Nutritional Assessment of patients with Inborn Errors of Metabolism Attending Maternity and Children Hospital in Makkah, Saudi Arabia: A Preliminary Study

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Abstract: Background: Inherited metabolic disorders are a heterogeneous group of genetic conditions mostly occurring in childhood. **Objectives:** To assess the nutritional status of children with inborn errors of metabolism (IEM) attending the pediatric outpatient clinic of Maternity and Children Hospital in Makkah, Saudi Arabia. **Subjects and methods**: A Cross-sectional study was carried out including 24 patients with IEM. A questionnaire was designed to collect demographic, medical, and dietary histories. Weight for age, height for age, weight for height, and BMI for age Z scores were carried out using the WHO Anthro Plus. Analysis of red blood cell indices was done in the hospital lab. **Results:** Cases were identified as 7 patients with maple syrup urine disease (MSUD), 5 patients phenylketonuria (PKU), 4 patients methylmalonicacidemia (MMA), and 3 patients propionic acidemia (PA). One case of biotinidase deficiency, isovalericacidemia, tyrosinemia, 3-Methylcrotonylglycinuria (3MCG) and galactosemia. The age of children ranged between1 month to 14.5 years. Stunting was evident in (75%) and (60.0%) of patients with MMA, and PKU, respectively. Moreover, (50.0%), (40.0%), and (33.3%) of cases of MMA, MSUD, and PA respectively had wasting. In addition, (66.7%) of cases of PA and (57.1%) of cases of MSUD were underweight. Anemia was detected in children below 2 years with a mean haemoglobin of (10.3 g/dl ± 2.8), and a mean haematocrite value of (32.6 % ±7.5).**Recommendations**: Nutritional surveillance for patients with IEM to support adequacy of nutrient intake and to guarantee growth within the relevant standards is required.
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Key words: Inborn errors of metabolism, growth retardation, dietary intake, nutritional management, anthropometric assessment, blood indices.

1. Introduction

Inborn errors of metabolism (IEM) individually are rare but collectively are common. Presentation is usually in the neonatal period or infancy but can occur at any time, even in adulthood. (Weiner, 2012). Genetic diversity among Arabs, high rates of inbreeding and large family size are optimal for the manifestation of many autosomal recessive disorders including IEM(Teebi, 2010).

Incidence of inherited metabolic disorders varies considerably among countries(Pourfarzam & Zadhoush, 2013), in United States the incidence is estimated to be approximately 1 in 4000 live births. The frequencies for each individual inborn error of metabolism vary, but most are very rare. (Weiner, 2012). The incidence of metabolic diseases in some Arab countries was 1:1327 in Qatar, 1:1,381 in Saudi Arabia, and 1:1555 in Oman(Al-Qa'qa', et al., 2012).

Nutrition therapy is integral to the treatment of IEM. Nutrition therapy should both correct the metabolic imbalance and ensure normal growth and development among affected individuals. Continual monitoring of nutrient intake, laboratory values, and the individual's growth are needed for evaluation of the adequacy of the prescribed diet (Hendricks & Duggan , 2005).

Objectives

This study was designed to assess the nutritional status of children with inborn errors of metabolism attending the pediatric outpatient clinic of Maternity and Children Hospital in Makkah, Saudi Arabia.

2. Subjects and Methods

Study design and setting

From July 2012 to October 2013, a cross sectional studywascarried out with cooperation ofpediatricnutritional clinic and metabolic specialists at Maternity and Children Hospital in Makkah, Saudi Arabia.

Subjects

We started by attending the pediatric nutritional clinic of the hospital to define patients with IEM. A total of 40 patients with IEM were identified, however only 24children with IEM disease were included in

this study (10 females and 14 males) as 10 of the patients were inaccessible; 3 cases with isovaleric academia, and 1 case in each of maple syrup urine disease (MSUD), methylmalonicacidemia (MMA), propionic acidemia (PA), glutaricaciduria type 1, glycogen storage disease, mucopolysaccharidosis and, 3hydroxyl-methyl glutaricaciduria (3HMG)), 3 were expired during the study (diagnosed with Glutaricaciduria, (PA), and Urea cycle disorder) and 3 with missed diagnosis.

Ethical clearance was obtained from the Maternity and Children Hospital board. Formal letters were given to the medical director and consent was obtained. Verbal consent was also obtained from parents of participants who were assured of confidentiality and anonymity.

