Neurofibromatosis Type 1 and Vitamin B12

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ABSTRACT

The aim of this study was to evaluate vitamin B12 levels in the patients diagnosed with neurofibromatosis type 1 (NF1) and to compare them with a healthy group. In this study, the files of the patients, who were admitted to the pediatric neurology outpatient clinic of a tertiary university hospital and were followed up after being diagnosed with neurofibromatosis type 1 during the 15-month period, were evaluated retrospectively (Study group). Demographic data, and laboratory test results (complete blood count, iron, iron-binding capacity, ferritin, vitamin B12 and folate) were recorded from the patient files. The cases admitted to the hospital for routine child health examination in the same period were taken as the control group. Vitamin B12 levels were statistically significantly lower in the study group compared to the control group (p=0.012). This study is the first study evaluating vitamin B12 levels in NF1 patients.

Key Words: *Neurofibromatosis type 1, Neurofibromin, Nutrition, Vitamin B12.*

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INTRODUCTION

Neurofibromatosis type 1 (NF1) is a disease inherited as autosomal dominant trait and affecting many different systems such as the skeletal, endocrine, and gastrointestinal systems as well as the skin, peripheral and central nervous systems. Its incidence is reported as 1/3000-1/4000.[1] The NF1 diagnostic criteria described by the National Institute of Health (NIH) in 1987 are as follows:[2]

(I) Six or more light brown spots on the skin (often called "*café-au-lait*" spots), measuring more than 5 millimeters in diameter before puberty or more than 15 millimeters after puberty, (II) Freckling in the area of the armpit or the groin, (III) Two neurofibromas or one plexiform neurofibroma, (IV) Optic pathway glioma, (V) Bone lesión at least two iris hamartomas (Lisch nodule), and (VI) First degree relatives with the diagnosis of NF1. The diagnosis was made by the coexistence of at least two of the above criteria.

Neurofibromin is a cytoplasmic protein expressed predominantly in neurons, Schwann cells, oligodendrocytes, astrocyte, and leukocytes. It is encoded by the NF1 gene found on chromosome 17 (17q11.2).[3]

There are no studies in the literature on vitamin B12 levels in the patients diagnosed with neurofibromatosis type 1.

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We think that clinical signs will be more severe due to the reasons listed above in cases where low vitamin B12 levels are observed in these patients. Therefore, the aim of this study was to evaluate vitamin B12 levels in patients followed up with the diagnosis of neurofibromatosis type 1 by comparing them with a healthy group in our study. In this study, the files of the patients who were admitted to the pediatric neurology outpatient clinic were followed up after being diagnosed with neurofibromatosis type 1 between October 2017 and December 2018, were evaluated retrospectively. The patients diagnosed with NF1 were included in the study group (Group 1). The patients admitted to the general pediatric outpatient clinic in the same period as the study with Z00.1: routine child health examination diagnostic code and whose vitamin B12 levels were examined, were included in the control group (Group 2). Exclusion criteria for the control group were presence of any previously existing acute or chronic systemic disease, vitamin B12 supplementation, and presence of malnutrition, obesity, or growth retardation. Children in both the study and control groups were selected during the same seasonal period.

Demographic data (age, gender) and laboratory test results [hemoglobin (Hgb), hematocrit (Hct), white blood cell count (WBC), mean corpuscular volume (MCV), mean platelet volume (MPV), iron, iron-binding capacity, ferritin, platelet count (PLT), vitamin B12, folate] were recorded from the patient files. The study was approved by the local Ethics Committee (Decision No. 2019/3-32).

SPSS (Statistical Package for Social Sciences) for Windows 23.0 programme was used for statistical analyses in the evaluation of the data obtained in this study. Qualitative values were expressed as frequency along with percentage; and quantitative values as mean ± S.D. [minimum, maximum and median (IQR)]. The normal distribution of the data was evaluated by the Shapiro-Wilk test.

Table I: The statistical analysis results of laboratory tests between the groups.

	Group 1 (n:24)	Group 2 (n:41)	p-value
Year (month)	88.13 ± 66.56 (3-209)	98.22 ± 57.80 (7-208)	0.523 [a]
WBC (/mm^3)	7120 (6048 – 8471)	7347 (6242 – 8680)	0.524 [b]
Hemoglobin (gr/dl)	12.7 ± 1.76 (8.8-16.2)	13.0 ± 1.46 (9.3–16.52)	0.486 [a]
Hct %	37.96 ± 5.01 (29.6-50.54)	39.55 ± 3.76 (32.3-47.6)	0.156 [a]
MCV (fL)	79.4 (75-84.2)	79.1 (76.6-84.4)	0.644 [b]
MPV (fL)	7.15 ± 1.33 (5.0-10.20)	7.13 ± 1.00 (4.9-9.8)	0.950 [a]
Platelet (103/µL)	263 (235-313)	287 (249-337)	0.288 [b]
Vitamin B12 (pg/ml)	223.17 ± 76.52(93-363)	292.32 ± 114.28 (111-571)	0.012 [a]
Iron (mg/dL)	69 ± 44 (17-137)	67 ± 28 (17-155)	0.896 [a]
Iron-binding capacity (mg/dL)	284 ± 152 (123-543)	275 ± 56 (148-396)	0.781 [a]
Ferritin (ng/ml)	17.8 (8.2-26.4)	21.1 (16.5-33.3)	0.102 [b]
Folate (ng/ml)	10.5 (7.3-15.9)	11 (7.5-16)	0.951 [b]

MCV: Mean corpuscular volume, MPV: Mean platelet volume; a: Independent student t-test and mean ± SD (minimum-maximum); b: Mann-Whitney U-test and median (IQR).

