Journal of Neurological Sciences [Turkish] **31:(1)**# 39; 001-010, 2014
http://www.jns.dergisi.org/text.php3?id=735
Research Article

Electrodiagnostic Studies in Neurologically Asymptomatic Patients with Vitamin B12 Deficiency

Füsun Mayda DOMAÇ[1,4], Geysu KARLIKAYA[2,4], Yılmaz ÇETİNKAYA[3,4], Mehmet GENCER[3,4], Tülin TANRIDAĞ[4], Önder US[4]

[1]Erenköy Mental and Neurological Disease. Training and Research Hospital, İstanbul [2]Acıbadem University, Department of Neurology, İstanbul [3]Haydarpaşa Numune Training and Research Hospital, Department of Neurology, İstanbul, Türkiye [4]Marmara University, Electrodiagnostic Neurology, Department of Neurology, İstanbul, Türkiye

Summary

Objectives: The aim of our study was to investigate the electrophysiologic parameters in neurologically asymptomatic patients with vitamin B12 deficiency, and to compare the results with the control group and also to investigate a correlation between vitamin B12 levels and the recorded parameters.
Methods: Asymptomatic and untreated patients with vitamin B12 deficiency were examined by nerve conduction studies, visual evoked potentials (VEPs), medial and tibial somatosensory evoked potentials (SEPs), and motor evoked potentials (MEPs), prospectively. Patients who have any other disease that can effect nerve conduction studies, VEPs, SEPs, and MEPs were excluded.
Results: Twenty-seven patients (22 women, 5 men) with a mean age of 37.65±13.08 and 21 healthy subjects were examined. The mean vitamin B12 level was 127±35.6 (N: 200-900) in the patient group and 301±67 in the control group. There was not a statistically significant difference between the patient and control groups according to nerve conduction studies, median SEP, tibial SEP, VEP, and MEP studies ($p>0.05$). There was no correlation between vitamin B12 levels and median SEP, tibial SEP, VEP, and MEP parameters ($p>0.05$).
Conclusion: To our knowledge, this is the first study that has investigated neurologically asymptomatic patients with B12 deficiency by nerve conduction studies, VEPs, SEPs, and MEPs. The electrophysiological findings may be normal in asymptomatic patients with vitamin B12 deficiency if the diagnosis is made early.

Key words: Vitamin B12 deficiency, electrodiagnostic study

Vitamin B12 Eksikliği Olan Nörolojik Açıdan Asemptomatik Hastalarda Elektrodiagnostik Çalışmalar

Özet

Amaç: Çalışmamızın amacı vitamin B12 eksikliği olan nörolojik açıdan asemptomatik hastalarda elektrofizyolojik parametrelerin incelenmesi, sonuçların kontrol grubu ile karşılaştırılması ve vitamin B12 düzeyleri ile kayıtlanan sonuçlar arasındaki korelasyonun araştırılmasıdır.
Metod: Vitamin B12 eksikliği olan asemptomatik ve tedavi edilmemiş hastalar prospektif olarak sinir ileti çalışmaları, görsel uyarılmış potansiyeller (VEP), medial ve tibial somatosensoriel uyarılmış potansiyeller (SEP) ve motor uyarılmış potansiyeller (MEP) tetkikleri ile incelenmiştir. Sinir ileti çalışmaları, VEP, SEP ve MEP'leri etkileyebilecek hastalığı olanlar çalışma dışı bırakılmıştır.

Bulgular: Yaş ortalaması 37.65±13.08 olan 27 hasta (22 kadın, 5 erkek) ile 21 sağlıklı gönüllü incelenmiştir. Ortalama vitamin B12 düzeyi hasta grubunda 127±35.6 pg/ml)(N: 200-900pg/ml), kontrol grubunda 301±67pg/ml idi. Hasta ve kontrol grupları arasında sinir ileti çalışmaları, median SEP, tibial SEP, VEP ve MEP parametreleri açısından anlamlı istatistiksel fark saptanmadı (p>0.05). Vitamin B12 düzeyleri ile median SEP, tibial SEP, VEP ve MEP parametreleri arasında korelasyon bulunmadı (p>0.05).

Sonuç: Bu çalışma vitamin B12 eksikliği olan nörolojik açıdan asemptomatik hastaları sinir ileti çalışmaları, VEP, SEP ve MEP tetkikleriyle inceleyen ilk çalışmadır. Eğer tanı erken konulursa vitamin B12 eksikliği olan asemptomatik hastalarda elektrofizyolojik çalışmalar normal olabilmektedir.