Methods

Questionnaire

To standardize data collection a questionnaire was designed which was filled in the nutrition clinic. This questionnaire included the following sections:

a) General characteristics: date of birth, gender, mother's age at birth, order of birth, gestational age, degree of consanguinity among parents etc.

b) IEM information: type, signs and symptoms, and age at diagnosis.

c) Dietary history: this was further classified into:

i. Food frequency questionnaire; the results of this questionnaire was not proceeded in final results due to incompleteness of records.

ii. Types of formulas:special, standard, and modular formulas.

Section (a) and (c) were fulfilled by face to face interview with parents of cases, while section (b) was taken from the medical records.

Anthropometric Measurements

a) Weight; to weigh infants and children who cannot stand we used a pediatric scale that is accurate to within 0.01 kg. For older children who can stand, we used an electronic scale that is accurate to within 0.1 kg (Yang, et al., 2010).

b) Height or length was measured to the nearest 0.1 cm. For children below 2years, recumbent length was measured with an anthropometric ruler. For children over 2 years old, a stadiometer available at the nutritional clinic was used for measuring standing height (Fisberg, et al., 1999).

The calculations of the anthropometric ratios of weight for age, height for age, weight for height, and BMI for age in the form of z scores were carried out using the computer software *WHO AnthroPlus version 3.2.2*.This module facilitates deriving nutritional status results for an individual child or adolescent based on the WHO standards (0-5 years) or WHO reference (5-19 years).The z-scores appear as not available (NA) if there is missing data or the raw data are beyond the standard/reference tables' ranges(WHO, 2009).

The WHO Global Database uses a Z-score cut-off point of <-2 SD to classify underweight (low weight-for-age), stunting (low height-for-age), wasting (low weight-for-height) and thinness (low BMI-for-age), and <-3 SD to define severe undernutrition. The cut-off point of >+2 SD classifies high weight-for-height, weight-for-age and BMI-for-age as overweight or obese, and tall for high height-for-age in children (Stephanie, 2011)

Laboratory investigations

Hematological indices including: Hemoglobin (Hb), Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin (MCH), Mean Corpuscular Hemoglobin Concentration (MCHC), Red Blood Cell (RBC) count and Hematocrit value (HCT), were analyzed in the lab of the hospital, patients were given appointment for lab test. This investigation was done for 18 patients out of the 24 cases involved in the study as 6 patients refused to come.The results were compared with standard normal ranges for age and gender (Ordooei, et al., 2012). The lower limit of the normal range is set at two standard deviations below the mean for age and sex for the normal population (Lanzkowsky, 2011).

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Science (SPSS) version 16.0 (SPSS Inc., Chicago, IL, USA.). Quantitative data were presented as mean and standard deviation. Qualitative data were expressed as percentages. For comparing the groups, the chi-square test was used for qualitative variables and the ANOVA or Kruskal-Wallis test for quantitative variables. $P < 0.05$ was considered to indicate statistical significance.

3. Results

Types of IEM diseases:

The study sample comprised 24 patients with IEM namely; 14(58.3%) patients with disorders of amino acid metabolism (7 patients (29.2%) MSUD, 5 (20.8%) PKU, 1 (4.2%) tyrosinemia, and 1(4.2%) 3MCG), 8(33.3%) patients with disorders of organic acid metabolism (4 (16.6%) MMA, 3 (12.4%) PA and 1 (4.2%) isovalericacidemia). Disorders of carbohydrate metabolism represented by 1 (4.2%) case of galactosemia, and disorders of urea cycle metabolism represented by 1(4.2%) case of biotinidasedeficiency (Figure1&2).

General characteristics of the studied sample:

Table (1) presents the generalcharacteristics of the studied patients; 14 patients (58.3%) were males and 10 (41.7%) were females.Most of the studied patients (75%) aged 24 months or less, age at diagnosis ranged between 1 day and 6 years with a

median of one day. Parental consanguinity was reported by (91.7%) where 19 (79.2%) were 1st Cousins. Family history of the same disease was reported by parents of 11 patients (45.8%).

Table (2) shows that maternal age at birth ranged between 22 to 44 years with a mean of 30.4 years ± 5.0. Eleven mothers (45.8%) gave history of abortion either once (33.3%), twice (8.3%) or thrice (4.2%). Moreover, 6 mothers (25.0%) had given birth of 1 to 2 died children.

