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ORIGINAL ARTICLE

Demographic Features of Phenylketonuria (PKU) Patients, Sharkia Governorate, Egypt

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ABSTRACT

Background: Phenylketonuria (PKU) is an autosomal recessive disease. Early diagnosis could act as an effectual public health intervention in order to prevent neurological impairments.

Aim: Demonstration of epidemiological data of early treated PKU children in Sharkia Governorate and evaluation of their nutritional status and anthropometric measures in relation to metabolic control.

Methods: This is a cross sectional study that was conducted on 64 early diagnosed and treated PKU patients. They were recruited from the clinical genetics and metabolic disorders outpatient clinic in Zagazig University Children Hospital. The patients were divided into two groups: group 1:included 30 early treated and metabolically controlled PKU and group 2: included 34 early treated PKU patients with poor metabolic control.

Results: There is statistically significant relation between metabolic control and gender (Females showed higher prevalence among patients with good control). There is statistically significant relation between control and alkaline phosphatase, mean PHE and PHE/TYR (alkaline phosphatase, mean PHE and PHE/TYR were significantly lower in patients with good control).There is high percentage of consanguinity among Egyptian PKU patients.

Conclusions: The number of early diagnosed and treated PKU patients is increasing in Egypt since the application of NBS in 2015 allowing further studies on early treated Egyptian PKU patients including their metabolic control, psychological assessment and nutritional status.

Keywords: Metabolic;Phenylketonuria,;Mental retardation

INTRODUCTION

A metabolic disorder known as phenylketonuria (PKU) is brought on by a lack of the enzyme phenylalanine hydroxylase (PAH), which converts phenylalanine to tyrosin. High quantities of phenylalanine are brought on by this enzyme deficit in the blood [1].

The majority of patients are expected to suffer from significant neurological abnormalities, lower IQs, and mental retardation if they are not treated. On the other hand, it is thought that receiving proper care during the first two weeks of life could significantly change the disease's course [2].

One crucial step is to diagnose the illness as soon as possible, ideally in the first few days of life. So, for the past 50 years, newborn screening has gained widespread recognition as an essential public health measure [3]. Neonatal screening was recommended by the US Preventive Services Task Force (USPSTF) as an A- category intervention with a high confidence of benefits. Numerous studies have examined the benefit-cost ratio of PKU screening, and many of them have confirmed the method's significant advantages [4].

The incidence of PKU varies based on the global location, from one per 10,000–20,000 live births. The prevalence of the condition is estimated to range from one per 4000 live births in Northern Ireland to one per 71000 live births in Finland, depending on the country and race of the patients [5]. In European and American countries, the prevalence is as high as one every 10000–20000 live births.

In these areas, consanguineous marriages are recognized as one of the major causes of PKU [5]. High amounts of phenylalanine are caused by a PAH enzyme shortage in the blood and other bodily fluids, particularly the CSF and urine [6].

Furthermore, by creating an imbalance in the central nervous system, hyperalaninemia is known to result in issues like seizures, microcephaly, and severe mental impairment. Among the mentally handicapped who were institutionalized in long-term care facilities, there was a reportedly greater incidence of PKU [7].

It is assumed that PKU is more common in newborns from consanguineous marriages. A high prevalence of the disease is directly correlated with a high rate of marriages between relatives[8].

Mental retardation is the disease's most noticeable sign. PKU patients were found to have lower IQs, weaker verbal functions, poorer attention spans, and less developed motor control skills when compared to the control group [9].

A few months after birth is when developmental impairment first appears. Vomiting, eczema rashes, severe mental impairment, urine stench, convulsions, and cutaneous hypopigmentation are a few of the condition's typical symptoms. Patients with PKU also frequently exhibit hyperactivity [10].

Hyperalaninemia is the primary factor used in the diagnosis of PKU, an autosomal recessive condition. Limiting phenylalanine intake is thought to lower blood levels of this amino acid, minimizing neurological damage. To the best of our knowledge, managing phenylalaninemia before the end of the first month of life is the most effective way to prognosticate the illness [11].

The current study aimed to demonstrate of epidemiological data of early treated PKU children in Sharkia Governorate and evaluate of their nutritional status and anthropometric measures in relation to metabolic control.