Anahtar Kelimeler: Vitamin B12 eksikliği, elektrodiagnostik çalışma

INTRODUCTION

Vitamin B12 or cobalamin is a water soluble vitamin that is required as a cofactor in several enzymatic reactions and performs an important function in organic metabolism(17). Even though vitamin B12 stores in the human body last for up to five years, its deficiency is not uncommon(1). Vitamin B12 deficiency is frequently seen in vegetarians and can also occur as a result of malabsorption, gastrointestinal surgery, drugs, parasitic diseases, autoimmune diseases and genetic defects(7,29).

Though, vitamin B12 deficiency effects all age groups it is relatively common in the elderly population(9,34). Vitamin B12 deficiency may lead to decreased bioavailability and functional deficiency of cobalamin and may cause heamatological, gastrointestinal, psychiatric, dermatological and neurological disorders(1,2,8,13,27). 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(8,13,35). Patients with neurological syndrome have been investigated with various electrophysiological techniques such as nerve conduction studies, visual evoked potentials (VEPs), somatosensory evoked potentials (SEPs) or motor evoked potentials (MEPs), but there are only a few studies that have examined asymptomatic patients with vitamin B12 deficiency(6,15,26,32)

The aim of this study was to evaluate the effects of vitamin B12 deficiency on the nervous system with electrophysiological studies in neurologically asymptomatic patients, and also to investigate a correlation between vitamin B12 levels and the recorded parameters.

MATERIAL AND METHODS

This study was conducted in the Department of Electrodiagnostic Neurology, Marmara University, İstanbul, Turkey. Patients diagnosed as vitamin B12 deficiency in the outpatient clinic of internal medicine with low serum vitamin B12 values (<200pg/ml) and high serum concentrations of homocysteine and methyl malonate but without neurological complaints, signs or symptoms were included in the study. Electrophysiological studies were conducted before treatment and neurologically asymptomatic and untreated patients with vitamin B12 deficiency were examined prospectively. Age-matched healthy subjects with normal serum values of vitamin B12, homocysteine and methyl malonate were chosen as control group.

Patient and control groups were subjected to a detailed clinical history, family history, dietary intake, drug exposure, gastrointestinal surgery, small bowel disease (malabsorption, ileal by-pass or resection, Crohn's disease) and history of systemic, rheumatological or autoimmune diseases including thyroid disorders and diabetes mellitus.

Detailed neurological and general examination were performed for both of the groups. The examination of muscle power, tone, tendon reflex, coordination and sensation to pinprick, joint position and vibration was normal. Mental status of each of the patient was evaluated by the Mini Mental State Examination (MMSE-total score of 30). In neuroophtalmological examination visual acuity, colour vision, field of vision and fundus oculi were detected and found to be normal in each patient and control subject. Hemoglobin, RBC indices, mean corpuscular volume, folate, homocysteine, methyl malonate, routine biochemical and microbiological tests, HIV and thyroid profile were detected. The findings were in normal ranges in both of the groups except for megaloblastic anemia in the patient group. Vitamin B12 level was detected by chemiluminescent immunoassay method (normal:200-900pg/mL).

All patients and control subjects underwent conventional sensory and motor **nerve conduction studies** recorded in a warm room and the skin temperature was maintained between 35-37°C. 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. 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. Sensory nerve potentials were recorded antidromically 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 with a distance of 14cm), ulnar nerve (fifth finger- wrist with a distance of 12cm) and sural nerve (lateral malleolus-foreleg with a distance of 14cm) were measured.

Visual evoked potentials were elicited by monoocular pattern reversal stimulation recording from Oz with a reference electrode on Fz (10-20 system) and ground electrode on Cz. The electrode impedance was kept below 5Ω with a band pass of 1-300Hz and sweep time of 500ms. Stimulation rate was 1 Hz, producing reversal pattern every 500msec. Stimuli were presented as a checkerboard pattern of black and white squares with a check size of 56, arc luminance of central fieldwas 50cd/m^2 (contrast 100%) at a reversal frequency of 3 Hz. The distance between the eye and the center of the screen was 100cm. With one eye patched, subjects were instructed to fixate on a point in the middle of the screen. One hundred and twenty-eight epochs were averaged twice, to check the reproducibility of wave forms. The latencies of N75, P100 and N145 were measured. We compared VEP latencies between the right and left eyes within each population.

