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PREVALENCE OF VITAMIN D DEFICIENCY IN IRON DEFICIENT AND NORMAL CHILDREN UNDER THE AGE OF 24 MONTHS

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ABSTRACT

Objective: To elucidate the potential association between iron status and vitamin D levels in infants. **Methods:** A cross sectional study was conducted on patients who presented in Consultant Clinics, Department of Pediatrics, The Indus Hospital, Karachi from 1st November 2015 till 31st April 2016. Medical records of infants aged three to 24 months were analyzed retrospectively. Data was entered and analyzed using SPSS version 21.0. **Results:** A total of 87 patients were enrolled in the study, out of which 47 (54%) patients had iron deficiency anemia, 23 (26.4%) had iron deficiency and 17 (19.5%) had no anemia. Out of 87 patients, 43 (49.4%) had vitamin D deficiency, 8 (9.2%) were vitamin D insufficient and 36 (41.4%) were vitamin D sufficient. Iron deficient anemic patients had significantly higher proportion of vitamin D deficiency as compared to iron deficient and normal patients (57.4% vs 47% and 29.4% respectively. Significant difference in median hemoglobin was found between vitamin D deficient patients and vitamin D insufficient patients. P-value of <0.05 was considered as significant. **Conclusion:** Iron-deficient children are more prone to vitamin D deficiency. Therefore, every child with IDA should also be evaluated for vitamin D deficiency. Educational efforts are needed to increase compliance with iron and vitamin D supplementation guidelines.

KEYWORDS: Iron deficiency anemia, Vitamin D deficiency, 25(OH)D.

INTRODUCTION

Iron and vitamin D are important micronutrients for normal growth and development of infants, yet they are frequently overlooked.[1] Numerous adverse effects have been observed in infants aged ≤24 months with iron and vitamin D deficiencies. Even in asymptomatic cases, these adverse effects may be problematic because infants are rapidly growing at this age. Decreased vitamin D levels during infancy might result in type 1 diabetes mellitus.[2] Iron and vitamin D deficiencies cause a variety of health issues in children which might have long lasting effects even in asymptomatic cases. The long-term consequences of concurrent deficiencies remain unknown.

Full-term infants receive the necessary iron through the placenta, which are sufficient for approximately 6 months after birth.[3] Thereafter, infants are able to absorb sufficient levels of iron on their own. Iron deficiency (ID) can lead to growth and developmental delay, cognition and memory problems, impaired immune function, frequent infections, and iron deficiency anemia (IDA). Intestinal iron absorption is controlled and dependent on the body's need for iron. Since proteins such as flavoprotein and cytochrome are involved in this process, the effects of iron deficiency are diverse.[4,5] Iron passes through the blood-brain barrier, enters nerve cells, and is involved in neurotransmission and myelin formation.[6]

Vitamin D is primarily involved in bone metabolism. Vitamin D deficiency may cause rickets in childhood, which primarily occurs at 3-18 months of age.[7] It was recently discovered that vitamin D receptor is widely expressed in osteoblasts, lymphocytes, mononuclear cells, and most organs such as the small intestine, colon, brain, heart, skin, gonads, prostate, and breast.[8]

A significant association between vitamin D deficiency and anemia has been reported throughout the world.[9] Several studies in various populations all over the world suggest a high degree of association between Iron deficiency anemia and vitamin D deficiency. Vitamin D receptor has already been reported in bone marrow and levels of 1, 25-dihydroxyvitamin D (1, 25-(OH) 2D) (Active form of vitamin D) is several hundred folds higher in bone marrow compared to plasma.[10] It imparts an important role in erythropoiesis the mechanism of Red Blood Cell (RBC) formation. Several mechanisms have been proposed to explain the association of vitamin

D deficiency and anemia. Vitamin D influences Hemoglobin levels through a direct effect on erythropoiesis. Erythroid precursors are directly stimulated by vitamin D suggesting the latters immense role in erythropoiesis. The storage and retention of iron and reduction of proinflammatory cytokines is also aided by vitamin D.[11] Thus vitamin D deficiency reduces the ability of RBCs to become active. Vitamin D possibly modulates the level of systemic cytokine production, thus reducing the inflammatory milieu leading to anemia of chronic diseases. Absorption of vitamin D may be impaired due to iron deficiency in the same way it impairs fat and vitamin A intestinal absorption. It is still controversial which deficiency causes the other but this association should be addressed in view of better treatment proposal.[12]

Anemia and vitamin D deficiency are both very important health issues, recent accumulating evidence shows that vitamin D deficiency is prevalent in individuals with anemia; we aimed to detect a potential relationship between vitamin D deficiency and iron deficiency anemia in patients presenting to us so that management can be planned accordingly.

SUBJECTS AND METHODOLOGY

A cross sectional study was conducted on patients who presented in Consultant Clinics, Department of Pediatrics, The Indus Hospital, Karachi from 1st November 2015 till 31st April 2016. Medical records of infants aged 3 to 24 months were analyzed retrospectively. Approval was obtained from Institutional Review Board.

