

## Polyneuropathy in Asymptomatic Patients with Vitamin B12 Deficiency

Ece Boylu<sup>1</sup>, Halit Yaşar<sup>2</sup>, Mehmet Saraçoğlu<sup>3</sup>

### SUMMARY

Vitamin B12 deficiency is a systemic disease that often affects the nervous system and peripheral neuropathy is frequently seen in symptomatic patient. In our study, neurologically asymptomatic patients with vitamin B12 deficiency were included. Nerve conduction study and tibial somatosensory evoked potentials (SEP) were performed. Patients that have another reason for polyneuropathy or another disease that can effect nerve conduction studies and tibial SEP were excluded. Twenty patients with vitamin B12 deficiency ( 12 women, 8 men) and 15 healthy subjects were examined. The median patient age was 47.65±16.08. The mean vitamin B12 level was 163.65±26 pg/ml (N: 180-900 pg/ml) in the patient group and 292.30±15.86 pg/ml in the control group. There was a statistically significant difference in distal latency, nerve conduction velocity and F wave latency of the common peroneal nerve (p=0.04, p=0.005 and p=0.000 respectively) between patient and control groups. There was a negative correlation between the latency and conduction velocity of the sural nerve with vitamin B12 levels (p=0.04). There was not a correlation between tibial SEP and vitamin B12 levels (p>0.05). In conclusion, nerve conduction study may show pathological findings in patients with vitamin B12 deficiency neurological syndrome although asymptomatic and nerve conduction study is a method for detection of early peripheral neuropathy in vitamin B12 deficiency.

**Key words:** Polyneuropathy, vitamin B12 deficiency, tibial SEP, nerve conduction study

### B12 VİTAMİNİ EKSİKLİĞİ OLAN ASEPTOMATİK HASTALARDA POLİNÖROPATİ ÖZET

Vitamin B12 eksikliği sistemik bir hastalık olup genellikle sinir sistemini etkilemekte olup semptomatik hastalarda polinöropati sıklıkla görülür. Bizim çalışmamıza nörolojik açıdan asemptomatik olan vitamin B12 eksikliği olan hastalar alınmıştır. Çalışma grubuna sinir ileti çalışması ve tibial somatosensoryel uyandırılmış potansiyeller (SUP) tetkikleri yapılmıştır. Sinir ileti ve tibial SUP çalışmasını etkileyen herhangi bir hastalığı olanlar çalışma dışı bırakılmıştır. B12 eksikliği tanısı alan 20 hasta (12 kadın ve 8 erkek) ve 15 sağlıklı gönüllü çalışmaya alınmıştır. Hastalarda ortalama yaş 47.65±16.08 idi. Ortalama vitamin B12 düzeyi de hasta grubunda 163.65±26 pg/ml (N:180-900 pg/ml), kontrol grubunda 292.30±15.86 pg/ml olarak bulunmuştur. Peroneal sinir distal latansı, sinir ileti hızı ve F dalga latansı hasta ve kontrol grubu arasında belirgin farklı bulunmuştur (sırasıyla p=0.04, p=0.005 ve p=0.000). Vitamin B12 düzeyleri ve sural sinir latansı ve ileti hızı arasında negatif korelasyon saptanmıştır (p=0.04). Tibial SUP ve vitamin B12 değerleri arasında korelasyon bulunmamıştır. Asemptomatik B12 eksikliğinde sinir ileti çalışmasının erken periferik nöropatiyi belirlemede katkısı olabileceği düşünülmüştür.

