Original Article

Anemia in Patients with Phenylketonuria in Yazd

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Abstract

Background

Phenyl ketonuria (PKU) is a congenital metabolic disease. Irreversible brain damage is the result of phenyl alanin accumulation, so its amount should be restricted in patients diet. In their diet, trace elements such as hem Iron, folic acid, vitamin B_{12} and, etc are also limited, and could represent anemia. In this study, the frequency of anemia in PKU patients in Yazd was investigated and compare with non-affected individuals.

Materials and Methods

In this case-control study, all the PKU patients of Yazd who were under diet at least for 6 months were selected. The controls were selected from non PKU population and matched with cases according to age, gender and socioeconomic level. Hematologic factors were measured in both groups and analyzed using SPSS software using T-Test.

Results

This study consisted of 18 patients aged between 1 to 18 years old. Full blood count and blood indices did not show significant difference ($p>0.05$), except MCHC ($p<0.05$). The blood level of vitamin B_{12} and Folic acid were significantly higher in the cases than controls ($p<0.05$), but ferritin was not significantly different between them ($P>0.05$).

Conclusion

Our results did not show significant difference in presentation of anemia in patients with PKU and normal controls. Screening for anemia among PKU patients and taking supplements is recommended.

Keywords

Phenyl ketonuria, Ferritins, Vitamin B_{12}, Blood Cell Count

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Introduction

Phenyl ketonourea is a congenital metabolic disease characterized by phenyl alanin accumulation in the body due to the enzyme deficiency. Phenylalanine hydroxylase (PAH) is the enzyme needed to convert excess phenyl alanin into thyrosin which is then further metabolized but patients with PKU inherit a defective gene of PAH as an autosomal recessive trait(1). High concentration of phenyl alanin in blood can lead to irresistible brain damage, but it can be prevented by early diagnosis and restriction of the amount of phenyl alanin in diet especially proteins. On the other hand, the main source of natural nutrients, especially Fe, vitamin B_{12} and folic acid in food dietary of normal children are proteins, so its restriction in dietary management of PKU can lead to essential element's deficiency, anemia and failure to thrive (2-3). The aim of this study was to investigate hematologic factors and anemia status as the aftermath of dietary restriction among PKU patients in Yazd, Iran.

Materials and Methods

In this case- control study, all the patients diagnosed as PKU in Yazd who were at least 6 months under dietary management contributed to this study as the case group. Control group was matched with the cases according to the gender, age and socioeconomic status from normal population.

Case members were interviewed whether they consume any complementary consist of Fe, folic acid and multi vitamin tablets or not. Blood samples were harvested from both groups for laboratory tests consist of CBC (Hb, HCT, MCV, MCH, MCHC, RBC count, WBC count, Plt count), blood level of vitamin B_{12}, folic acid and ferritin. Blood indices of CBC were measured using Sysmexkx21in Shahid Sadoughi Hospital's laboratory. Ferritin was measured using ELISA technique (ELISA reader - orens Statfax 3200). Folic acid and B_{12} were measured using Elexis In Kasra laboratory. The results of CBC indices tests were compared with standard normal ranges for age and gender from Manual of pediatric hematology and oncology book (fourth edition) (Table-1). The results of other hematologic factors were compared against its normal ranges reported from laboratory. If the Hb was less than the normal range, it was assumed as anemia, and if the MCV was less than the normal range, the type of anemia was reported as microcytic , and if it was more, it was reported as macrocytic . If MCH was less than the normal range, anemia was reported as hypo chromic and if more was reported as hyper chromic.

Statistical Analysis

Lab results from both groups were compared against each other using SPSS software (version 18) and T-test for statistical analysis. P-value less than 0.05 was considered to be significant.

Results

All the patients with phenyl ketonuria in Yazd contributed to this study were 18 consist of nine boys (50%) and nine girls (50%) between the ages of 1 to 18 years old. All the control members were matched by each case member due to age, gender and socioeconomic status. Six patients (33.3%) consumed Fe complementary, four patients (22.2%) took folic acid tablets and seven patients (38.9%) took multivitamin tablets. Four PKU patients consist of two girls and two boys equivalent to 22.2% presented anemia. Hematologic factors of these patients are defined as following:

Patient Number 1: a 14-year old boy with microcytic hypo chromic anemia, whose ferritin level was lower than normal range but vitamin B_{12} and folic acid, lay between their normal ranges. This patient did not consume any kind of complementary.