Table (1): Socio-demographic characteristics and family history of studied patients (n=24)

Variables	No	%	
Agegroupsin months			
0-6	7	29.2	
>6-12	5	20.8	
>12-24	6	25.0	Range (1month -14.5 years)
>24-48	3	12.5	Mean (25.1± 37.3months)
>48	3	12.5	Median (12.5 months)
Gender			
Male	14	58.3	
Female	10	41.7	
Age at diagnosis			
1 week	14	58.3	Range (1 day – 6 years)
7- <28 days	4	16.7	Mean (5.2± 16.0 months)
≥ 28 days	6	25.0	Median(1 day)
Nationality			
Saudi	23	95.8	
Non- Saudi	1	4.2	
Family income (Saudi Riyal)			
<3000	7	29.2	
3000-5000	14	58.3	
>5000	3	12.5	
Father education level			
Illiterate/primary	3	12.5	
Intermediate/ Secondary	9	37.5	
University	12	50.0	
Mother education level			
Illiterate/primary	7	29.2	
Intermediate/ Secondary	3	12.5	
University	14	58.3	
parental Consanguinity			
Yes	22	91.7	
No	2	8.3	
degree of consanguinity			
1st Cousins	19	79.2	
2nd Cousins	3	12.5	
Non-consanguineous	2	8.3	
Family history of the samedisease			
Yes	11	45.8	
No	13	54.2	
Family history of other congenital diseases			
Yes	3	12.5	
No	21	87.5	

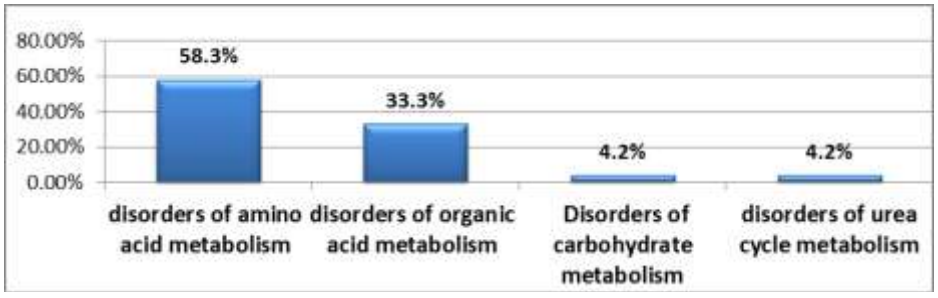

Figure (1): Categories of IEM diseases

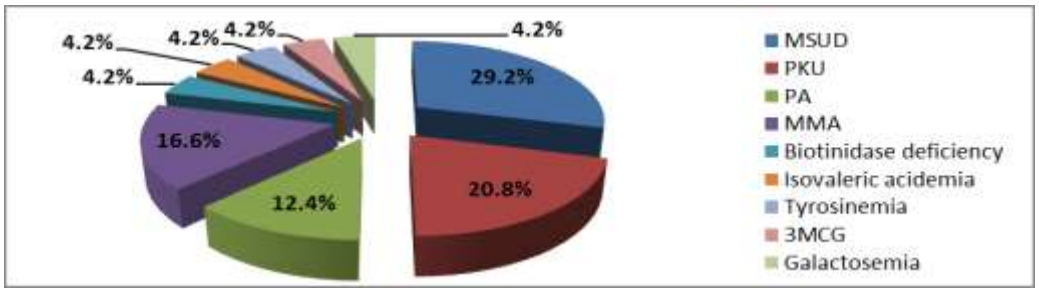

Figure (2): Types of metabolic diseases among the studied cases

Table (2): Maternal characteristics of the studied cases (n=24)

Variables	No	%
Mother age at birth (years)		
< 35	21	87.5
≥35	3	12.5
Mean 30.4± 5.0		
Range (22.0-44.0)		
Order of birth of the IEM case		
1	9	37.5
2	3	12.5
≥3	12	50.0
Gestational age		
Pre-term	1	4.2
Full-term	23	95.8
No. of full-term births		
None	1	4.2
1	9	37.5
2	2	8.3
3	5	20.8
≥4	7	29.2
No. of abortions		
1	8	33.3
2	2	8.3
3	1	4.2
None	13	54.2
No. of died children		
1	3	12.5
2	3	12.5
None	18	75.0

Clinical manifestations of the studied cases

Results shows that, the most frequent clinical manifestations at time of diagnosis were lethargy, unexplained neurological signs and persistent vomiting (16.7% for each), followed by unexplained developmental delay (12.5%), and poor feeding, seizure, hair changes and jaundice (8.3% for each) (data not shown).