The infants were classified into iron deficiency anemia (IDA), iron deficiency (ID) and normal groups according to hemoglobin and ferritin levels. They were then classified into vitamin D deficiency (VDI) and vitamin D sufficiency (VDS) groups according to (25(OH)D) levels. Only those patients were enrolled in the study in which hemoglobin and vitamin D levels were done and there was no suspicion of any hemolytic anemia, based on records available of history, physical examination and investigations. In case of non-availability of ferritin or in subjects with an inaccurate ferritin result due to inflammation, Low mean corpuscular volume (MCV) (<70fL) was checked.

- IDA was defined as Hb≤11 g/dL and ferritin ≤12 ng/mL.
- ID is defined as Hb>11 g/dL and ferritin<12ng/mL.
- VDD was defined as 25OHD<20 ng/mL, VDI as 25OHD of 20-30 ng/mL and normal (VDS) as >30ng/mL.

Data were entered and analyzed using SPSS version 21.0. Mean ± SD or Median (IQR) were reported for all the quantitative variables as appropriate. Frequency and percentage were computed for all the qualitative variables. Chi-square test/Fisher-exact test was applied as appropriate to assess the significant association between gender, vitamin status and iron deficiency anemia. Independent sample T-test/Mann-Whitney U test was applied as appropriate to assess the difference in age, hemoglobin and vitamin D levels between both the genders. ANOVA/ Kruskal Wallis test was applied as appropriate to assess the difference in age, hemoglobin and vitamin D levels between iron deficiency anemia statuses. P-value<0.05 was considered as significant.

RESULTS

A total of 87 patients enrolled in the study, out of which 47 (54%) patients had iron deficiency anemia, 23 (26.4%) had iron deficiency and 17 (19.5%) had no anemia. Out of 87 patients, 43 (49.4%) had vitamin D deficiency, 8 (9.2%) were vitamin D insufficient and 36 (41.4%) were vitamin D sufficient. 53 (60.9%) patients were male and 34 (39.1%) were female as shown in table 1.

There is no significant association of vitamin D status and anemia status with gender (Table 2). Moreover, iron deficient anemic patients had significantly higher proportion of vitamin D deficiency (57.4%) as compared to iron deficient (47%) and normal patients (29.4) (p=0.038) as illustrated in table 2. Whereas, no significant difference was found in mean age (15.5 vs 15.16 months, p=0.0768), Hemoglobin (9.27 vs 9.61 g/dL, p=0.349) and vitamin D level (23 vs 25 ng/dL, p=0.807) in males and females. (Table 3)

Lastly, no significant difference was observed in mean age between three groups of vitamin D status and anemia status. Whereas, significant difference in median hemoglobin was found between vitamin D deficient patients and vitamin D insufficient patients (Table 4)

Table 1: Demographical information of Patients n=87	
Age (months)	
Mean ± SD	15.31 ± 6.23
Min-Max	3 – 24
Hemoglobin	
Mean ± SD	9.40 ± 1.61
Min-Max	5.2 - 13.1
MCV	
Mean ± SD	70.5 ± 13.2
Min-Max	34 – 99
Ferritin	
Mean ± SD	7.8 ± 4.3
Min-Max	2 – 19
Vitamin D	
Mean ± SD	29.43 ± 22.3
Min-Max	3 – 82
Gender n (%)	
Male	53 (60.9)
Female	34 (39.1)
Grouping of patients on the bases of Anemia level n (%)	
IDA	47 (54)
ID	23 (26.4)
Normal	17 (19.5)
Grouping of patients on the bases of Vitamin D level n (%)	
VDD	43 (49.4)
VDI	8 (9.2)
VDS	36 (41.4)

Table 2: Association Between various variables (n=87)					
Gender	**VDD n (%)**	**VDI n (%)**	**VDS n (%)**	**Total n (%)**	**P value**
Male	27 (50.9)	5 (9.4)	21 (39.6)	53 (100)	0.946†
Female	16 (47.1)	3 (8.8)	15 (44.1)	34 (100)	
Total	43 (49.4)	8 (9.2)	36 (41.4)	87 (100)	
Anemia status					
IDA	27(57.4)	4(8.5)	16(34.0)	47(100)	0.038*ł
ID	11(47.8)	3(13.0)	9(39.1)	23(100)	
Normal	5(29.4)	1(5.9)	11(64.7)	17(100)	
Total	43(49.4)	8(9.2)	36(41.4)	87(100)	
Gender	**IDA n (%)**	**ID n (%)**	**Normal n (%)**	**Total n (%)**	**P value**
Male	31 (8.5)	13 (24.5)	9 (17.0)	53 (100)	0.565ł
Female	16 (47.1)	10 (29.4)	8 (23.5)	34 (100)	
Total	47 (54.0)	23 (26.4)	17 (19.5)	87 (100)	
*P-value<0.05, † Pearson Chi-square test, ł Fisher exact test, ł Linear by linear Association					