As a result of Shapiro-Wilk test, Mann-Whitney U-test was used for values that did not show normal distribution, and the independent sample t-test was used for parameters with normal distribution. The Chi-square test was used to evaluate categorical variables. A value of $p<0.05$ was considered statistically significant.

A total of 12 males and 12 females in Group 1 with mean age of 88.13 ± 66.56 (3-209) months and 20 males and 21 females in Group 2 with mean age of 98.22 ± 57.8 (7-208) months, were included in the study. There was no statistically significant difference between the groups in terms of age ($p=0.523$) and gender ($p=0.924$).

A statistically significant difference was observed between the study and control groups in terms of vitamin B12 levels ($p=0.012$). Table I shows the statistical analysis results of laboratory tests of the two groups.

The importance of vitamin B12 for the neurological system stems from the enzymatic reactions, in which it plays a role. Vitamin B12 is a cofactor involved in choline synthesis. It plays a role in the conversion of methylmalonyl CoA, which is important for myelin sheath, to succinyl CoA. As a cofactor, it is involved in the homocysteine / methionine cycle, as well as DNA synthesis, methylation, and neurotransmitter synthesis. In vitamin B12 deficiency, increased methylmalonic acid due to the decrease in the activity of cobalamin-dependent methylcobalamin esterase enzyme, decreases normal myelin synthesis, and abnormal fatty acids are incorporated into neuronal lipids. Histopathologically, swelling of myelin sheaths, intra-myelin vacuole formation, and myelin lamellae separations occur first in vitamin B12 deficiency. Hypotonia, irritability, lethargy, apathy, psychomotor retardation, tremor, ataxia and seizures have also been reported as the neurological signs in Vitamin B12 deficiency. As a result of prolonged vitamin B12 deficiency, demyelination develops in the spinal cord and brain, resulting in permanent neurological injury.[4] One-third of the cases with vitamin B12 deficiency were reported to be admitted to the hospital without any neurological signs in the literature.[5]

Neurofibromin is a cytoplasmic protein expressed predominantly in neurons, Schwann cells, oligodendrocytes, astrocytes and leukocytes. It is encoded by the NF1 gene found on chromosome 17 (17q11.2).[3] The relationship between neurofibromin and vitamin B12 was investigated, but no relationship was observed in the literature. The only relationship between these two is that vitamin B12 is an important step in myelin sheath formation in the central and peripheral nervous systems, and neurofibromin is expressed from oligodendrocytes and Schwann cells.

Reynolds reported that vitamin B12 deficiency was rare in typical multiple sclerosis (MS) observed in young adults, and the cause of this deficiency was unclear in a review. In the same study, it was emphasised that peripheral neuropathy, which is typical in MS, was not surprisingly seen in the patients with vitamin B12 deficiency. It was stated that the nature of the relationship between MS and vitamin B12 deficiency was not clear, and questions such as: 'Is it related to the result of overlapping autoimmune disorders? Does the deficiency reflect an increasing demand for vitamin B12 in myelin repair? Is there a more direct causal relationship?' were tried to be addressed.[6] Souza *et al.* reported the nutrient intake of patients with NF1 in a 2015 cross-sectional study. In this study,

total energy, carbohydrate, protein, fat, electrolytes, minerals, vitamin A, B1, B2, B3, B6, C and D levels were determined in 60 NF1 patients, aged between 18-64 years but vitamin B12 was not mentioned.[7] This study is the first study evaluating vitamin B12 levels in NF1 patients. It was found that vitamin B12 levels were statistically significantly lower in NF1 patients compared to the control group; however, the authors currently do not know the reason why vitamin B12 levels were low. We believe that whether this was incidental or due to a defect found in vitamin B12 metabolism (low intake, transport or absorption level) will be clarified by further studies. Vitamin B12 levels must be monitored in NF1 cases.

ETHICAL APPROVAL:
All procedures performed in this study involving human participants were in accordance with the ethical standards of The Institutional Research Committee and with the 1964 Helsinki Declaration, and its later amendments or comparable ethical standards. This study was approved by Adiyaman University Medical Ethics Committee, (2019/3-32) Turkey.

PATIENTS' CONSENT:
Because this study was retrospective, the patients' consent was waived.

CONFLICT OF INTEREST:
Authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
HA, İHB: Conceived the study design, involved in data collection, performed the statistical analysis, interpreted data and prepared the manuscript draft.
All the authors critically reviewed the final version of the manuscript and approved it for publication.

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