Somatosensory evoked potentials were elicited by bilateral percutaneous stimulation (0.2ms square wave pulse) at 3 Hz and 256 epochs were averaged twice to check the reproducibility of wave forms. Stimuli were delivered at an intensity just above motor threshold. The electrode placements were done according to the 10/20 system. Medial SEPs were recorded 2cm posterior and 7cm lateral to Cz. Reference electrode was put on Fz and ground electrode was placed on the same extremity proximally. The stimulus was given from the median nerve at the contrlateral wrist and the intensity was increased until thumb movement was seen bilaterally. Band width was 10-2000 Hz and analysis time was 100msec and the latencies of N20 and P25, the cortical responses were evaluated. Tibial SEPs were carried out by stimulating the tibial nerve behind the medial malleolus bilaterally, recording from Cz′(2cm posterior to Cz) with a reference electrode on Fpz′ (2cm behind Fp). Band width was 10-2000 Hz with an analysis time of 200msec. The latencies of N35 and P40 were evaluated.

Motor evoked potentials (MEPs) were recorded bilaterally with surface electrodes from abductor pollicis brevis (APB) muscles and stimulated with a round coil at the vertex and C7 spinous process with %20 above motor threshold. (Medtronic, Magpro 200, Denmark). During cortical stimulation a slight voluntary contraction of the target muscles was maintained (10% of maximum force). Three responses were obtained and the potential with shortest latency was analysed. Latency differences were used to estimate central motor conduction time (CMCT).

Patients under 50 years of age without cognitive impairment, paresthesia, abnormal sensory or motor findings, changes in reflex examination were included in the study. Patients with previous diagnosis and treatment of vit B12 deficiency, servical or lomber radiculopathy, demyelinating disease, optic neuropathy, systemic, autoimmune or rheumatological diseases, treatment with drugs that could effect the absorbtion of vitamin B12 or any other diseases that could affect nerve conduction studies, pattern reversal VEPs, median and tibial SEPs or MEPs were excluded.

The objective of the study was described and informed consent was obtained from all patients and control subjects and local ethical committee approval regarding this study had been obtained from local 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 serum vitamin B12, homocysteine and methyl malonate levels was examined by Pearson's Correlation Test. $p < 0.05$ was considered to be significant.

RESULTS

Sixty five patients with vitamin B12 deficiency were admitted. Thirthy eight patients who did not have the inclusion criteria (10 patients with diabetes mellitus, 7 patients with thyroid disease, 6 patients with previous diagnosis of vitamin B12 deficiency, 5 patients under cobalamine treatment, 4 patients with cervical radiculopathy, 3 patients with lumbar radiculopathy, 2 patients with optic neuropathy and 1 patient with additional folate deficiency) were excluded. Neurologically asymptomatic 27 young patients with isolated vitamin B12 deficiency (22 females, 5 males) and 21 age-matched healthy subjects (16 females, 5 males) with the inclusion criteria were examined. Mean age was 37.7±12.1 in the patient group and 37.9±11.7 in the control group. The mean vitamin B12 level was 127±35.6 (N: 180-900) in the patient group and 351±67 in the control group. MMSE scores were 30 both in patient and control groups.

Dietary lack was observed in 10 of the patients. Upper gastrointestinal endoscopy was performed in 17 patients and atrophic gastritis was observed in 7, and ulcus at duodenum in 2 of the patients. As in 8 patients no aetiology was found schilling test was applied and 4 patients had pernicious anemia, 1 had pancreatic enzyme defect. After all of the electrophysiological tests have been applied, intramuscular application of cobalamin was started.

The results of sensory and motor nerve conduction studies are shown in Tables 1&2. There was not a statistically significant difference between the patient and control groups according to nerve conduction studies (p>0.05). There was no correlation between serum vitamin B12 homocysteine or methyl malonate levels and nerve conduction studies (p>0.05).

There was not a statistically significant difference between the patient and control groups according to VEP, median SEP, tibial SEP, and MEP studies (p>0.05). The results of the studies are shown in Tables 3&4. There was not a right to left asymmetry in all of the studies. There was also no correlation between serum vitamin B12, homocysteine and methyl malonate levels and VEP, median SEP, tibial SEP, and MEP parameters (p>0.05).

