who were detected by neonatal screening and treated early had a good physical and nearly normal

mental development. This indicates that early detection and diagnosis of metabolic diseases improve their outcome.

Regarding lab investigations routine lab showed no significant difference between 3 groups except for CRP that was significant higher in cases diagnosed metabolic non PKU, also increased levels of ammonia, lactate and metabolic acidosis were significant higher in diagnosed metabolic non PKU as well as suspected not diagnosed group. This was in agreement with **Gu et al. [16]** who reported that many patients diagnosed PKU by neonatal screening had normal lab findings.

CONCLUSIONS

Inborn errors of metabolism (IEMs) are rare diseases worldwide and usually presented with poor suckling and lethargy and diagnosed during infancy period. Early diagnosis of metabolic diseases and starting its proper treatment improve outcome and decrease morbidity and mortality rates.

Conflict of Interest: Nil

Financial Disclosures: governmental, Faculty of medicine Zagazig university

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