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DEFICIENCY OF VITAMIN B12 IN EXPECTANT MOTHERS AND INFANTS ASSOCIATED TO POOR SOCIO-ECONOMIC STATE, CHOLESTASIS AND HYPERBILIRUBINEMIA

[1]Dr. Muhammad Hassan Rafique, [2]Dr. Resham Khan, [3]Dr. Bazgha Mushtaq

[1]Allama Iqbal Medical College, Lahore

[2]Central Park Medical College, Lahore

[3]PG Trainee Medicine Department DHQ Hospital Sheikhupura

Abstract:

Objective: *Our research was aimed for the study of association between deficiency of "Vitamin – B12", cholestasis and hyperbilirubinemia in young age children.*

Methods: *Our research population was 215 infants; every infant was evaluated for serum "B – 12" and levels of bilirubin at Service Hospital, Lahore (January 2016 to February, 2017). We documented demographic data, family history, background, folate, "Vit - B12" serum, levels of urine MMA (Methyl Malonic Acid); plasma homocysteine and indirect and direct total levels of bilirubin.*

Results: *Almost (48.8 %) patients were observed with deficiency of "Vit – B12". In the comparison of deficiency of Vit-B12 cases and without deficiency of Vit-B12 cases no variation was observed in terms of direct, total or indirect levels of bilirubin. Cholestasis was found in only two infants (0.9 %).*

Conclusion: *It is suggested through the outcomes of this study that deficiency of "Vit – B12" was commonly observed in 48.4 %. Therefore, incidence of "Vit – B12" deficiency in hyperbilirubinemia or cholestasis cases is also associated with it. More research work is required, in order to prove a strong relation between them.*

Keywords: *Hyperbilirubinemia, Cholestasis and Vitamin "Vit – B12" deficiency.*

*** Corresponding author:**

Dr. Muhammad Hassan Rafique,
Allama Iqbal Medical College,
Lahore

QR code

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INTRODUCTION:

An intake of animal origin food (meat, eggs and milk) is necessary to gain "Vit – B12", because human body is not capable of synthesizing "Vit – B12". In the case of poor and lower social and economic circles it is more true as poor are unable to maintain such diet on regular basis for them and their family. If the mother is not affected by the deficiency of "Vit – B12" than infants are also not deficient in "Vit – B12"; because it transfers through placenta in the fetus in the course of pregnancy [1].

Numerous health issues are linked with the deficiency of "Vit – B12" such as development and growth. It has been learnt through hematological outcomes that "Vit – B12" is cofactor in methylation, DNA synthesis, methionine / homocysteine cycle and neurotransmitter synthesis [2]. The importance of "Vit – B12" for erythrocytes proliferation and maturation cannot be overruled. If the "Vit – B12" is deficient than maturity of erythrocytes cannot be gained followed by hyperbilirubinemia and hemolysis [3]. It is also observed in the outcomes of numerous research studies that folic acid and "Vit – B12" deficiency causes hemolysis [4].

Our research was aimed for the study of association between deficiency of "Vitamin – B12", cholestasis and hyperbilirubinemia in young age children.

METHODS:

Our research population was 215 infants; every infant was evaluated for serum "B – 12" and levels of bilirubin at Service Hospital, Lahore (January 2016 to February, 2017). We documented demographic data, family history, background, folate, "Vit – B12" serum, levels of urine MMA (Methyl Malonic Acid); plasma homocysteine and indirect and direct total levels of bilirubin. Every case excluding only one case were mature and referred on the basis of deficiency of biotinides or phenylketonuria suspicion. Every case was noted for age, gestational age, sex, birth weight, pregnancies count, mother's age, consanguineous marriage existence, serum Vit B12, previous diagnoses, plasma homocysteine, folate, level of urine (MMA) methyl malonic acid, total serum, direct & indirect levels of bilirubin.