Table (3) shows the presenting signs and symptoms and age at diagnosis for the different cases of IEM. The most common presentations for PKU cases were unexplained developmental delay, and hair changes (40.0% for each), for cases of MSUD seizures were the most common represented (28.6%). For cases of MMA equal percentage was reported for ophthalmic abnormalities, coma, persistent vomiting, lethargy, hyperammonemia, thrombocytopenia, shortness of breath, cardiovascular disease and cognitive impairment, while (66.7%) of PA cases presented with lethargy. Late onset for diagnosis was reported for cases of PKU, MMA, and tyrosinemia.

Special and modular formulas for IEM cases

Table (4) reviews special formulas suitable for each disease. For PKU disease, 4 patients were using Phenex-2 and one patient was using Phenex-1. The cases of isovalericacidemia, and tyrosinemia were using Valex-2 and Tyrex1 designed for infants and toddlers, respectively. Regarding MSUD disease, 5

patients were using Ketonex-2 and 2 patients were using Ketonex-1.For PA, 2 patients were on Propimex-1 and one patient was using Propimex-2. Among MMA cases 3 patients were on Propimex-2 and 1 patient was using Propimex-1. Ronalac lactose free formula was used by the case of galactosemia. Regarding the modular formulas, Polycose was the one used by most of the cases.

Table (3): Clinical manifestations of IEM cases presented by patients according to the type of disease (n=24)

Diseases	Clinical manifestations	%	Age at diagnosis
PKU **No.= 5**	(Unexplained developmental delay and hair change) (Unexplained neurological signs and jaundice)	40.0%* 20.0% *	(1day – 6 years)
MSUD **No. = 7**	Seizures (Unexplained neurological signs, unexplained developmental delay, skin changes and diarrhea)	28.6% 14.3%*	(1 day – 2weeks)
MMA **No. = 4**	Ophthalmic abnormalities, coma, persistent vomiting, lethargy, hyperammonemia,thrombocytopenia, shortness of breath, cardiovascular disease and cognitive impairment	25.0% *	(1 day-7months)
PA **No. = 3**	Lethargy (Persistent vomiting,metabolicacidosis,hypoglycemia,tachypuoea,unexplained neurological signs and poor feeding)	66.7% 33.3%*	(1-6weeks)
Isovaleric academia **No. = 1**	Persistent vomiting,lethargy	100.0%	10 day
Biotinidase deficiency **No. = 1**	Persistent vomiting, unexplained neurological signs, poor feeding	100.0%	35 day
Tyrosinemia **No. = 1**	Rickets, failure to thrive, abdominal distention, neurodegeneration	100.0%	4 months
Galactosemia **No. = 1**	Jaundice	100.0%	1day
3MCG **No. = 1**	No clinical manifestations	100.0%	1day

*****percentage for each clinical manifestation

Table (4): Distribution of cases of IEM as regard special and modular formulas (n=24)

Special formulas*	No	%	Modularformulas	No	%
PKU			Prophree	1	20.0
Phenex-1	1	20.0	Polycose	3	60.0
Phenex-2	4	80.0	None	1	20.0
Isovalericacidemia					
I- Valex-2	1	100.0	Polycose	1	100.0
Tyrosinemia	1	100.0			
Tyrex1			Polycose	1	100.0
MSUD			Prophree	1	14.3
Ketonex-1	2	28.6	Polycose	4	57.1
Ketonex-2	5	71.4	None	2	28.6
PA			Prophree	1	33.3
Propimex-1	2	66.7	Polycose	2	66.7
Propimex -2	1	33.3			
MMA			Prophree	1	25.0
Propimex-1	1	25.0	Polycose	2	50.0
Propimex -2	3	75.0	None	1	25.0
Galactosemia	1	100	None	1	
Ronalac (lactose free)					
Biotinidase deficiency	1	100.0		1	100.0
3MCG			None		
None	1	100.0		1	100.0

***** Each formula followed by a number that stand for the age group suitable for it (1 mean that formuladesigned for infants and toddlers, and 2 for children and adults)

Anthropometric assessment

Table (5) displays the WHZ levels of patients with IEM. Over weight patients represented (1/4; 25.0%) of cases of PKUand MMA, on the contrast (2/4; 50.0%), (2/5; 40.0%), and (1/3; 33.3%) of patients with MMA, MSUD, and PA respectively had wasting. on the other hand high percentage of cases of PKU (3/4; 75.0%), PA (2/3; 66.7%), and MSUD (3/5; 60.0%) had normal WHZ. However, the difference between the IEM diseases as regarding the WHZ levels was not significant (p > 0.05).