1. GATA Haydarpaşa Eğitim Hastanesi, Nöroloji Departmanı, Yard. Doç. Doktor

2. GATA Haydarpaşa Eğitim Hastanesi, Nöroloji Departmanı, Uzman Doktor

3. GATA Haydarpaşa Eğitim Hastanesi, Nöroloji Departmanı, Profesör Doktor

**Anahtar kelimeler:** Polinöropati, vitamin B12 eksikliği, tibial SEP, sinir ileti çalışması

### INTRODUCTION

Vitamin B 12 deficiency may cause hematological, gastrointestinal, psychiatric, dermatological and neurological disorders (1,13, 25). Even though vitamin B12 stores in the human body last for up to five years, its deficiency is not uncommon (1). Neurological features are related to the pathologies in the peripheral and optic nerves, posterior and lateral columns of the spinal cord and in the brain leading to myelopathy, myeloneuropathy, peripheral neuropathy, optic neuropathy, encephalopathy and neuropsychiatric abnormalities (13, 32). Vitamin B12 deficiency effects all age groups, but it is relatively common in the elderly population therefore diagnosing vitamin B12 deficiency as a cause of polyneuropathy is problematic as the frequency of both disorders increases with age (2). Patients with neurological syndrome have been investigated with various electrophysiological techniques and the severity, time course and spatial involvement of the neuraxis due to vitamin B12 deficiency was predicted, but there are only a few studies that have examined asymptomatic patients with vitamin B12 deficiency (18, 24, 30).

The aim of this study was to evaluate the effects of vitamin B12 deficiency on the nervous system of the neurologically asymptomatic patients with nerve conduction and somatosensory evoked potential studies.

### MATERIAL AND METHODS

This study was conducted in the Division of Electrodagnostic Neurology, GATA Haydarpaşa Training Hospital, Istanbul between July-December 2007. Patients with low vitamin B12 level (<180pg/ml) diagnosed in the outpatient clinic of internal medicine were referred to our department and patients without neurological complaints, signs or symptoms were included in the study and were examined prospectively.

Patient and control groups were subjected to a detailed clinical history, family history, dietary intake, drug exposure, gastrointestinal surgery, jaundice and chronic diarrhea, and history of autoimmune disease including thyroid disorders.

Detailed neurological and general examination were performed. Muscle power, tone, tendon reflex, coordination and sensation to pinprick, joint position and vibration were tested. Hemo- globin, RBC indices, blood counts, serum chemistry, HIV and thyroid profile were recorded. Vitamin B12 level was detected by chemiluminescent immunoassay method (nor-

**Table 1.** The averages of age and vitamin B12 levels and results of Tibial Somatosensory Evoked Potentials (P40) in the Patient and Control Groups

	PATIENTS	CONTROL	p
AGE	47.65±16.08	46.70±16.73	p>0.05
B12 LEVEL	163.65±26.1	325.23±18.15	p= 0.04*
P40 LATENCY(ms)	40.66±3.03	39.12±1.77	p>0.05

(\*: Statistically significant)

**Table 2.** Sensory Nerve Conduction Studies

	PATIENTS	CONTROL	P
MEDIAN NERVE LATENCY(ms)	3.51±0.43	3.26±0.37	p>0.05
ULNAR NERVE LATENCY (ms)	3.06±0.34	2.86±0.39	p>0.05
SURAL NERVE LATENCY (ms)	3.62±0.44	2.66±0.51	p=0.002 *
MEDIAN NERVE AMPLITUDE (_V)	13.74±10.66	27.54±7.45	p=0.028 *
ULNAR NERVE AMPLITUDE (_V)	16.95±9.45	25.78±10.89	p=0.040 *
SURAL NERVE AMPLITUDE (_V)	7.58±5.26	14.73±8.77	p=0.003 *
MEDIAN NERVE NCV (cm/ms)	54.17±8.50	53.79±2.89	p>0.05
ULNAR NERVE NCV (cm/ms)	52.61±8.42	54.43±4.52	p>0.05
SURAL NERVE NCV (cm/ms)	39.83±7.00	46.79±6.62	p=0.034 *

(\*: Statistically significant NCV: Nerve conduction velocity)

