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Relationship Between Prolonged Jaundice and Vitamin B12 Levels in Term Newborns

Term Yenidoğanlarda Uzamış Sarılık ile Vitamin B12 Düzeyleri Arasındaki İlişki

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Abstract

Aim: Vitamin B12 deficiency, when observed during the neonatal period, can generally be traced back to maternal causes. In cases of vitamin B12 deficiency, hyperbilirubinemia may occur due to hem overproduction as the result of erythrocyte lysis. Prolonged jaundice is common during the neonatal period, and its underlying etiological causes should be analyzed. The aim of this study was to analyze whether vitamin B12 deficiency has any effect on prolonged jaundice formation in infants.

Material and Method: The study examined 89 infants; this included 45 that had been diagnosed with prolonged jaundice and 44 in the control group. Their clinical and demographic characteristics were recorded. Patient group was formed with term infants with prolonged jaundice excluding possible etiological causes of prolonged jaundice. Both the maternal and infant vitamin B12 levels were analyzed.

Results: An indirect bilirubin level of 11.8 mg/dl in the prolonged jaundice group and 3.16 mg/dl (p<0.001), a hemoglobin level of 14.18 gr/dl and 15.7 gr/dl (p=0.005), and infant vitamin B12 level of 168 pg/ml and 205.2 pg/ml (p=0.013) in the patient and control groups, respectively, showed significant differences between the two. Maternal vitamin B12 levels were found to be similar in the patient and control groups (p=0.315), and there was no significant correlation between the vitamin B12 levels of the infants and mothers (r=0.278, p=0.064).

Conclusion: Vitamin B12 deficiency can be related to prolonged jaundice in neonatals, and an early diagnosis of vitamin B12 deficiency in high risks group in the neonatal period can be useful in terms of potentially identifying and controlling related conditions.

Keywords: Jaundice, newborn, vitamin B12 deficiency

Öz

Amaç: Yenidoğan döneminde görülen vitamin B12 eksikliği genellikle maternal nedenlerle ilişkilidir. Vitamin B12 eksikliğinde yenidoğan döneminde eritrosit lizisi sonucunda aşırı hem üretimine bağlı hiperbilirubinemi gelişebilmektedir Uzamış sarılık ise yenidoğan döneminde yaygın görülen bir durumdur, allta yatan etiyolojik nedenler araştırılmalıdır. Bu çalışmanın amacı, bebeklerde uzamış sarılık gelişiminde vitamin B12 eksikliğinin etkisinin olup olmadığını araştırmaktır.

Gereç ve Yöntem: 45 uzamış sarılık tanısı alan yenidoğan ile 44 kontrol grubunun yer aldığı toplam 89 bebek çalışmaya dahil edildi. Klinik ve demografik özellikleri kaydedildi. Hasta grubu uzamış sarılığa neden olabilecek etiyolojik nedenler dışlanmış, uzamış sarılığı olan term bebeklerden oluşturuldu. Anne ve bebeklerden vit B12 düzeyleri ile çalışıldı.

Bulgular: Uzamış sarılık grubunda indirekt bilirubin düzeyi 11.8 mg/dl, kontrol grubunda 3.16 mg/dl (p<0.001), hemoglobin düzeyi hasta grubunda 14.18 gr/dl, kontrol grubunda 15.7 gr/dl (p=0.005), bebek vitamin B12 düzeyleri hasta grubunda 168 pg/ml (p=0.013) olmak üzere kontrol grubuna 205.2 pg/ml (p=0.013) göre anlamlı farklılık vardı. Anne vitamin B12 düzeyleri hasta ve kontrol grubunda benzer bulundu (p=0.315). Bebek ve annelerden bakılan vitamin B12 düzeyleri arasında anlamlı bir korelasyon olmadığı saptandı (r=0.278, P=0.064).