METHODS

This is a cross sectional study that was conducted on 64 early diagnosed and treated PKU patients. They were recruited from the clinical genetics and metabolic disorders outpatient clinic in Zagazig University Children Hospital , during the period from May 2023 to January 2024.

The patients were divided into two groups: group 1:included 30 well metabolically controlled early diagnosed and treated PKU and group 2: included 34 poor metabolically controlled early diagnosed and treated PKU .

Early treated PKU cases diagnosed by national neonatal screening program, aged between 3 and 7 years old of both genders were included in the study.

Patients with BH4 deficiency treated with BH4 replacement therapy, BH4 responder patients, late diagnosed or untreated PKU patients and patients with another acquired CNS or genetic problem were excluded from the study.(Late diagnosed refers to children diagnosed between the ages of 3 months to 7 years (≥3 months - <7 years), untreated PKU refers to patients untreated by 7 years of age and over)) **[12].**All patients were subjected to a detailed history taking with a detailed pedigree with special focus of consanguineous marriage and other affected family members. , age of diagnosis of PKU, detailed nutritional history including type of used formula and number of scoops per day .Thorough clinical examination was done with particular emphasis on chronological age which was revised from patients files and birth certificates, anthropometric measurements including height, weight, head circumference and plotting them on percentiles for age and sex according to Egyptian growth charts and nutritional evaluation. The following laboratory investigations were performed for each patient including CBC with emphasis on hemoglobin level, serum iron profile, serum electrolytes with emphasis on calcium and phosphorus levels, serum alkaline phosphatase levels, serum vitamin D level and monthly PHE levels during last year to classify patients into well controlled and poorly controlled groups according to European consensus for management of PKU which defines poorly controlled patients as those having more than 50 %of phenylalanine levels higher than top normal over one year **[12].**

RESULTS

This study included 64 patients with age range from 3 to 7 years , 53.1% of them were males, 59.4% of them had positive consanguinity and 31.2% had positive family history. Median mean PHE was 429.35 while they were diagnosed at ages ranged from 1 to 30 days (Table 1). According to level of control, patients were classified into those with good control (46.9%) and poor control in 53.1% (Figure 1). There is statistically significant relation between control and gender (Females showed higher prevalence among patients with good control). There is statistically non-significant relation between control and either age, consanguinity, order in family, similar condition in family, initial PHE or age at diagnosis (Table 2). There is statistically non-significant relation between control and either height, weight, body mass index, or head circumference (Table 3). There is statistically significant relation between control and alkaline phosphatase, mean PHE and PHE/TYR (alkaline phosphatase, mean PHE and PHE/TYR were significantly lower in patients with good control R) while there is statistically non-significant relation between control and either hemoglobin, calcium, phosphorus, vitamin D, TYR or serum iron (Table 4).

Table (1) Baseline data of studied patients

	Mean ± SD	Range
Age (year)	4.77 ± 1.54	3 – 7
	N=64	**%**
Gender		
Male	34	53.1%
Female	30	46.9%
Consanguinity		
Negative	26	40.6%
Positive	38	59.4%
Order in family:		
First	20	31.3%
Second	14	21.9%
Third	18	28.1%
Fourth	10	15.6%
Fifth	2	3.1%
Family history		
Negative	44	68.8%
Positive	20	31.2%
Control		
Good	30	46.9%
Poor	34	53.1%
	Median (IQR)	**Range**
Intial PHE level	900(657.5-1275)	350 – 2500
Age at diagnosis (day)	7(1.5 – 14.75)	1 – 30

Table (2) : Comparison between the studied groups regarding demographic and baseline data

	Good control group n= 30(%)	Poor control group n=34(%)	χ^2	p
Gender				
Female	20 (58.8%)	14 (41.2%)	4.158	0.041*
Male	10 (33.3%)	20 (66.7%)		
Consanguinity				
Negative	14 (53.8%)	12 (46.2%)	0.855	0.355
Positive	16 (42.1%)	22 (57.9%)		
Order in family				
First	10 (50%)	10 (50%)		
Second	8 (57.1%)	6 (42.9%)	1.252§	0.263
Third	8 (44.4%)	10 (55.6%)		
Fourth	4 (40%)	6 (60%)		
Fifth	0 (0%)	2 (100%)		
Family history				
Negative	20 (45.5%)	24 (54.5%)	0.114	0.736
Positive	10 (10%)	10 (50%)		
	Mean ± SD	**Mean ± SD**	t	p
Age (year)	5.0 ± 1.52	4.56 ± 1.55	1.148	0.255
	Median (IQR)	**Median (IQR)**	Z	p
Age at diagnosis	7(1 – 10)	7(6 – 15.5)	-1.552	0.121
Initial PHE level	800(600 – 1200)	1000(725 – 1450)	-1.645	0.1