**Table 3.** Motor nerve conduction studies

	PATIENTS	CONTROL	p
MEDIAN NERVE LATENCY(ms)	3.55±0.37	3.31±0.43	p>0.05
ULNAR NERVE LATENCY (ms)	2.74±0.36	2.58±0.27	p>0.05
PERONEAL NERVE LATENCY (ms)	5.98±0.43	4.95±0.63	p=0.04*
TIBIAL NERVE LATENCY (ms)	4.89±0.53	4.85±0.65	p>0.05
MEDIAN NERVE AMPLITUDE(mV)	5.89±2.42	7.98±2.62	p= 0.03*
ULNAR NERVE AMPLITUDE (mV)	4.79±1.94	6.39±1.82	p>0.05
PERONEAL NERVE AMPLITUDE (mV)	2.30±1.19	4.20±1.53	p= 0.02*
TIBIAL NERVE AMPLITUDE (mV)	3.66±1.56	5.55±2.63	p= 0.03*
MEDIAN NERVE NCV (cm/ms)	58.17±5.47	58.43±5.00	p>0.05
ULNAR NERVE NCV (cm/ms)	55.51±4.03	58.36±6.83	p>0.05
PERONEAL NERVE NCV (cm/ms)	40.15±4.35	47.03±4.19	P=0.005*
TIBIAL NERVE NCV (cm/ms)	44.10±3.35	44.38±2.91	p>0.05
MEDIAN F WAVE LATENCY (ms)	27.09±2.04	25.79±1.79	p>0.05
ULNAR F WAVE LATENCY (ms)	27.37±2.23	26.43±2.13	p>0.05
PERONEAL NERVE F WAVE LATENCY (ms)	57.67±4.04	46.40±3.91	p=0.000*
TIBIAL NERVE F WAVE LATENCY (ms)	47.96±3.53	49.63±4.51	p>0.05

(\*: Statistically significant NCV: Nerve conduction velocity)

mal:180-900pg/mL). Patients who have paresthesia, abnormal sensory or motor findings, changes in reflex examination or another disease that can effect nerve conduction studies and tibial SEPs were excluded. All patients and control subjects underwent conventional sensory and motor nerve conduction studies. In each subject, the median, ulnar, sural, tibial, and common peroneal nerves were tested using a Synergy electromyograph (Medelec Ltd., UK) with surface recording and stimulating electrodes bilaterally. Sensory nerve potentials were recorded by antidromic technique with surface recording and stimulating electrodes bilaterally. The amplitude and latency of the sensorial action potentials (SNAP) and sensorial nerve conduction velocity (SNCV) of median nerve (third finger- wrist), ulnar nerve (fifth finger-wrist) and sural nerve (lateral malleolus-foreleg) were measured. Amplitude and the latency of the compound muscle action potentials (CMAP) and motor nerve conduction velocity (MNCV) were measured with the stimulation of the median nerve (wrist/ elbow), ulnar nerve (wrist, below and upper elbow), common peroneal nerve (ankle/ fibula head/knee), and tibial nerve (ankle/ knee) with a special care to insure that stimulation was supramaximal at all points. F wave latency of each motor nerve was evaluated. Tibial somatosensory evoked potentials were elicited by bilateral percutaneous stimulation (0.2ms square wave pulse) at 3 Hz. Stimuli were delivered at an intensity just above motor threshold. Potentials were recorded from Cz-Fz and the latency of P40 was evaluated.

The objective of the study was described to all patients and control subjects and informed consent was obtained. Local ethical committee permission had been obtained from our hospital's ethical committee.

### STATISTICAL ANALYSIS

The student's t test using a 95% confidence interval was applied to evaluate the differences between the patient and matched control groups. The correlation between the parameters and vit B12 levels was examined by Pearson's Correlation Test.  $p < 0.05$  was considered to be significant.

### RESULTS

Twenty patients with vitamin B12 deficiency ( 12 female, 8 male) and 15 healthy subjects (9 female, 6 male) were examined. The median age was 47.65±16.08 in the patient group and 46.70±16.73 in the control group. The mean vitamin B12 level was 163.65±26 pg/ml (N: 180-900 pg/ml) in the patient group and 323.25±15.86 in the control group (table 1). After all of the electrophysiological tests have been applied, intramuscular application of cobalamin was started.

In motor nerve conduction studies there was a statistically significant difference in distal latency, NCV and F wave latency of the common peroneal nerve ( $p=0.04$ ,  $p=0.005$  and  $p=0.000$  respectively) between patient and control groups (table 2). In the patient group the amplitude of median motor, peroneal and tibial nerves were smaller than the control group. According to the sensory nerve conduction studies,

the latency of the sural nerve was prolonged, the amplitude and the nerve conduction velocity were diminished as compared with the healthy subjects ( $p=0.002$ ,  $p=0.03$  and  $p=0.034$  respectively). The amplitude of median and ulnar sensory nerves of the patients were also smaller than the control group (table 3). There was a negative correlation between the latency and conduction velocity of the sural nerve with vitamin B12 levels ( $p=0.04$ )

There was not a statistically significant difference between the patient and control groups according to tibial SEP ( $p>0.05$ ). There was not a correlation between vitamin B12 levels and the latency of P40 ( $p>0.05$ ) (table 1). In none of the studies there was not a right to left asymmetry.