Patient Number 2: a 4 year old girl with normocytic norm chromic anemia, whose

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Ferittin and vitamin B_{12} level lay between the normal ranges but folic acid level was higher than normal range. This patient consumed all three kinds of complementary.
Patient number 3: an 18 months girl with normocytic norm chromic anemia, whose ferittin level lay between normal ranges but folic acid and vitamin B_{12} were higher than normal ranges. This patient did not consume any kind of complementary. Patient number 4: a 5 year old boy with macrocytic hyperchromic anemia, all three indices lay in their own normal ranges. This patient did not consume any kind of complementary. In addition, a 9 year old girl presented pre iron deficiency anemia and was in negative balance phase. In other words blood ferritin level was lower than normal range but CBC indices were all normal. Five people (four girls and one boy) in control group equivalent to 27.7% presented anemia which three of them showed macrocytic hyper chromic anemia, one showed macrocytic hypo chromic anemia, and one showed normocytic norm chromic anemia. Furthermore, one girl presented pre iron-deficiency anemia that had normal CBC indices, but her ferittin level was lower than normal ranges. The comparison between CBC indices in both groups did not show any significant differences (P>0.05) except MCHC (P=0.032). The results of ferittin blood level in case group indicates that just two patients (11.1%) had lower level than normal ranges which one of them presented microcytic hypochromic anemia (patient number one in table 2), and the other was in pre anemic phase (patient number 5 in table 2).

In control group also two people showed a lower ferittin blood level which one of them had normocytic normochromic anemia, and the other was in pre anemic phase. Comparison between ferittin blood levels of both groups was not statically significant (P-value>0.05). The results of folic acid in case group showed that nine patients (50%) had higher level of folic acid than its normal ranges that four of them consumed folic acid tablets as complementary. Other nine patients had normal folic acid level, but in control group just one person had higher level of folic acid, and others remain in normal ranges. Comparison between two groups indicates that folic acid level was significantly higher in case group than control. (P-value=0.00) The results of vitamin B_{12} level in case group showed that eleven patients (61.1%) had higher level than its normal ranges. However other's folic acid level lay in its normal ranges. Five out of eleven patients consumed multi vitamin tablets as complementary. All the people in the control group presented normal vitamin B_{12} level. The comparison between two groups indicates that vitamin B_{12} level in the case group was significantly higher than control group (P-value=0.00).

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Table 1. Normal ranges of CBC indices from Manual of pediatric hematology and oncology book (fourth edition)

Age	Hemoglobin		Hematocrit		Red cell count		MCV		MCH		MCHC		Reticulocytes	
	Mean	-2SD	Mean	-2SD	Mean	-2SD	Mean	-2SD	Mean	-2SD	Mean	-2SD	Mean	-2SD
0.5-2y	12.0	10.5	36	33	4.5	3.7	78	70	27	23	33	30	1.0	0.2
2-6y	12.5	11.5	37	34	4.6	3.9	81	75	27	24	34	31	1.0	0.2
6-12y	13.5	11.5	40	35	4.6	4.0	86	77	29	25	34	31	1.0	0.2
12-18yFamale	14.0	12.0	41	36	4.6	4.1	90	78	30	25	34	31	1.0	0.2
12-18 male	14.5	13.0	43	37	4.9	4.5	88	78	30	25	34	31	1.0	0.2

Table 2. Details of hematologic factors in anemic PKU patients from case group

	Age/sex	WBC	RBC	Hb	Hct	MCV	MCH	MCHC	Plt	Vitamin B_{12}	Folic acid	ferritin
1	14y-male	5900	4.68	11.4	35.8	76.5	24.5	34.6	243	256	7	**6**
2	4y-female	3300	3.51	8.7	26.7	75.8	24.8	32.7	246	571	20	**45**
3	18Mon-female	9100	4.03	9.8	30.6	75.9	24.3	32	368	1598	17.7	**20.19**
4	5y-male	8000	3.69	10.1	30.5	82.7	27.4	33.1	292	850	17	**35**
5	9y-female	4500	4.37	12.6	37.1	84.9	28.8	34	226	1418	17.3	**4.1**

Table 3. The comparison of Mean ± Standard Deviation (SD) of hematologic factors in case and control groups

Hematologic factors	Mean±SD In control group	Mean±SD In case group	P Value
WBC	8252.63±2968.9	7028±1897	0.146
RBC	4.5121±0.47	4.43±0.47	0.50
Hb	12.78±1.57	12.63±1.87	0.80
Hct	38.52±4.36	37.03±5.03	0.343
MCV	85.61±5.83	83.95±7.12	0.442
MCH	28.26±2.79	28.48±2.86	0.819
MCHC	32.37±2.81	33.95±1.05	0.032
Plt	319.37±128.24	254±68.79	0.064
Vitamin B_{12}	437.16±342.53	1074.28±562.83	0.00
Folic acid	8.77±3.4	15.51±4.46	0.00
ferritin	31.72±31.9	38.28±41.01	0.594

Discussion

The results of this study showed four anemic PKU patients (22.2%) but in a similar study conducted by Ashraghi et al reveals that 28.6% of PKU patients in Babol were anemic (4). The other study done on 69 PKU patients by Keshavarz et al in Tehran, 73.5% had iron deficiency and 71% were anemic, which indicates more nutritional problems than Yazd patients (5). In Giorgianne study six patients (15%) were anemic and 10% were in pre anemic phase thus iron deposits in their body decreased but did not lead to anemia which is called negative balance(6). In our study just one PKU patient (5.5%) was in pre anemic phase. In addition, hemoglobin level was not statically significant against its normal ranges but hematocrit and RBC count in PKU patients were significantly lower than normal ranges, MCV lay between normal ranges but MCH was higher in PKU patients(6). In our study,

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none of these indices were significant except MCHC, which was higher in PKU patients. The reason may go back to the fewer constructions of RBC in PKU patients that cause a slightly increase amount of hemoglobin per cell (6).