*p<0.05 is statistically significant χ^2Chi square test t independent sample t test §Chi square for trend test Z Mann Whitney test

Table (3) : Comparison between the studied groups regarding anthropometric data

	Good control group	Poor control group	t	p
	Mean ± SD	Mean ± SD		
Height (cm)	100.73 ± 16.26	100.47 ± 13.04	0.072	0.943
Head circumference(cm)	51.2 ± 1.53	50.44 ± 1.51	1.997	0.05
	Median (IQR)	**Median (IQR)**	**Z**	**p**
Weight (kg)	19(14 – 23)	19(14.5 – 20.5)	-0.27	0.787
BMI (kg/m^2)	17.68(16.32 – 18.9)	17.91(15.5 – 19.26)	-0.538	0.59

t- independent sample t test. Z Mann Whitney test

Table (4): Comparison between the studied groups regarding laboratory data

	Good control group	Poor control group	t	p
	Mean ± SD	Mean ± SD		
Hemoglobin (g/dl)	11.13 ± 1.07	10.57 ± 1.15	2.041	**0.045***
Calcium (mg/dl)	10.19 ± 0.48	10.07 ± 0.63	0.922	0.36
Phosphorus (mg/dl)	4.37 ± 0.44	4.57 ± 0.96	-1.079	0.286
Vitamin D	24.53 ± 3.64	23.19 ± 5.51	1.164	0.249
	Median (IQR)	**Median (IQR)**	**Z**	**p**
ALP	164(132 – 200)	213(154 – 269.75)	-1.965	**0.049***
Serum iron	93(75 – 120)	78(57.5 – 90)	-1.911	0.056
Mean PHE	257.5(223.9 – 381.2)	569.4(473.35 – 629.5)	-6.73	**<0.001****
TYR	68(41.8 – 96)	76(56.13 – 92.05)	-0.915	0.36
PHE/TYR	3.7(2 – 5.2)	5.3(4.7 – 7.15)	-4.039	**<0.001****

t independent sample t test Z Mann Whitney test *p<0.05 is statistically significant **p≤0.001 is statistically highly significant

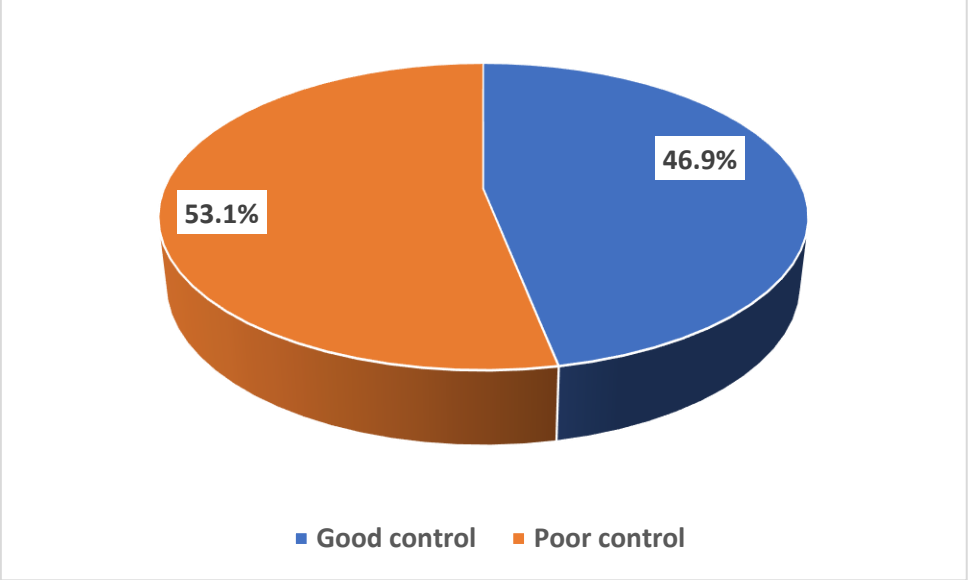

Figure (1) :Pie chart showing distribution of patients according to level of control.