Table 1: Motor Nerve Conduction Studies: Controls/*Patients*

	Latency (ms) Mean ± SD (p)	CMAP amplitude (mV) Mean ± SD (p)	NCV (m/s) Mean ± SD (p)	F Wave Latency (ms) Mean ± SD (p)
Median	3.1±0.6/ ***3.2±0.4*** p=0.29	7.1±2.1 / ***7.2±3.7*** p=0.61	59.6±4/ ***56.6±4*** p=0.06	25±2/***25.1±2*** p=0.85
Ulnar	2.4±0.4/ ***2.5±0.1*** p=0.44	6.9±1.5 / ***7±3.3*** p=0.32	63±5/ ***63±5*** p=0.53	25.1±2/ ***25.4±2*** p=0.62
Peroneal	4.1±0.7/ ***3.9±0.6*** p=0.22	4.1±0.8 / ***3.9±1.5*** p=0.14	48.9±4/ ***49.2±5*** p=0.71	44.2±3/ ***44.4±3*** p=0.93
Tibial	4.4±0.3/ ***4.5±1.1*** p=0.43	5.0±1 / ***4.5±2*** p=0.29	45.2±2/ ***45.1±3*** p=0.89	47±4/***47±5*** p=0.38

Table 2: Sensory Nerve Conduction Studies: Controls/***Patients***

	Latency (ms) Mean ± SD (p)	SNAP amplitude (µV) Mean ± SD (p)	NCV (m/s) Mean ± SD (p)
Median	2.4 ± 0.1 / ***2.5 ± 0.4*** p=0.07	41.5 ± 22 / ***38.4 ± 24*** p=0.45	56.7 ± 5 / ***54 ± 7*** p=0.21
Ulnar	2.1 ± 0.3 / ***2.2 ± 0.2*** p=0.30	44 ± 23/ ***41 ± 33*** p=0.83	55.4 ± 5/ ***55 ± 4*** p=0.56
Sural	2.5 ± 0.4 / ***2.6 ± 0.3*** p=0.87	21 ± 6/ ***21 ±12*** p=0.91	50.2 ± 5/ ***49 ± 5*** p=0.17

Table 3: Results of Visual Evoked Potentials (N75, P100, N145), Median Somatosensorial Evoked Potentials (N20, P25) and Tibial Somatosensorial Evoked Potentials (N35,P40) in the Control and Patient Groups

Latency (ms)	Control Group Mean ± SD	Patient Group Mean ± SD	p
Right N75	71.7 ±2.2	73.1 ±2.6	0.07
Right P100	102 ±4.3	103.2 ±3.1	0.96
Right N145	135.5 ±9.3	136.2 ±9.8	0.91
Left N75	73.3 ±3.1	74.4 ±3.5	0.62
Left P100	101.8 ±4.6	102.4 ±4.3	0.93
Left N145	133.8 ±10.7	134 ±10.2	0.62
Right N20	19.6 ±1.5	19.9 ±1	0.48
Right P25	24.2 ±2.7	25 ±2.5	0.08
Left N20	19.2 ±1.5	19.6 ±1	0.46
Left P25	24.1 ±2.8	24.9 ±2.4	0.15
Right N35	33.4±4.8	32.5 ±2.0	0.57
Right P40	39.3 ±3.4	39.5 ±2.8	0.65
Left N35	33.4 ±1.5	33.6 ±1.1	0.56
Left P40	39.1 ±2.2	39.3 ±1.8	0.62

Table 4: Results of Motor Evoked Potentials in the Control and Patient Groups Recorded from APB Muscles

	Controls	Patients	p
Right cortical latency (ms)	20.1 ±1.7	20.8 ±1.9	0.15
Right central motor conduction time (ms)	8.2 ±1.3	8.7 ±1.6	0.38
Left cortical latency (ms)	19.9 ±1.9	20.9 ±2.0	0.28
Left central motor conduction time (ms)	8.3 ±1.5	8.9 ±1.9	0.49

DISCUSSION

Vitamin B12 (cobalamin) is a water-soluble vitamin that is required as a cofactor in several enzymatic reactions. One of them is the conversion of methylmalonyl Co A to succinyl CoA in which adenosylcobalamin is required as a cofactor. Lack of adenosylcobalamin may lead to accumulation of methylmalonyl CoA, causing a decrease in normal myelin synthesis and leading to incorporation of abnormal fatty acids into neuronal lipids(4). Vitamin B12 deficiency is therefore suggested to result in defective myelin synthesis leading to diverse central and peripheral nervous system dysfunction(23).