Table (5): Weight for Height z-scores for patients with IEM

	PKU (n= 5)		MSUD (n= 7)		MMA (n=4)		PA (n= 3)		Test	p
	No	%	No	%	No	%	No	%		
WHZ										
< -2	0	0.0	2	40.0	2	50.0	1	33.3	X^2=	0.56
-2 to +2	3	75.0	3	60.0	1	25.0	2	66.7	4.84	
> +2	1	25.0	0	0.0	1	25.0	0	0.0		
Range	(-0.96)-(3.35)		(-7.36)-(1.84)		(-4.80)-(2.99)		(-5.36)-(0.46)			
Mean ±SD	0.56 ±2.00		-2.36 ± 4.08		-1.13 ± 3.28		-1.70 ± 3.18		F=0.61	0.62

WHZ: Weight for height z-score. The z-scores appear as not available (NA) for one case of PKU and two cases of MSUD. X^2: Chi square test.

Table (6) shows that high percentage of cases of PA, and MSUD (2/3; 66.7%), (4/7; 57.1%) respectively were underweight, while normal WAZ was found in (3/4; 75.0%) of cases of both PKU and MMA. However, the difference between the IEM diseases as regarding the WAZ levels was not significant (p > 0.05).

Table (6) Weight for age z-scores for patients with IEM

	PKU (n= 5)		MSUD (n= 7)		MMA (n= 4)		PA (n= 3)		Test	p
	No	%	No	%	No	%	No	%		
WAZ										
< -2	1	25.0	4	57.1	1	25.0	2	66.7	X^2=	0.18
-2 to +2	3	75.0	3	42.9	3	75.0	0	0.0	8.84	
> +2	0	0.0	0	0.0	0	0.0	1	33.3		
Range	(-2.78)-(0.96)		(-6.07)-(-0.09)		(-3.38)-(-0.23)		(-4.28)-(3.62)			
Mean (SD)	-0.82 ± 1.83		-2.85± 2.49		-1.63 ± 1.35		-1.42 ± 4.38		F=0.61	0.62

WAZ: Weight for age z-score. The z-scores appear as not available (NA) for one case of PKU.X^2: Chi square test.

Table (7) presents the distribution of cases according to their HAZ. Stunting was detected more in patients with MMA (3/4; 75.0%), and PKU (3/5; 60.0%), while (4/7; 57.1%) of cases with MSUD, and (2/5; 40.0%) of cases of PKU had normal HAZ. However, the difference between the IEM diseases as regarding the HAZ levels was not significant (p > 0.05).

Table (7) Height for age z-scores for patients with IEM

	PKU (n= 5)		MSUD (n= 7)		MMA (n= 4)		PA (n= 3)		Test	p
	No	%	No	%	No	%	No	%		
WAZ										
< -2	1	25.0	4	57.1	1	25.0	2	66.7	X^2=	0.18
-2 to +2	3	75.0	3	42.9	3	75.0	0	0.0	8.84	
> +2	0	0.0	0	0.0	0	0.0	1	33.3		
Range	(-2.78)-(0.96)		(-6.07)-(-0.09)		(-3.38)-(-0.23)		(-4.28)-(3.62)			
Mean (SD)	-0.82 ± 1.83		-2.85± 2.49		-1.63 ± 1.35		-1.42 ± 4.38		F=0.61	0.62

HAZ: Height for age z-score. X^2: Chi square test.

Table (8) shows that high percentage of cases of PKU, MMA and PA had normal BAZ (4/5; 80.0%), (3/4; 75.0%), (2/3; 66.7%) respectively. On the other hand, (3/7; 42.9%) of cases with MSUD, (1/3; 33.3%) of cases of PA, and (1/4; 25.0%) of cases of MMA

were thin. Despite this apparent difference between cases, this result was insignificant (p>0.05).