DISCUSSION

In the current study, the gender composition was 53.1% males and 46.9 % females with mean PHE levels in the preceding 12 months ranging from 71.1 and 1087 mmol/L with a mean of429.35 mmol /L . There are Similar results a study conducted in Zurich and Berne by **Landolt et al. [13]** who studied a group of 37 children and found that 51.4% of them were males and 48.6 % females with mean age of 10.9 +/-4.3 years ranging from 3 – 18 years with mean PHE levels in the past 12 months 331+/- 169 mmol/L ranging from 85-729 mmol/L. Furthermore we found that 59.4 % of subjects were of consanguineous marriage and 31.2% had positive family history of one or more siblings suffering from PKU , which is a finding similar to that of several other studies such as **Dababneh et al. [14]** who found in a study held in

MOH in Jordon that 74.2%of his 294 studied patients had a first degree positive consanguinity , 9.9% had a second degree positive consanguinity and only 12.6% were not consanguineous with 12% of patients having other affected siblings . In addition, **Araby et al. [15]** found a rate of consanguinity 57% among PKU patients in Menoufia governorate.

Since PKU is an autosomal recessive disorder, its prevalence will increase along with the increase in family marriages. Due to the considerable rates of consanguineous marriages in Egypt the awareness should be raised regarding the newborn screening programs and early management of PKU cases as a vital part of public health preventive measures.

In the current study, patients were diagnosed and started treatment at ages ranging between 1 -30 days with mean age of 7 days. In agreement with our study **Kenneson et al. [16]** studied a group of 203 PKU patients in the NBS -PKU registry in USA where 108 patients (53.2%) started treatment before age of 1 week ,79 patients(38.9%) between age of 1-2 weeks and only 16 patients (7.8%) between age of 1 and 9 months . In Menoufia governorate mean age of diagnosis and initiation of treatment was 9.3 +/- 2.43 days **[15]**. Also , in a meta analysis of data collected by **Gizewska et al. [17]** from 59 medical centers in 22 south and easter European countries , they found that 19.4 % of their 8600 studied patients were diagnosed at age of 0-9 days , 51.6 % between 10-15 days , 22.6% between 16-28 days and only 3.2% were diagnosed after age of 29 days .

In contrast , **Al Tai et al. [18]** found through a single center observational study conducted in the rare and inherited metabolic diseases unit in AL Emamain Al Khadimain medical city in Baghdad on 23 cases , 65.2% of them were males with all 23 cases of positive consanguinity (100%) and high percentage of positive family history (65.2 %), the range age of diagnosis and initiation of treatment was 45 days – 11 years with mean age of 1.3 years ,10 patients were diagnosed below age of 6 months (43.5%) , 13 patients (56.5%) were diagnosed at older ages through selective screening programs of symptomatic children .

In another study carried out by **Vela-Amieva et al. [19]** at the national institute of pediatrics in Mexico city , out of 57 studied cases aged between 1-5 years 47 of them (82%) were diagnosed after age of 30 days with mean age at time of diagnosis 2years and 8 months while only 10 patients were diagnosed before age of 30 days with mean age of diagnosis 18 days (range 3-30 days).the main reason behind the delay in diagnosis as revealed by this study was absence of routine newborn screening system in the Mexican health care system.

From the previous results, it is shown that the age of diagnosis is much younger in countries with newborn screening programs such as USA , Egypt ,southern and eastern Europe .

Unfortunately , to date only few countries in the middle east region like Egypt , Saudi Arabia , UAE, Qatar and Turkey have implemented comprehensive NBS with relatively high coverage including PKU among other treatable disorders aiming to start early treatment and decrease disability rates .