Sonuç: Yenidoğanlarda vitamin B12 eksikliğinin uzamış sarılık ile ilişkili olabileceği ve yenidoğan döneminde riskli grupta erken konulan vitamin B12 eksikliği tanısının buna bağlı gelişebilecek durumların kontrol altına alınmasında fayda sağlayabileceğini düşünmekteyiz

Anahtar Kelimeler: Sarılık, yenidoğan, vitamin B12 eksikliği

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INTRODUCTION

Vitamin B12 deficiency is an important global public health problem, and its deficiency is known to cause various hematological and neurological diseases. Vitamin B12 (cobalamin), a water-soluble vitamin, plays a significant role, especially in tissues with high cellular circulation. [1] Vitamin B12 functions in two coenzyme forms, namely methylcobalamin (MeCbl) and adenosilcobalamin (AdoCbl). MeCbl functions as a cofactor for methionine synthase and plays a role in its transformation into tetrahydrofolate, which is necessary for both DNA synthesis and the maturation of red blood cells. Thus, MeCbl deficiency results in megaloblastic anemia.[2] Varying degrees of hyperbilirubinemia can manifest depending on the lysis in eryhtocytes due to ineffective erythropoesis.[3]

Vitamin B12 deficiency in newborns, which mostly originates from their mothers, is a treatable condition. In a previous study, neonatal screenings for this condition presented a deficiency rate of between 3.3-18.7 in 100.000 infants in Germany [4.5] and 0.88 in 100.000 in the USA. [6] Conversely, low B12 levels were detected in 30-40% of the infants in countries like Nepal,[7] Mexico[8] and India.[9] A study from 2019 in Germany reported a predicted birth prevalence of vitamin B12 deficiency as 26 in 100.000; the same study detected previously undetected vitamin B12 deficiency in the mothers of affected neonatal (81%) and emphasized that they were given specific treatment afterwards.[10]

Prolonged jaundice is a common condition in infancy; tests of the transcutaneous bilirubin (TcB) value after week two should be ≥5 mg/dL in term infants.[11] 2-15% of all newborns and 40% of breast-fed infants were reported to be affected.[12] This study aimed to investigate the effect of vitamin B12 deficiency in prolonged jaundice formation in newborns by checking vitamin B12 levels in newborns with prolonged jaundice and their mothers.

MATERIAL AND METHOD

Newborns suffering from jaundice for a minimum period of 37 weeks in the 2nd-3rd level Neonatal Intensive Care Unit and the general pediatrics polyclinics at Kütahya Health Sciences University Evliya Çelebi Training and Research Hospital between January 2021 and February 2022 were included in this prospective study after receiving parental consent. Infants with jaundice lasting for more than two weeks and a total bilirubin level ≥ 5 mg/dl were included in the patient group. A total of 89 infants, 45 in the prolonged jaundice group and 44 in the control group, were included in the study. Hemogram, reticulocyte, maternal and infant blood group, direct Coombs test, urinary reducing substance, urine culture, glucose-6-phosphate dehydrogenase (G6PDH), free thyroxine (fT4), thyroid-stimulating hormone (TSH), maternal and infant vitamin B12 levels, lactate dehydrogenase (LDH), hemogram, and reticulocyte were planned to be taken from the patient group with prolonged jaundice and hemogram, reticulocyte, total and direct bilirubin, and maternal and infant vitamin B12 levels were planned to be taken from the control group. Infants with ABO and Rh incompatibility, abnormality in thyroid function tests, urinary culture positivity, reducing substance positivity in urine and G6PDH enzyme deficiency were not included in prolonged jaundice group. Children of mothers who were mostly on vegetarian diet, had a chronic disease, and took vitamin B12 supplements during pregnancy were not included in the study. Infants who had only been fed formula and those who suffered from additional diseases (cardiac disease, congenital abnormalities, etc) were excluded from the study. Demographical characteristics, such as admission day, sex, gestational week, delivery method, birth weight, height, head circumference, maternal age, APGAR score at first and fifth minutes, and weight at the time of admission were recorded.