Table (8) Body Mass Index for age z-scores for patients with IEM

	PKU (n= 5)		MSUD (n= 7)		MMA (n=4)		PA (n= 3)		Test	p
	No	%	No	%	No	%	No	%		
BAZ										
< -2	0	0.0	3	42.9	1	25.0	1	33.3	X^2=	0.66
-2 to +2	4	80.0	3	42.9	3	75.0	2	66.7	4.14	
> +2	1	20.0	1	14.2	0	0.0	0	0.0		
Range	(-1.93)-(3.51)		(-7.25)-(2.39)		(-5.37)-(1.78)		(-5.65)-(-0.46)			
Mean ±SD	0.34 ± 2.14		-1.51 ± 3.78		-1.49 ± 2.99		-2.22 ± 2.97		F=0.54	0.67

BAZ: Body Mass Index for age Z-score. X^2: Chi square test.

Results of z scores for patients with biotinidase deficiency, isovalericacidemia, tyrosinemia, 3MCG, and galactosemia are presented in Table (9); the z-score levels ofpatients with BD, galactosemia, and tyrosinemia fell all within the normal range, while z-score levels of isovalericacidemia patient revealed that the patient had wastingand thin, and that the 3MCG patient was stunted.

Table (9): Z-scores for children with biotinidase deficiency, isovalericacidemia, tyrosinemia, 3MCG, and galactosemia (n=1 for each)

Diseases	Weight (kg)	Height (cm)	WHZ	WAZ	HAZ	BAZ
Biotinidase deficiency	10.70	85.00	-0.59	0.33	1.50	-0.76
Isovaleric academia	9.40	82.00	-2.26	-0.39	3.14	-2.99
Tyrosinemia	14.50	90.00	1.44	0.72	-0.58	1.56
3MCG	6.00	59.00	0.59	-1.73	-2.89	-0.01
Galactosemia	14.00	94.00	0.16	-0.20	-0.57	0.20

WHZ: Weight for height z-score. WAZ: Weight for age z-score. HAZ: Height for age z-score.
BAZ: Body Mass Index for age z-score.

Haematological indices for cases of IEM

Table (10) presents the different haematological indices for cases of IEM. The subjects were sorted into 3 groups defined by age, the mean value for each age group were compared with the normal range. The mean levels of the studied indices were within the normal range for (27.8%) of the cases. However, the mean values of HGB and HCT for children aged below 2 years were lower than the normal range (10.3 ± 2.8 and 32.6 ±7.5) respectively.

Table (10): Mean and standard deviation of red blood cell indices among the studied patients (n=18)

Age groups	No	%	RBC (10^{12}\L) Mean (SD)	HGB (g\dL) Mean (SD)	HCT (%) Mean(SD)	MCV (fl) Mean (SD)	MCH (pg) Mean(SD)	MCHC (g/dl) Mean (SD)
0.5 - <2 y	13	72.2	4.2 (0.9)	10.3 (2.8)	32.6 (7.5)	78.3 (15.7)	25.2 (6.09)	31.9 (2.1)
2 - <6 y	4	22.2	4.8 (0.3)	12.5 (1.1)	39.5 (1.0)	83.1 (3.9)	26.2 (2.1)	31.4 (2.3)
6 -12y	1	5.6	4.8	13.1	40.4	84.8	27.5	32.4
Total	18	100	4.3 (0.8)	11.0 (2.6)	34.6 (7.1)	79.8 (13.5)	25.5 (5.2)	31.8 (2.0)

y: years

Table (11) shows the different red blood cell indices for the different IEM cases. Significant difference was found between cases of PA and MMA regarding both MCH, and MCHC (p<0.05). However, no difference was detected between IEM cases regarding the other indices (p>0.05). In addition, the mean hemoglobin levels for cases of MSUD, MMA, and biotinidase deficiency were all below normal.

Table (11): Mean and standard deviation of red blood cell indices of individual diseases of IEM (n=18)

Diseases	No	RBC (10^{12}\L) Mean (SD)	HGB (g\dL) Mean (SD)	HCT (%) Mean (SD)	MCV (fl) Mean (SD)	MCH (pg) Mean (SD)	MCHC (g/dl) Mean (SD)
MSUD	4	4.2 (0.9)	10.4 (2.2)	32.5 (6.1)	79.8 (18.4)	25.6 (5.6)	32.0 (1.3)
PKU	3	4.7 (0.1)	11.6 (0.7)	37.5 (2.3)	80.4 (6.2)	24.9 (1.9)	31.1 (2.7)
PA	3	3.7 (1.0)	11.7 (4.4)	34.2 (11.8)	87.8 (17.4)	29.7[a] (7.3)	33.6[a] (1.7)
MMA	4	4.3 (0.9)	8.9 (2.9)	29.2 (7.3)	67.7 (10.2)	20.5[b] (4.1)	30.2[b] (2.2)
Biotinidase deficiency	1	3.3	10.4	36.9	95.1	32	34
Isovaleric academia	1	5.3	13.0	42.8	81.3	24.8	30.5
Tyrosinemia	1	4.7	13.3	40.7	89.9	28.3	32.5
Galactosemia	1	5.2	13.4	40.0	77.7	26	33