## **DISCUSSION**

Vitamin B12 deficiency can occur as a result of malabsorption, gastrointestinal surgery, drugs, parasitic diseases, autoimmune diseases and genetic defects (27). Low vitamin B-12 intake may lead to decreased bioavailability and functional deficiency of cobalamin. Although early noticeable symptoms of vitamin B-12 deficiency are nonspecific (unusual fatigue, digestion problems, frequent upper respiratory infections), the best-known clinical manifestations of cobalamin malabsorption are hematologic (pernicious anemia) and neurologic symptoms (7). Though the pathophysiological mechanism of the neurological damage is not clear vitamin B12 deficiency leads to different pathological mechanisms in the central and peripheral nervous system (20, 24).

Vitamin B12 deficiency should be considered in the differential diagnosis of all spinal cord, peripheral nerve, and neuropsychiatric disorders. Vitamin B12 replacement should not be withheld from patients with borderline vitamin B12 levels, since the consequences of allowing myelopathy, neuropathy dementia, and mental disorders to worsen clearly outweigh any disadvantage of therapy (23).

The best-known neurologic manifestation of vitamin B12 deficiency is subacute combined degeneration. (24). Isolated neuropathy or myelopathy may occur independently, but often appear concurrently. Peripheral neuropathy is frequently observed in symptomatic patients with vitamin B12 deficiency (31). Lack of vitamin B12 was suggested to effect sensory nerves primarily. Nerve conduction studies of vitamin B12 deficient patients with clinically apparent neuropathy have shown

decreased amplitudes of mostly sensory nerves in a majority of cases (8,9,10,19). The other studies did not observe axonal changes but observed primary demyelinating sensory neuropathy (3, 11, 28) whereas some studies have shown that motor nerves could also be effected due to vitamin B12 deficiency (5, 9,13,20, 26).

In our study, though the patients were neurologically asymptomatic, the amplitudes of both motor and sensory nerves were diminished. Distal latency and F wave latency of the common peroneal nerve and the latency of sural nerve were prolonged and NCV of the both nerves were diminished in the patients with vitamin B12 deficiency. In the literature we have found only one study that have investigated the neurologically asymptomatic patients with vitamin B12 deficiency with nerve conduction studies. Their study population was younger than our study group and they have found no significant difference for any of the nerve conduction study parameters between the asymptomatic patients with vitamin B12 deficiency and the control group (18). Abnormalities of somatosensory evoked responses in individuals with vitamin B12 deficiency were observed and higher frequency of tibial compared to median SEP changes were revealed. Patients ( $n=10$ ) with diminished position and vibration sensation were examined and the prolongation of latency of the median SEP was found in 40% of the patients, while peroneal SEP was abnormal in all of the patients (9). In another study, patients with myelopathy in 8, myeloneuropathy in 5, neuropathy in 2 patient were examined with nerve conduction studies and tibial SEP. Tibial SEP was abnormal in 12 out of 15 and right to left asymmetry was present in 4 patients. Conversely, no peripheral or central SEP abnormalities were seen in 18 vegetarians with low vitamin B12 levels, although 6 reported mild sensory symptoms suggestive of peripheral neuropathy and 3 had corroborative clinical signs. In our study, in tibial SEP study there was not a statistically difference between patient and control groups and there was no right to left asymmetry.

In a few studies serum vitamin B12 level were found to be correlated with the latencies of P39 and sural SNAP (24). In our study, similarly we have found a negative correlation between the latency and conduction velocity of the sural nerve with vitamin B12 levels but there was not a correlation between the latency of P40. In conclusion, nerve conduction study may show pathological findings in neurologically asymptomatic patients with vitamin B12 deficiency and therefore nerve

conduction study is a method for detection of early peripheral neuropathy in vitamin B12 deficient patients. Early diagnosis is important, because a myriad

of adverse outcomes that can be progressive and irreversible neurological abnormalities can be averted with substitutive treatment.

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