After storing venous blood samples at -20°C, vitamin B12 levels were analyzed through an electrochemiluminance method using a Roche brand kit (07212771 190) on a Roche-Hitachi E411 hormone device. The study was approved by the Kütahya Health Sciences University Clinical Researches Ethics Board (Decision no: 11466, Date: 11.12.2020).

Statistical Analysis

The distribution of each continuous variable was tested for normality using the Shapiro-Wilk test. An unpaired t-test was used for normally distributed variables while a Mann Whitney U test was used for non-normally distributed variables; the results were expressed as a median value [25%-75%] and a mean±standard deviation (SD). The Pearson's Chi-square test was used to compare categorical variables, which were expressed in frequencies and percentages. Spearman's rho correlation coefficient was used for correlation analysis. Receiver Operating Characteristic (ROC) Curve analysis was used to determine the cut-off value of B12 level and the area under the curve (AUC). A p-value <0.05 was considered significant. All analyses were performed using the SPSS version 25.0 software (SPSS Inc., Chicago, IL, USA) and Medcalc Software 15.8 (Oostende, Belgium)

RESULTS

45 infants with prolonged jaundice were included in the study, and the control group consisted of 44 healthy infants. In terms of clinical and demographical characteristics, no difference was detected among the two groups in terms of gestational week, sex, delivery method, Apgar score, and admission day. Birth weight was found to be lower in the prolonged jaundice group (p=0.043) (**Table 1**). The mean admission day was 20.42±4.59 days in prolonged jaundice group.

Table 1: Comparison of patient and control groups based on demographical characteristics

	Patient (n=45)	Control (n=44)	P values
Gestational age (weeks)	37(37-38)	38(37-39)	0.116
Sex (%)			
Female	15 (45.5%)	18 (54.5%)	0.603
Male	30 (53.6%)	26 (46.4%)	
Birth weight (g)	2875±582	3105±466	0.043
Delivery method (%)			
C/S	32 (50.8%)	31 (49.2%)	1.000
VD	13 (50.0%)	13 (50.0%)	
Apgar score 1st (min)	8 (7-9)	8(7-9)	0.914
Apgar score 5th (min)	9 (9-10)	9(9-10)	0.947
Age (days)	20.42±4.59	21.06±1.02	0.602

Based on the laboratory values of the groups, the total bilirubin level was 11.8 mg/dL in the prolonged jaundice group and 3.16 mg/dL (p<0.001) in the control group, and the hemoglobin (Hb) level was 14.18±2.60 g/dL in the patient group and 15.7±2.35 g/dL (p=0.005) in the control group. No difference was detected in reticulocyte values among the groups. LDH level was detected as 361.38±134.45 U/L in the prolonged jaundice group. Vitamin B12 levels were detected as 168 (120-202) pg/mL in the prolonged jaundice group and were significantly lower than in the control group (p=0.013). Although maternal vitamin B12 levels were lower in the prolonged jaundice group, the difference was statistically insignificant (p=0.315) (**Table 2**).

Table 2: Comparison of patient and control groups based on laboratory characteristics

	Patient (n=45)	Control (n=44)	P values
Total bilirubin (mg/dL)	11.8 (10.75-13.75)	3.16 (2.57-3.50)	<0.001
Hemoglobin (g/dL)	14.18±2.60	15.7±2.35	0.005
Reticulocyte count (%)	1.49 (1.14-2.37)	1.59 (1.10-2.12)	0.992
Infant B12 levels (pg/mL)	168 (120-202)	205.2 (143.4-266)	0.013
Maternal B12 levels (pg/mL)	202 (160-258)	219.5 (189.3-255.3)	0.315

The mean vitamin B12 level was 185.66±68.33 pg/mL for 89 infants and 217.17±64.89 pg/mL for the mothers included in our study. The ROC curve analysis revealed that the best cut-off value for Vitamin B12 level for detecting jaundice was 207 (p=0.010), with 80% sensitivity, 50% specificity, 62% positive predictive value (PPV), 71% negative predictive value (NPV), and 65% accuracy. This analysis showed an AUC of 0.65 (**Figure 1**).