Though there is much debate regarding the appropiate method for the diagnosis of vitamin B12 deficiency, the diagnosis is often made according to the low levels of serum vitamin B12(23). Classic laboratory findings of low serum vitamin B12, macrocytic red blood cell indices, and megaloblastic anemia were not always present(25). Hematologic indices are normal in up to 30% of patients with vitamin B12 deficiency, and results of the Schilling test may be normal in patients with symptoms of deficiency(11).

A wide variety of neurologic symptoms and signs were encountered including ataxia, loss of cutaneous sensation, muscle weakness, diminished or hyperactive reflexes, spasticity, urinary or fecal incontinence, orthostatic hypotension, loss of vision, dementia, psychoses, and disturbances of mood(16). In our study, we have excluded the patients with neurologic symptoms and examined asymptomatic patients.

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(10,12,20). Some studies have shown sensory demyelinating polyneuropathy(3,30) or motor demyelinating polyneuropathy(5) or sensory-motor demyelinating polyneuropathy findings(11,13,22,28). F-wave latency may be prolonged, and there may be an increase in F wave chronodispersion(26). Most of the patients have improved after the administration of vitamin B12(22,28,30) unless the irreversible damage of the axons was seen in predominantly axonal neuropathy(11,20).

In the literature there are a few studies that have investigated the electrophysiologic parameters in neurologically asymptomatic patients with B12 deficiency. Boylu et al have found the prolongation of the latencies and reduction of nerve conduction velocities of common peroneal and sural nerves of the patients with vitamin B12 deficiency as compared with healthy subjects(6). In our study, there was no significant difference for any of the nerve conduction study parameters between the neurologically asymptomatic patients with vitamin B12 deficiency and the control group ($p>0.05$). This maybe due to the younger age of our study population and detailed examination of the patients for any disease that could effect nerve conduction studies.

Vitamin B12 deficiency is known to effect the visual pathways(10,11,21,22). Optic neuropathy is a rare complication of vitamin B12 deficiency which may proceed to visual failure if not diagnosed early(19,26). Chronic vitamin B12 deficiency was suggested to result in chronic demyelination and remyelination which had resulted in prolongation of P100 latency(11,22,24). In a few studies, patients with B12 deficiency but without visual symptoms were examined and a delay of P100 latency was displayed(26,32) that usually returned to normal after treatment(24). In our study, neuroophtalmogical examination of the patients was normal and no prolongation of P100 latency was observed as compared with healthy subjects.

Somatosensorial evoked potentials have also been reported to be abnormal in patients with neurological syndrome[1,10,11,14,15,23]. A significant correlation was found between the disease duration and N20 latency, whereas similar correlation was not found between P37 latency[26]. Some studies have revealed higher frequency of abnormalities in lower extremity nerves (tibial and peroneal) compared to upper extremities (median) of the patients with neurological syndrome[11,13,21] and a right to left asymmetry was observed in tibial SEP[22].

There are a few studies that have investigated neurologically asymptomatic patients with SEP studies. Jones et. al have examined vegetarian patients with low vitamin B12 levels and have reported mild sensory symptoms suggestive of peripheral neuropathy in 33% of them and 16% had clinical signs as diminished sensation and depressed tendon jerks while the remaining patients were asymptomatic. No peripheral or central SEP abnormalities were seen in both neurologically asymptomatic and symptomatic Patients[15]. Boylu et al. have investigated the patients with tibial SEP and found no prolongation of P40 latency[6]. In our study, we have found all of the latencies of median and tibial SEPs in normal ranges. There was also no right to left asymmetry (p>0.05).

Motor pathways may also be effected in vitamin B12 deficiency. Prolongation of CMCT can be mild to moderate and can be due to desynchronisation of descending volleys in the motor pathways[13,22,23,31,35]. TheCMCT changes are consistent with the demyelination of lateral column and histopathologically pyramidal pathways are regularly involved at cervicodorsal region in vitamin B12 deficiency[18]. All of these studies have investigated neurologically symptomatic patients. In the literature we could not find a study that has examined the asymptomatic patients with vitamin B12 deficiency with MEP studies. In our study, there was not an impairment in MEP parameters. We suspect that, vitamin B12 deficiency has been detected so early that demyelinating changes have not begun yet.