In total, an acceptable threshold value was (200 pg / ml) to diagnose deficiency of "Vit – B12" [5]. We also established cholestasis laboratory diagnosis: in case of higher direct level of bilirubin level (> 20 %) of bilirubin total level in case of bilirubin total level (> 5 mg / dL) or in the case of level of direct bilirubin (> 1 mg / dL) in case of bilirubin total level as (< 5 mg / dL) [6].

Laboratory outcomes were collected through biochemistry laboratory with the help of various tolls such as Architect i2000, Immulite2000, Perkin Elmer, and Architect c16000. Ethical standards were maintained in every procedure. Consent was also obtained before the commencement of research.

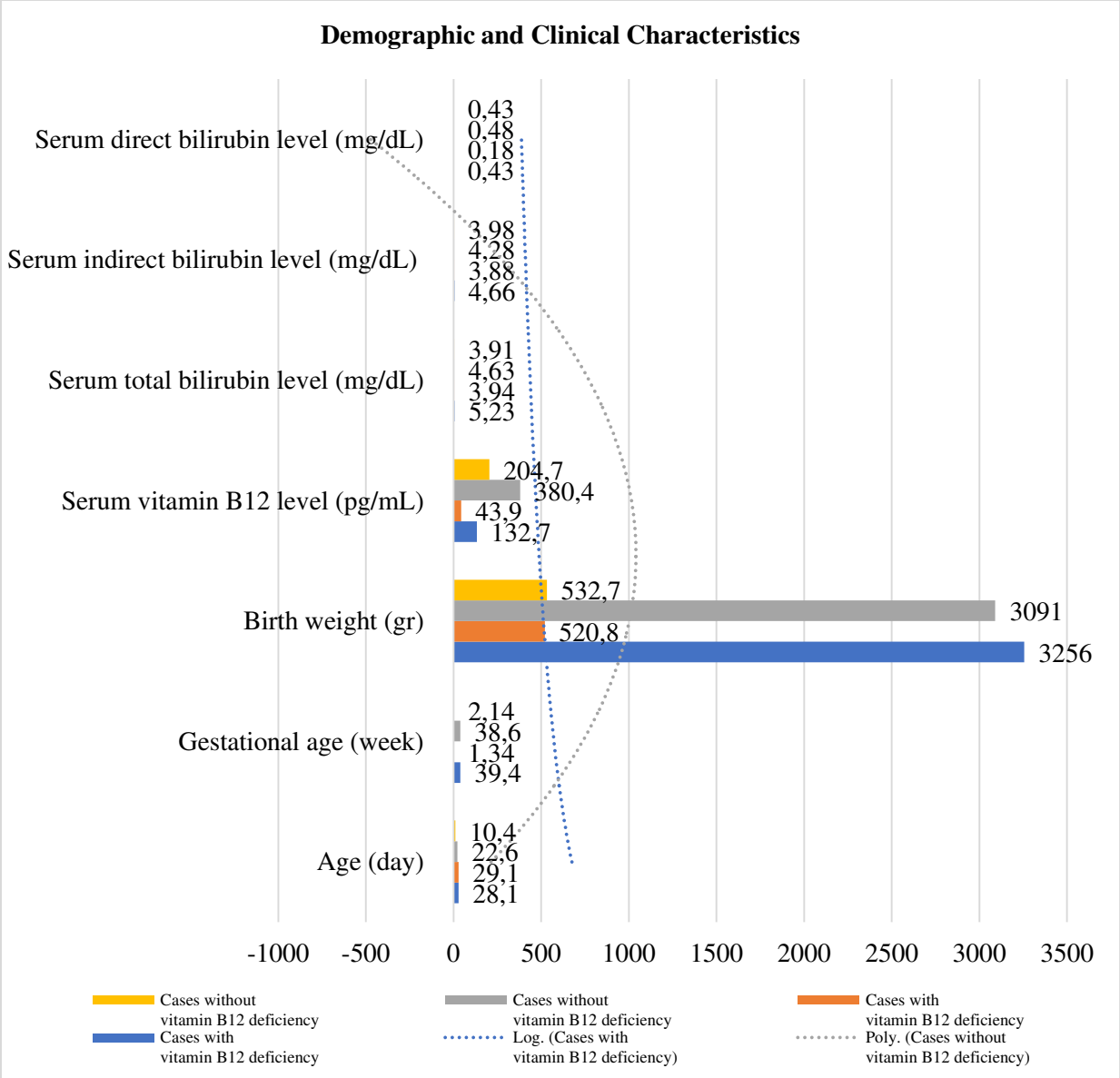
Evaluation of the normal consistency was confirmed through "Shapiro-Wilk test". T-test was used for the comparison of consistent variables. Normal distribution inconsistency was compared through "Mann–Whitney U-test". Inter group comparison was made through Pearson's Chi-square test variables relationship was verified through Spearman's correlation. SPSS was used for statistical analysis with a significant P-value (< 0.05).