Ferittin blood level in our study was not significantly different that goes along with the results of Arnold study(7) but in contrast, Scaglioni reached a lower ferittin level in PKU patients under dietary treatment in their results(8). In Reilly (9) and Gropper (10) studies, although PKU patients had more intakes of Fe but its blood level was not significantly different. In some studies lack of Fe in PKU patients is reported (2-13). In our results, vitamin B_{12} level was higher in PKU patients than control group, but the result of Rabinson's study was completely different from our findings, thus their results indicate a lower level of vitamin B12 than normal ranges but a higher level in Folate in comparison to its normal ranges that is the same as our results (14). In our study, the higher level of vitamin B_{12} and folic acid can be explained by the complementary consumption by PKU patients. 38.9% and 22.2% of patients used multivitamin and folic acid tablets, respectively. In addition, the level of these two factors is precious besides having megaloblastic anemia otherwise no decision on them would be rational. For further studies and confirmation the measurement of folic acid and vitamin B_{12} in RBCs is recommended.

Conclusion

Although there was no significant different in presenting anemia in patients with PKU and control group but screening these patients for diagnosing anemia and nutritional deficiencies is highly needed with regard to growth period. On the other hand, lack of Fe can cause behavioral problems, anorexia, irritability and, etc that can worsen the primary disease. With regard to the high prevalence of anemia between normal children, screening for anemia and prescribing complementary is recomm-ended.

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Conflict of Interest

None declared.

References

1-Acosta PB, Wenz E, Williamson M. Methods of dietary inception in infants with PKU. J Am Diet Assoc. 1978 ;72(2):164-9.

2-Aggett PJ, Davies NT. Some nutritional aspects of trace metals. J Inherit Metab Dis. 1983;6 Suppl 1:22-30.

3-Hanley WB, Linsao L, Davidson W, Moes CA. Malnutrition with early treatment of phenylketonuria. Pediatr Res. 1970 ;4(4):318-27.

4-Ashraghi P., Abbas khanian A., Bijani A., Hoseinzadeh S., Evaluation of nutritional status and incidence of iron deficiency in PKU patients in Mazandaran province,Babol university medical journal.1390;13(5):58-62.

5-Keshavarz A., Jalali., Ebrahimi M. : Microcytic anemia in children in phenyl ketonuria in Tehran.Tehran university medical journal. 1377; 56(1):25-29.

6-Arnold GL, Kirby R, Preston C, Blakely E. Iron and protein sufficiency and red cell indices in phenylketonuria. J Am Coll Nutr. 2001 ; 20(1):65-70.

7-Arnold GL, Kirby R, Preston C, Blakely E. Iron and protein sufficiency and red cell indices in phenylketonuria. J Am Coll Nutr. 2001 ; 20(1):65-70.

8-Scaglioni S, Zuccotti G, Vedovello M, Rottoli A, Paccanelli S, Longhi R, et al. Study of serum ferritin in 58 children with classic phenylketonuria and persistent hyperphenylalaninaemia. J Inherit Metab Dis. 1985;8(3):160.

9-Reilly C, Barrett JE, Patterson CM, Tinggi U, Latham SL, Marrinan A. Trace element nutrition status and dietary intake of children with phenylketonuria. Am J Clin Nutr. 1990 ;52(1):159-65.

10-Gropper SS, Acosta PB, Clarke-Sheehan N, Wenz E, Cheng M, Koch R. Trace element status of children with PKU and normal children. J Am Diet Assoc. 1988 ;88(4):459-65.

11-Sievers E, Oldigs HD, Dörner K, Schaub J. Trace element excess in PKU diets? J Inherit Metab Dis. 1990;13(6):897-905..

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12-Farhud DD, Kabiri M. Incidence of phenylketonuria (PKU) in Iran. Indian J Pediatr. 1982; 49(400):685-8.
13-Kabiri M. :a report on the incidence of phenylketonuria in Tehran, Iran, Acta Medica Iranica, 1982;24:107-113.
14-Robinson M, White FJ, Cleary MA, Wraith E, Lam WK, Walter JH. Increased risk of vitamin B12 deficiency in patients with phenylketonuria on an unrestricted or relaxed diet. J Pediatr. 2000 ; 136(4):545-7.

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