There was no significant correlation between the vitamin B12 levels of the infants and their mothers in our study (r=0.278, p=0.064). We also detected no correlation between vitamin B12 levels and reticulocyte (r=0.160, p=0.293), LDH (r=0.145, p=0.344), and indirect bilirubin (r=0.036, p=0.812) levels in the patient group.

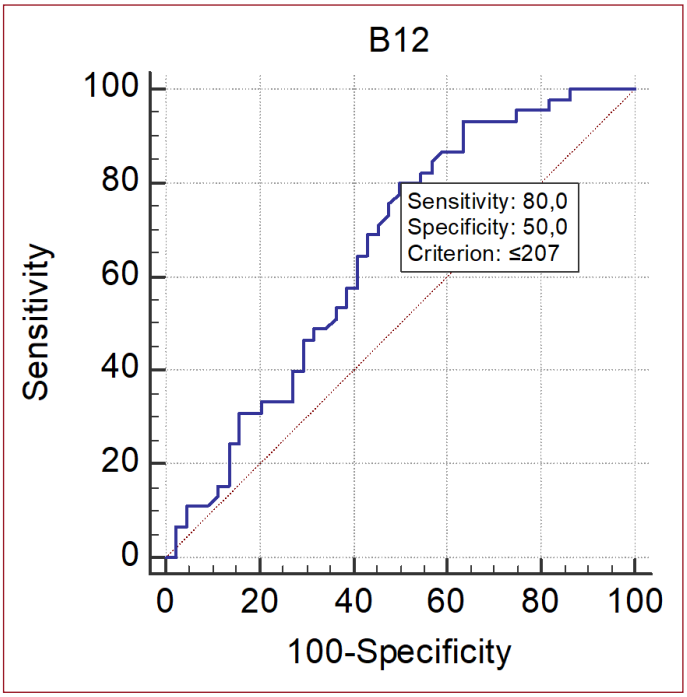

Figure 1. ROC curve analysis for the cut-off value of B12 level in detecting jaundice

DISCUSSION

B12 vitamin also plays an important role in cellular DNA synthesis and efficient erythropoesis.[13] Vitamin B12 deficiency is a common problem across all age groups in most societies; this deficiency leads to an increase in indirect bilirubin levels, often mildly, due to hemolysis.[14]

Jaundice occurs in nearly 60-80% of the infants and is very common in neonatal period. It is more common in breast-fed infants, and jaundice continues in 10% of these infants when they are one month old.[15] Prolonged neonatal jaundice is defined as a TcB value ≥5 mg/dL and persistent jaundice lasting more than two weeks in term infants. The National Institute for Health and Clinical Excellence (NICE) recommends the analysis of direct bilirubin, urine culture, glucose-6-phosphate dehydrogenase, complete blood count, and blood group in the evaluation of prolonged jaundice.[16]

The mean indirect bilirubin level was detected as 11.8 mg/dL in the prolonged jaundice group and as 3.16 mg/dL in the control group in this study. Gundur et al.[17] detected a mean total bilirubin level of 11.6±3.7 mg/dL in their study on 71 infants with prolonged jaundice. In our group with prolonged jaundice, the mean Hb level was 14.1 g/dL and the reticulocyte count was 1.49%. Considering these levels, although the Hb level was low in the patient group, no difference was found between that and the control group in terms of reticulocyte levels. LDH level was also normal in the prolonged jaundice group. The lack of high LDH and reticulocyte levels shows that there was no significant hemolysis in prolonged jaundice group.