There are few studies proposing a correlation between laboratory findings and neurological findings in vitamin B12 deficiency. Serum vitamin B12 level was found to correlate with sural SNAP and prolonged latency of tibial SEP responses[26] while in another study no correlation was found between electrophysiological and laboratory findings[33]. In our study, there was no correlation between serum vitamin B12 levels and electrophysiological parameters (p>0.05).

In conclusion, to our knowledge, this is the first study that has investigated neurologically asymptomatic patients with B12 deficiency by nerve conduction studies, visual evoked potentials, somatosensory evoked potentials, and motor evoked potentials. The electrophysiological findings may be normal in neurologically asymptomatic patients with vitamin B12 deficiency if the patients are diagnosed early and the suitable treatment is important to prevent neurological symptoms, progressive adverse outcomes and irreversible neurological complications.

Acknowledgement: We gratefully thank to Miss Sercan Davulcu (Electrodiagnotic Neurology Laboratory, Marmara University, İstanbul, Turkey) for her assistance.

This study was presented as an oral presentation at the 13th European Congress of Clinical Neurophysiology, İstanbul, Turkey, May 4-8, 2008.

Correspondence to:
Füsun Mayda Domaç
E-mail: fusundomac@yahoo.com.tr

Received by: 19 December 2012
Revised by: 31 December 2013
Accepted: 16 January 2014

The Online Journal of Neurological Sciences (Turkish) 1984-2014
This e-journal is run by Ege University Faculty of Medicine,
Dept. of Neurological Surgery, Bornova, Izmir-35100TR
as part of the Ege Neurological Surgery World Wide Web service.
Comments and feedback:
E-mail: editor@jns.dergisi.org
URL: http://www.jns.dergisi.org
Journal of Neurological Sciences (Turkish)
Abbr: J. Neurol. Sci.[Turk]
ISSNe 1302-1664

REFERENCES

1. *Aaron S, Kumar S, Viyajan J, Jacob J, Alexander M, Gnanamuthu C. Clinical and laboratory features and response to treatment in patients presenting with vitamin B12 deficiency-related neurological syndromes. Neurol India 2005;53:55-8.*
2. *Allen LH. How common is vitamin-B12 deficiency? Am J Clin Nutr 2009; 89:2:693-6.*
3. *Andres E, Affenberger S, Vinzio S, et al. Food-cobalamin malabsorption in elderly patients: clinical manifestations and treatment. Am J Med. 2005 Oct;118(10):1154-9.*
4. *Beck WS: Diagnosis of megaloblastic anemia. Annu Rev Med 1991;42:311-22.*
5. *Brieva L, Ara JR, Bertol V, Canellas A, Del Agua C. Polyneuropathy caused by vitamin B12 deficiency secondary to chronic atrophic gastritis and giardiasis. Rev Neurol 1998;26(154):1019-20.*
6. *Boylu E, Yaşar H, Saraçoğlu M. The peripheral neuropathy in asymptomatic patients with vitamin B12 deficiency. The Medical Journal of Haydarpaşa Training Research Hospital 2010;50 (1):24-8.*
7. *Dali-Youcef N, Andress E. An update on cobalamin deficiency in adults. QJM 2009;102-17.*
8. *Dalla Töre C, Lucchetta M, Cacciavillan M, Campagnolo M, Manara R, Briani C. Reversible isolated sensory axonal neuropathy due to cobalamin deficiency. Muscle Nerve 2012;45(3):428-30.*
9. *Elmadfa I, Singer I. Vitamin-B12 and homocysteine status amond vegeterians: a global perspective. Am J Clin Nutr 2009 89(5):1693-1698.*
10. *Fine EJ, Hallett M. Neurophysiological study of subacute combined degeneration. J Neurol Sci 1980; 45(2-3):331-6.*
11. *Fine EJ, Soria E, Paroski MW, Petryk D, Thomasula L. The neurophysiological profile of vitamin B12 deficiency. Muscle Nerve 1990; 13(2):158-64.*
12. *Fine EJ, Soria ED. Myths about vitamin B12 deficiency. South Med J 1991;84(12):1475-81.*
13. *Hemmer B, Glocker FX, Schumacher M, Deuschl G, Lücking CH. Subacute combined degeneration: clinical, electrophysiological, and magnetic resonance imaging findings. J Neurol Neurosurg Psychiatry. 1998;65(6):822-7. Comment in: J Neurol Neurosurg Psychiatry. 1998 ;65(6):807.*
14. *Jia ZR, Wang TT, Pan T, Wang HX, Shi X, Liang W. Diagnostic significance of spinal cord conduction velocity in the diagnosis of central lesions in subacute combined degeneration Zhonghua Yi Xue Za Zhi 2011;91(37):2641-3.*
15. *Jones SJ, Yu YL, Rudge P, Kriss A, et al. Central and peripheral SEP defects in neurologically symptomatic and asymptomatic subjects with low vitamin B12 levels. J Neurol Sci 1987;82(1-3):55-65.*
16. *Healton EB, Savage DG, Brust JC, Garrett TJ, Lindenbaum J. Neurologic aspects of cobalamin deficiency. Medicine (Baltimore) 1991;70(4):229-45.*
17. *Kumar N. Nutritional neuropathies. Neurol Clin 2007;25(1):209-55.*
18. *Kunze K, Leitenmaier K. Vitamin B 12 deficiency and subacute combined degeneration of spinal cord. In: Venken PJ, Bruyn GW eds, Hand book of clinical Neurology, Elsevier, Amsterdam 1976;141-98.*
19. *Larner AJ. Visual failure caused by vitamin B12 deficiency optic neuropathy. Int J Clin Pract 2004;58(10):977-8.*
20. *Mc Combe PA, Mc Leod JG. The peripheral neuropathy of vitamin B12 deficiency. J Neurol Sci 1984; 66(1):117-26.*
21. *Min YK, Kim SM, Kim SH, Kwon KH, Sunwoo IN. Sequential involvement of the nervous system in subacute combined degeneration. Yonsei Med J 20112;53(2):276-8*
22. *Mısra UK, Kalita J, Das A. Vitamin B12 deficiency neurological syndromes: a clinical, MRI and electrodiagnostic study.Electromyogr Clin Neurophysiol. 2003 ;43(1):57-64.*
23. *Mısra UK, Kalita J. Comparison of clinical and electrodiagnostic features in B12 deficiency neurological syndromes with and without antiparietal cell antibodies. Postgrad Med J 2007;83:124-7.*
24. *Pandey S, Kalita J, Mısra UK. A sequential study of visual evoked potential in patients with vitamin B12 deficiency neurological syndrome. Clin Neurophysiol. 2004;115(4):914-8*
25. *Petchkrua W, Litlle JW, Burns SP, Stiens SA, James JJ. Vitamin B12 deficiency in spinal cord injury: a retrospective study. J Spinal Cord Med. 2003 ;26(2):116-21. Comment in: J Spinal Cord Med. 2003 ;26(2):122-3.*