SD: Standard deviation. Values with different superscript letters in the same column are significant at p <0.05 (2-tailed)

4. Discussion

Inborn errors of metabolism, a group of genetic disorders, affect various biochemical pathways in the body. Early diagnosis followed by initiation of disease-specific management may help improve survival in these patients (Choudhry, et al., 2013).

It was reported that the high incidence of pediatric congenital or genetically-determined disorders in Arabian Peninsula resulted from the heavy consanguineous marriages and the tribal nature of the marriages.Al-Aqeel (2004), reported that Middle East countries including Saudi Arabia had first cousin marriages account for 60 -70% of all marriages (Al-Aqeel, 2004; Al Bu Ali, et al., 2011).

The current study revealed that parental consanguinity constitutes 91.7% of the studied sample of whom first cousin was the most. A study conducted in the Maternity Hospital in Al Ahsa, Eastern Region, Saudi Arabia in 2011, reported that consanguinity represented the most significant risk factor for inborn errors of metabolism found in 54.0% of cases of IEM (Al Bu Ali, et al., 2011). Similar results were reported from Oman (Joshi, et al., 2002), and in Jordan another study conducted at King Hussein Medical Center where, parental consanguinity was noted in 137 out of 151 families (Al-Qa'qa', et al., 2012).

Although metabolic diseases are inherited, symptoms often are not present at birth. Age for presentation varies for individual IEM and variant forms within the IEM. The timing of presentation depends on significant accumulation of toxic metabolites or on the deficiency of substrate. (Rao, et al., 2009).

In the present study (75.0%) of the cases presented in the neonatal period with 58.3% presented in the first week (age at presentation varied from the first day to six years; median one day), this result goes in accordance with(Al Riyami, et al., 2012), however inconsistent with Al-Qa'qa et al, (2012) who reported a relatively late age at the diagnosis of patients with IEM, with a mean age at diagnosis of 11.8±11.1 months (range 1-50 months) (Al-Qa'qa', et al., 2012). As shown by a number of researchers, newborn screening would diagnose a significantly higher number of cases, with significantly more favorable prognosis and this highlights the importance of screening (Wilson, et al., 2007). In view of this, The Saudi National Newborn Screening program has been implemented to detect and prevent selected congenital and heritable disorders.

Moreover, many symptoms prominent in patients with inborn errors of metabolism are not very specific and can be caused by more common conditions, (De Meirleir, 2005). It is therefore very important to be familiar with the major signs and symptoms of these diseases and with the initial laboratory workup necessary to arrive at an initial diagnosis (Glass, et al., 2006).

The most frequent clinical findings as presented in the current study were lethargy, unexplained neurological signs and, persistent vomiting (16.7% for each), developmental delay (12.5%), followed by poor feeding, seizures, hair changes, and jaundice (8.3% for each). A study conducted in São Paulo, in Brazil on (101) neonates reported that hypoglycemia (61.4%) as the most common followed by jaundice (55.4%), metabolic acidosis (50.5%), respiratory disturbance (43.6%), and seizures (13.9%)(De Oliveira, et al., 2001).Another study conducted by Raoand his colleagues (2009) reported that the most

common presentations were (10.6%) seizures, (7.2%) metabolic acidosis, (6.4%) lethargy, (6.0%) delayed milestones, (4.3%) poor feeding(Rao, et al., 2009).

Nutritional status, especially in children has been widely assessed by anthropometric measures in both developing and developed countries. Expressing anthropometric measures in terms of z-scores is recommended by the World Health Organization (WHO)(Markowitz, et al., 2008).

. Growth retardation was observed in PKU patients in comparison with a reference population. Several independent European studies have arrived at the same conclusion for PKU patients treated with a Phe-restricted diet. They found similar growth retardation between the first and third years of life (Dobbelaere, et al., 2003).