In our study, the first time PHE levels measured at time of diagnosis before therapy had values between 350 – 2500 mmol/L with mean PHE levels during the past 12 months ranging from 71.1-1087 mmol/L .patients were classified according to their monthly PHE levels over a period of 1 year into metabolically well controlled (46.9%) and poorly controlled (53.1%) according to the European guidelines which defines good metabolic control as 50% or more of PHE levels measured over one year to be 360 mmol /L or less with a statistically significant higher percentage of females among well controlled patients (58.8%) and higher percentage of males among poorly controlled patients(66.7%).

The percentage of good metabolic control in this study is close to the findings of **Kanufre et al. [20]** who studied a sample of 87 patients (48% females) ranging from 1- 11 years with median age of 8 years and found that 49% were of good metabolic control with females having better overall metabolic control than males with a percentage of 74% of well controlled patients females.

The current study showed no statistically significant relation between metabolic control, psychological problems and either age ,initial PHE level at time of diagnosis, consanguinity , order in family or other affected family members , a result similar to that of **Jahja et al. [21]** who studied a group of 64 Dutch children , their ages ranging between 7-14 years with mean age of poorly controlled patients 10.9+/- 2.3 years and mean age of well controlled patients 10.9 +/- 2.1 years all diagnosed and treated before age of 2 weeks showing no significant correlation between age and metabolic control .

Jusiene et al. [22] found significant negative correlation between psychological problems and presence of other affected family members and explained this finding by the fact that there is a common human tendency to compare one self in a social situation to significant others. Children as well as adults are sensitive to all indicators of whether they are treated in the same way or better

or worse than others , so being offered different food may be interpretated by them as an offence or injustice, hence the presence of other family members with the same condition can eliminate this sensation and further decrease the risk of psychological problems. He also stated that IDC (index of metabolic control) defined as the mean of all median PHE levels during lifetime was significantly related to yearly PHE means but with no significant correlation between metabolic control and initial PHE levels during first month of life.

In our study there was no statistically significant relationship between control and either height , weight BMI or head circumference . In agreement with our study **Nogueria et al. [23]** conducted a cohort study included 33 children, 18 of them were of good metabolic control and 15 were of poor metabolic control and he stated that short stature was only observed in 1 patient, underweight was observed in 2 patients and overweight was found in 9 patients with no significant difference between the good and poor metabolically controlled groups. Also, **Dobbelaere et al. [24]** in a study included 20 patients 11 of them were females and 9 were males with mean age of 4.5+/- 1.6 years all diagnosed by NBS , they found that although the anthropometric data of pku children showed moderately decreased growth regarding weight for age and height for age which were below the reference population , there was no significant correlation between metabolic control (determined by lifetime PHE levels) an growth retardation in PKU children .

The low prevalence of anthropometric changes suggest that regular nutritional and clinical follow up contributes to better monitoring and early intervention to achieve normal anthropometric development.

But on the other hand **Tansek et al. [25]** in a study conducted on 158 PKU patients divided into poor metabolically controlled group that included 96 patients with mean age of 10.7 years and good metabolically controlled group including 62 patients with mean age of 11.7 years all were diagnosed by NBS .the study showed the mean serum PHE levels indicating metabolic compliance was negatively related to the height although there was no significant impact on weight , head circumference or BMI **Sena et al. [26]** found in a systematic review that although many studies tend to correlate between PKU and overweight as restriction of natural protein in diet may force the patients to consume a diet rich in CHO and fat as alternative source of energy which could predispose PKU patients to obesity , non of these studies could relate the variability of PHE levels as an indicator of metabolic control to obesity or increased BMI.

Our study showed statistically significant relation between metabolic control and all ALP , mean PHE , and PHE /TYR ratio (ALP , mean PHE , PHE /TYR ratio were significantly lower among good metabolic control group) while there was no significant relation between metabolic control and either Ca , Ph or s. vitamin D. In agreement with us **Crujeiras et al. [27]** reported in a study involved 127 PKU children that serum Ca and Ph levels were within normal range with no significant relation to metabolic control , but 14% of patients showed lower serumvitamin D levels. Also, **Ambroszkiewicz et al. [28]** studied a group of 37 PKU children attending at the department of pediatrics at the institute of mother and child in Warsaw . patients were divided into 2 groups , group A involved 12 well metabolically controlled children with median age of 4.5 years ranging from 3- 10 years and group B that included 25 poor metabolically controlled children with median age of 6 years ranging from 3- 10 years with metabolic control was determined by the mean serum PHE levels during past 3 years .serum Ca , Ph and ALP were measured in both groups all within normal ranges showing serum ALP levels lower among good metabolically controlled group .