RESULTS:

Male to female proportion was respectively 119 males (55.3 %) and 96 females (44.7 %) in the total research population. An average age of referring was (25.3 ± 1.48) days, birth week (39 ± 0.12) weeks and birth weight was (3.171 ± 36.6) grams. It was observed that cholestasis or hyperbilirubinemia was not caused because of any inherited metabolic disease. All the cases shown no disease which may cause pathological hyperbilirubinemia. No phototherapy was administered to these cases. Detailed outcomes analysis in the form of Mean and SD vales have been reflected in the given table.

Table: Demographic and clinical characteristics of cases with and without vitamin B12 deficiency

Characteristics	Cases with vitamin B12 deficiency		Cases without vitamin B12 deficiency		P-Value
	Mean	±SD	Mean	±SD	
Gender (M/F)	42/63		54/56		0.18
Age (day)	28.1	29.1	22.6	10.4	0.06
Gestational age (week)	39.4	1.34	38.6	2.14	0.006
Birth weight (gr)	3256	520.8	3091	532.7	0.024
Serum vitamin B12 level (pg/mL)	132.7	43.9	380.4	204.7	0.001
Serum total bilirubin level (mg/dL)	5.23	3.94	4.63	3.91	0.3
Serum indirect bilirubin level (mg/dL)	4.66	3.88	4.28	3.98	0.529
Serum direct bilirubin level (mg/dL)	0.43	0.18	0.48	0.43	0.294



There was no variation between groups having deficiency or without any deficiency of "Vit – B12" as per sex, age, total serum bilirubin, indirect and direct level of bilirubin. Significant variation was observed regarding birth weight and week with respective values as shown in the Table. Greater average birth weight and gestational age among "Vit – B12" deficient infants were because "Vit – B12" was obtained through the active transport from expectant mother. There was a direct relation of gestation period with "Vit – B12" deficiency.

There was no significant variation in the total serum, direct & indirect levels of bilirubin due to the manifested deficiency of "Vit – B12" (< 100 pg / mL) [7]. There was no association between an increased homocysteine which is considered as vital laboratory "Vit – B12" deficiency indicator, increase in the total serum, direct and indirect levels of bilirubin. Level of plasma homocysteine (> 10 µmol / L) was significantly associated with the deficiency of "Vit – B12" [8]. It is therefore a comparison was made among the total serum, direct & indirect level of bilirubin among cases with level of homocysteine above or under (10 µmol / L) without any significant variation.

There was no significant association of level of urine MMA and total serum as observed through "Spearman's correlation analysis". Deficiency can be associated with the increased level of urine MMA (normal range: 0.3 – 1.9 mmol / mol creatinine), total serum, direct & indirect level of bilirubin between level of urine MMA less or more than (1.9 mmol /

mol creatinine) without any significant variation. Two cases (0.9 %) had incidence of cholestasis: with and without deficiency of "Vit – B12" in each case.

DISCUSSION:

Literature review shows very small amount of association in the hyperbilirubinemia and "Vit – B12" deficiency in very small number of research populations. A considerable number of cases suffered from hyperbilirubinemia and cholestasis because of deficiency of "Vit – B12". Therefore, to prove the association in a large scale population a research was mandatory.