Different values are available to define vitamin B12 deficiency. In some studies, vitamin B12 levels lower than 160 pg/mL are accepted as deficiency and those lower than 120 pg/mL are considered severe deficiency for both pregnancy and infants.[18] With regard to the definitions of the World Health Organization, children and mothers have "vitamin B12 deficiency" at <148 pmol/L; children and mothers are in the category of "low vitamin B12" at 148-221 pmol/L; and children and mothers show "vitamin B12 adequacy" at >221 pmol/L.[19] We accepted 207 pg/mL for vitamin B12 as cut-off point.

The mean vitamin B12 level was 168 pg/mL in neonatals with prolonged jaundice and 205.2 pg/mL in the control group; this is a significant difference in vitamin B12 levels. The cut-off value for the vitamin B12 level was determined as 207 pg/mL in our study. Studies showed that vitamin B12 levels in neonatals change between countries. These levels have been reported at 404 pg/mL in Norway, 357 pg/mL in Sweden, 240 pg/mL in China, and 201 pg/mL in India.[20-23] A study by Koç et al.[24] in Turkey detected a vitamin B12 value of 207 pg/mL in the umbilical cord.[23] The same study took the cut-off value for vitamin B12 as 160 pg/mL. Karademir et al.[25] detected serum vitamin B12 level as 236 pg/mL in their study on 204 term infants. It has been suggested that, by causing erythropoesis, vitamin B12 deficiency causes the premature death of both the erythroblasts in bone marrow and the macrocytes in peripheral circulation, leading to thus anemia. Vitamin B12 deficiency is particularly prevalent in India, and a study conducted there reported that B12 and folate deficiency and high homocysteine is related to low birth weight and neonatal hyperbilirubinemia.[23] Eroglu et al.[26] detected mean vitamin B12 levels of 119.9 ng/L in the patient group and as 286.17 ng/L in the control group in their study investigating the relationship between vitamin B12 deficiency and neonatal hyperbilirubinemia. The literature reported on indirect hyperbilirubinemia with severe vitamin B12 deficiency (<30 pg/mL) in a 12 year old female patient.[27] Our study did not detect a significant relationship between vitamin B12 levels and indirect bilirubin values in the prolonged jaundice group. Erdol et al.[28] reported no relationship between total bilirubin levels and B12 deficiency, which is in line with our study. Clinical findings have a mild course in vitamin B12 deficiency, and may cause growth retardation as well as hematological and neurological problems, especially in infants with untreated, severe deficiencies. Vitamin B12 deficiency has been detected in infants due to neonatal screening programs, indicating that it may be mainly maternal-sourced.[6,10,29] Prospective studies have shown that maternal vitamin B12 levels during pregnancy and B12 levels in either the cord blood or serum of the infant at birth are related.[29,30] Balcı et al.[31] reported a significant correlation between B12 levels in the mother and those in the cord blood. Hay et al.[20] showed that maternal vitamin B12 level is an important determinant of the vitamin B12 level of infants. Our study did not detect a significant correlation between maternal and infant vitamin B12 levels in either the patient group or the control group. Reischl-Hajiabadi et al.[32] found results similar to those of this study. In our case, we thought that it may be due to the fact that the blood was obtained from the cord in infants in studies that correlated B12 levels between mothers and infants, and that in our study, it was taken at an average of 20.42 days postnatal.

Some of the limitations of this study included a limited sample size and an analysis of only one biomarker.

CONCLUSION

In this study, it was determined that vitamin B12 deficiency in the infant led to the development of jaundice. We thought that the development of hyperbilirubinemia due to hemolysis might be more pronounced, especially in severe vitamin B12 deficiency. In investigating the etiology of prolonged jaundice, we believe that monitoring vitamin B12 levels, especially in developing countries such as ours and in regions with low socioeconomic status and high incidence of vitamin B12 deficiency, will provide early diagnosis and treatment and will be beneficial for maternal and infant health.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by the Kütahya Health Sciences University Clinical Researches Ethics Board. (Decision no: 11466, Date: 11.12.2020).

Informed Consent: Informed consent forms were obtained from the parents of all patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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