26. *Puri V, Chaudhry N, Goel S, Gulati P, Nehru R, Chowdhury D. Vitamin B12 deficiency: a clinical and electrophysiological profile. Electromyogr Clin Neurophysiol. 2005, 45(5):273-4.*
27. *Russell JSR, Batten FE, Collier J. Subacute combined degeneration of the spinal cord. Brain 1990;10:849-50.*
28. *Sakly G, Hellara O, Trabelsi A, Dogui M. Reversible peripheral neuropathy induced by vitamin B12 deficiency. Neurophysiol Clin 2005;35(5-6):149-53*
29. *Scalabrino G. Cobalamine (Vit B12) in subacute combined degeneration and beyond: traditional interpretation and novel theories. Exp Novel 2005;192:463-79.*
30. *Steiner I, Kidron D, Soffer D, Wiraguin I, Abramsky O. Sensory peripheral neuropathy of vitamin B12 deficiency: a primary demyelinating disease. J Neurol 1988;235:163-4.*
31. *Thompson PD, Dick JPR, Assellman P,et al. Examination of motor functions in lesions of the spinal cord by stimulation of the motor cortex. Ann Neurol 1987;21:389-6.*
32. *Troncoso J, Mancall EL, Schatz NJ. Visual evoked responses in pernicious anemia. Arch Neurol 1979;36(3).168-9.*
33. *Turgut B, Turgut N, Akpınar S, et al. Dorsal nerve conduction study in vitamin B(12) deficiency with megaloblastic anemia. J Peripher Nerv Syst 2006;11(3): 247-2.*
34. *Wang YH, Yan F, Zhan WB, et al. An investigation of vitamin B12 deficiency in elderly inpatients in neurology department. Neurosci Bull 2009;25(4):209-15*
35. *Wu T, Chu NS. Recovery patterns of motor and somatosensory evoked potentials following treatment of vitamin B12 deficiency. J Formos Med Assoc 1996;95:157-61.*