As a result of imbalance of the bilirubin elimination and production the incidence of hyperbilirubinemia arises. In the intrauterine period produced fetal hemoglobin is catabolized quickly which leads to increased bilirubin production; which is not eliminated in the same speed as it produces in newborns. This phenomenon is known as hyperbilirubinemia. In few of the states like Rh and ABO group incompatibility, glucose – VI phosphate, hypothyroidism, deficiency of dehydrogenase or UTI (urinary tract infection), level of bilirubin may reach up to the level of pathological and cause kernicterus (severe sequelae) [9]. Every case was in the time of neonatal period and no one of them presented any signs of jaundice.

For the synthesis of DNA crucial factors are folate metabolism and "Vit – B12", in case of any deficiency of these vitamins ineffective erythropoiesis may cause megaloblastic anemia. No definite data is available that proves hyperbilirubinemia as a result of deficiency of "Vit – B12". An ineffective erythropoiesis may lead to the incidence of immature formation of erythrocyte which increases indirect hyperbilirubinemia and hemolysis [10]. Studies also relate the deficiency of "Vit – B12" with hyperbilirubinemia; such as, Dasari observed the same relation in a forty-one years aged patients [11]. Twenty cases were compared in a case control research by Eroglu N having indirect hyperbilirubinemia (> 5 mg / dL) with another twenty cases with indirect bilirubin (< 5 mg / dL); outcomes reflected deficiency of "Vit – B12" in the first group. We included large population in comparison to the other studies as observed in the literature review.

Total population reflected deficiency of "Vit – B12" in 105 cases (48.8 %) and 110 non-deficient cases (51.2 %); the population was compared in the total, direct and indirect bilirubin levels having respective P-values as (0.300), (0.294) and (0.529) without any significant variation. Urine MMA and Plasma homocysteine tests shown higher levels of specificity and sensitivity in the determination of serum "Vit – B12" sufficiency against an intra cellular metabolism. Level of MMA in urine and blood and homocysteine level in plasma increased because of a reduced MMA -CoA activity; methionine synthase and mutase enzymes in the deficiency of "Vit – B12" [12]. Levels of urine MMA and plasma homocysteine and direct, indirect and total bilirubin levels were also compared but no variation was found significant in these comparisons. According to Ventura, folic acid and "Vit – B12" deficiency causes an increased level of homocysteine and hemolysis [4]. No significant variation was observed in our research about level of homocysteine above or under (10 µmol / L). No difference was seen in the level of total, direct and indirect bilirubin serum with respective P-values of (0.415), (0.811) and (0.254) regarding level of plasma homocysteine as (10 µmol / L) as proposed cut-off significant about deficiency of "Vit – B12" [8].

A reduced bile flow is categorized as cholestasis. In the incidence of cholestasis; cholesterol, bilirubin and bile salts excrete into bile; this excretion is not adequate and it is retained in the tissues as the bile flow is reduced. Pathological increased direct bilirubin is developed because of cholesteric jaundice (which needs rapid treatment and diagnosis). It is also reported that tyrosinemia, galactosemia, disorders of bile acid metabolism and antitrypsin (alpha-1) deficiency may also lead to the incidence of cholestasis related to the deficiency of "Vit – B12" [6]. Two cases (0.9 %) had incidence of cholestasis: with and without deficiency of "Vit – B12" in each case.

Poor societies are more prone to deficiency of "Vit – B12" as the dietary habits are not healthy than the developed countries. For example, mother (81.6 %) and newborn (42%) suffer "Vit – B12" deficiency as observed by Onal H [13]. A Turkish research explored level of serum "B12" in 250 mothers who were expecting babies; however, adults proportion who suffered deficiency of "Vit – B12" was respectively 2.6 % (Switzerland) & 3.4 % (Spain) [14].

CONCLUSION:

It is suggested through the outcomes of this study that deficiency of Vit – B12 was commonly observed in 48.4 %. Therefore, incidence of Vit – B12 deficiency in hyperbilirubinemia or cholestasis cases is also associated with it. More research work is required, in order to prove a strong relation between them.

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