In disagreement with us, serum vitamin D and Ca levels of patients with PKU were assessed by **Modan-Moses et al. [29]** and were found to be better in PKU patients with high adherence to diet .they linked their findings to high vitamin D and Ca content of free PHE amino acids formulas.

A recent study by **Adamczyk et al. [30]** found that the bone density of a group of adolescents with PKU who were not compliant and had high PHE levels had decreased when compared to an age-matched, well-metabolically regulated group. A DXA scan has shown a negative correlation between PHE content and bone density.

The two main aspects of poor dietary compliance that may have a detrimental impact on bone compartments are the relaxation of protein restriction, which increases the intake of natural proteins and causes chronic, sustained hyperphenylalaninemia, and the decrease in the consumption of dietary supplements, such as artificial foods that provide vitamins, minerals, and amino acids.

Since these compartments typically occur simultaneously, it is challenging to understand their effects, albeit the latter's seems to be more evident because the impact of hyperphenylalaninemia on bone mineralization is still poorly understood and mostly dependent on research using animal models.

Deficiency of essential micronutrients is one of the common concerns regarding the diet of PKU patients, having to follow a strict diet without taking supplements or formula makes the patients more susceptible to a deficiency of vitamins and minerals especially among poorly controlled patients.

However, interestingly, our study found no significant difference between the good metabolically controlled group and the poor metabolically controlled group regarding serum iron or hemoglobin levels. **Zamani et al. [31]** stated a result similar to ours when they studied a group of 46 PKU children their ages ranged between 1-12 years with mean age of 6.6+/- 3.9 years , 69% of patients were of poor metabolic control with no significant difference in level of serum iron , hemoglobin or serum vitamin D level than those of good metabolically controlled group as 100% of both groups showed normal serum iron and hemoglobin levels while for serum vit D 78.2% of well controlled group had normal levels vs 66% of poorly controlled group .

On the other hand, **Green et al. [32]** found in a study involved 30 PKU patients 16 of them where adherent to PHE restricted diet and 14 were not adherent to diet , the non adherent group showed significantly lower intakes and lower serum levels of iron , zinc , vitamin D and calcium than the well adherent group.

A different result was found by **Schulpis et al. [33]** in a study conducted on a group of 17 Greek PKU children with poor adherence to diet 10 of them were males and seven were females with mean age of 6.8+/- 1.4 years all diagnosed by NBS . Adherence to diet was assessed by their median PHE level which was high with a mean of 1763+/- 160 mmol/dl , they were requested to follow up their diet strictly for the next 60 days after which they presented with lower serum PHE levels (mean 492+/-100 mmol/dl) and then reevaluated with exclusion of regular consumers of supplementary vitamins or iron

Total iron daily intake as collected by dietetic diaries by parents was not affected by diet adherence but the results showed decrease iron stores in on diet patients despite adequate intake as reflected by s. ferritin with a mean of 33+/- 2.8 ng/ml in on diet patients vs 48.2+/-2.3 ng/ml when they ere off diet.

Also hemoglobin levels where compared to the normal range for age and showed that although iron deficiency was noted among on diet patients , it was mild enough not to cause anemia. The authors contributed the result of their study to the low bioavailability of iron obtained from vegetables and synthetic sources.

So, as a result of restricting animal protein rich in iron with high bioavailability, PKU patients are likely to ingest small amounts of micronutrients including iron . Therefor iron supplementation should be started in the 4th month of life providing a daily dose of 1 mg/kg to prevent iron deficiency anemia among PKU children.

CONCLUSIONS

The number of early diagnosed and treated PKU patients is increasing in Egypt since the application of NBS in 2015 allowing further studies on early treated Egyptian PKU patients including their metabolic control, psychological assessment and nutritional status.

LIMITATIONS

The first limitation was low sample size; however, this is a consequence of the rarity of the disease. The second limitation was age group limitation as patients older than 7 years were excluded as NBS in Egypt started in 2015.

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