Table 3: Mean difference of Age, Hemoglobin and Vitamin D between Gender.				
Variables	**Male Mean ± SD**	**Female Mean ± SD**	**Total Mean ± SD**	**P Value**
Age (months)	15.15 ±6.38	Female Mean ± SD	15.31 ± 6.23	0.768
Hemoglobin (g/dL	9.27 ±1.62	Female Mean ± SD	9.40 ± 1.61	0.349
Vitamin D (ng/dL)	28.96 ± 22.76	Female Mean ± SD	29.43 ± 22.31	0.807
*P-value<0.05, **P-value<0.0001; Independent sample T-test				

Table-4: Hemoglobin difference between vitamin D deficient patients and vitamin D insufficient patients.

Characteristics	VDD [a] n=43	VDI[b] n=8	VDS [c] n=36	Total n=87	
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	P-value
Age	15.93 ± 6.42	10.63 ± 4.24	15.61 ±6.08	15.31 ± 6.23	0.152[€]
Hemoglobin; Median (IQR)	9.0 (7.6 - 10.1)[b,c]	10.3 (9.9 - 10.7)	9.9 (9.0 - 11.1)	9.7 (8.1 - 10.7)	0.005[* ß]
	IDA [a] n=47	ID[b] n=23	Normal[c] n=17	Total n=87	P-value
Age	16.13 ± 5.97	14.65 ± 6.79	6.22 ± 13.94	15.31 ± 6.23	0.394[€]
Vitamin D; Median (IQR)	16.7 (9.4 - 40.8)	20.8 (14. - 45.5)	44.7 (16.3 - 59.6)	20.8 (11.0 - 45.5)	0.082 [ß]

Results are based on two-sided tests with significance level 0.05. For each significant pair, the key of the category with the smaller column proportion appears under the category with the larger column proportion.
[€] Anova, [ß] Kruskal Wallis

DISCUSSION

In our study, a total of 87 children were included out of which iron deficient anemic patients had significantly higher proportion of Vitamin D deficiency as compared to iron deficient and normal patients (57.4% vs 47% and 29.4% respectively. The results were similar to a study in which it was found that the level of vitamin D was significantly lower in group of patients who had low serum iron level as well as those who had low hemoglobin level.[13]

Our results did not show any significant association of vitamin D status and anemia status with gender, though female gender is a known risk factor associated with vitamin D deficiency. Also, no significant difference was found in mean age, hemoglobin and vitamin D level in males and females (15.5 vs 15.16 months). According to National Nutrition Survey published in 2011, 33.4% children were suffering from IDA.[14]

On reviewing Literature and as discussed before, our results are consistent with a study done in South Korea, a study of Asian children aged ≤ 2 years showed a significant association between coexisting iron deficiency and vitamin D deficiency. [15] Similar findings were also observed in recent Korean studies revealing that a coexisting vitamin D deficiency frequently accompanies iron deficiency and this association might be due to suppressive effect of vitamin D on iron deficiency anemia (IDA) via via iron regulating hormone, hepcidin which is a peptide hormone that acts as a master regulator of iron homeostasis. Macrophages also play a central role in iron recycling by engulfing senescent RBC.[16,17] Iron receptor ferroportin binds iron and retain it in macrophages with the help of hepcidin, recent studies suggest that vitamin concentration is inversely proportional to hepcidin concentration and directly proportional to hemoglobin and iron concentration. [18] There were numerous adverse effects that have been observed in under two year old children with iron and vitamin D deficiencies. Even in asymptomatic cases, these adverse effects may be problematic because children are rapidly growing at this age.[19]

In humans, there is no known study regarding the long-term adverse effects of concurrent ID and VDD. As the final hydroxylation of vitamin D is dependent on iron, in a study, iron-deficient rats had lower concentrations of the active form of vitamin D. Diaz-Castro et al., also reported that bone metabolism was impaired despite normal 25(OH)D levels in iron-deficient rats.[20]

As similar studies showed a significant association between coexisting ID and VDD, therefore, VDD evaluation is needed for pediatric patients with ID and vice versa. Vitamin D deficiency or nutritional rickets in children is almost eliminated in the developed countries by prophylactic means.[21] However, it remains a major health problem in under developed countries of Asia.[22-24] Several studies have assessed vitamin D deficiency rickets in Pakistani children.[25-26]

The limitations of our study was that, as this was a retrospective study, we used MCV in case of non-availability of ferritin or in patients with an inaccurate ferritin result due to inflammation.

CONCLUSION

Iron-deficient children are more prone to vitamin D deficiency. These two nutritional disorders cause significant morbidity in children. Therefore, every child with nutritional rickets should be screened for IDA and educational efforts are needed for prevention strategies and increasing compliance regarding iron and vitamin D supplementation.

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