The current study showed similar results where, 3/5 (60%) of PKU patients were stunted. Sibinga et al, while studying 60 children with PKU receiving treatment, found a substantial growth decrease (weight and height), regardless of the age at which the diet was initiated. When these results were compared to those from other centers, they concluded that phenylketonuria, was associated with height decrease(Fisberg, et al., 1999)**.** Similar results were reported by Dobbelaere, and his colleague (2003) who found the height/age z-score means were significantly lower in the PKU children than in the normal controls(Dobbelaere, et al., 2003).

Growth retardation was evident among cases of MSUD, where 4/7 (57.1%) of patients were underweight, 3/7 (42.9%) of patients were stunted, and 3/7 (42.9%) of patients were thin. Moreover 2/5 (40%) of patients had wasting.Reports from the 70s showed that patients with MSUD were not above the 25 percentile in weight or height. A study reported in the 90s involved 12 children with MSUD in the age range of 2.8 to 11 years revealed that they were shorter than normal (Brubacher, 1997).

Impaired physical development is a common problem in patients with PA. Grünert et al. (2013), have reported a tendency towards decreased body height in PA patients.In accordance with these studies, and despite of the few number of PA cases, our data are indicative of growth retardation in PA patients, where most PA patients were underweight; 2/3 (66.7%) had low weight/age, and 1/3 (33.3%) had low weight for height, height for age, and BMI for agewhich indicate wasting, stunting and thinness respectively. Failure to thrive has been postulated to be due to iatrogenic dietary protein restriction, frequent infections and metabolic decompensations(Grünert, et al., 2013)

Early invention and adequate nutrition management can result in normal growth and outcome in patients with MMA. Nonetheless, malnutrition and growth retardation are still frequently reported in these patients and adversely affect clinical outcome. Clinical symptoms of metabolic decompensation, including hyperammonemia and metabolic acidosis have been reported as a consequence of protein over-restriction and subsequent malnutrition. Long-term protein-energy malnutrition can lead to a decline in mental and physical development (Yannicelli, 2010).

Similarly in the current study results shows growth retardation in MMA patients; 2/4 (50.0%) had wasting, and 3/4 (75.0%) of MMA patients werestunted, and1/4 (25.0%) had low weight for age and BMI for ageindicating underweight and thinness respectively.

Previous studies have emphasized that children with isovaleric acidemia may fail to gain weight and grow at the expected rate (failure to thrive) and often have delayed development (Dinesh, et al., 2005). Similarly the isovaleric acidemia patient presented in the current study had moderate wasting and thinness with low weight /height (WH*Z;* -2.26), and BMI for age (BAZ; -2.99).

Haematological abnormalities that can be seen in many of the metabolic disorders due to congenital or acquired haematological diseases are still neglected. Additionally, if patients with various metabolic disorders are closely monitored and comply with the recommended diet, they might not have any nutritional anaemias(Tavil, et al., 2006).

In the current study anemia was detected in children below two years of age (72.2%) where their mean HB level (10.3g/dl ± 2.6) was 2 SD below the normal range. In addition, it was evident among patients with MSUD, and MMA (mean HB level 10.4 ± 2.2 and 8.9 ± 2.9 g/dl) respectively, however we cannot do further investigations to define the type of anemia.

Various cytopenias, have been reported in association with organic acidemia, particularly methylmalonic, propionic and isovalericacidemia(Guerra-Moreno, et al., 2003; Tavil, et al., 2006). This haematological picture results from the metabolic imbalance of the patient with organic academia(Hoffmann, 2002).

Arnold and colleagues (2001) reported that 6 (15%) out of 41 children with PKU had anaemia. They considered that restricted diet and combined depletion of iron and protein stores were most likely to result in anaemia. This results disagree with our finding, where all patients with PKU (n= 3) were normal. However, this can be explained by the small number of cases with PKU.

Conclusion

In conclusion growth retardation and anemia were observed in this preliminary study,

howeverresults of this study may not be amenable for generalization because of restricting participants to cases of one hospital, but it does add a piece of information to what is currently present.

Recommendations

1) Conduct a multicenter study with adequate sample from different regions to get results more amenable for generalization.

2) Set nutritional educational programs to improve public awareness of IEM disease and the nutritional management for each disease.

3) Emphasize premarital, preconception and prenatal genetic education and genetic counseling programs delivered at, family and community levels to facilitate the prevention of IEM.

4) Conduct nutritional surveillance for patients with IEM to support adequacy of nutrient intake and to guarantee growth within the relevant standards.

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