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Vitamin B₁₂ deficiency neurological syndromes: A clinical, MRI and electrodiagnostic study

U.K. Misra, J. Kalita, A. Das

Abstract

Background: Vegetarianism is an important cause of vitamin B₁₂ deficiency, especially in countries like India. We managed 17 patients with neurological syndrome due to vitamin B₁₂ deficiency in a tertiary care referral teaching hospital which caters to relatively affluent population.

Aim: To evaluate neurophysiological and MRI changes in patients presenting with vitamin B₁₂ deficiency neurological syndrome and interpret these in the light of reported autopsy findings.

Setting: Tertiary care referral teaching hospital.

Methods: Patients with vitamin B₁₂ deficiency neurological syndrome diagnosed by low serum vitamin B₁₂ and/or megaloblastic bone marrow were subjected to clinical evaluation and spinal MRI. The neurophysiological tests included nerve conduction studies, tibial somatosensory evoked potential (SEP), motor evoked potential (MEP) and visual evoked potential (VEP) studies. The recovery was defined on the basis of 6 months Barthel Index score into complete, partial or poor.

Results: There were 17 patients with vitamin B₁₂ deficiency neurological syndrome, 3 were females and 12 lactovegetarian. The clinical syndrome was that of myelopathy in 8, myeloneuropathy in 5, dementia myelopathy in 3 and neuropathy in 1 patient. All the patients had impaired joint position and vibration sensation in the lower limbs and 4 had in upper limbs as well. Lower limbs were spastic in 13 and upper limbs in 2 patients. Spinal MRI revealed T2 hyperintensity in cervicodorsal region in 6 and cord atrophy in 3 patients. Sural nerve conduction was abnormal in 8 and peroneal conduction in 5 patients. In one patient all sensory nerve conductances were unrecordable but motor conductances were normal. Tibial SEP was abnormal in 12 out of 15 and lower limb MEP in 8 out of 12 patients. P100 latency of VEP was prolonged in 7 out of 13 patients. Right to left asymmetry was present in tibial SEP in 4 and VEP in 2 patients. At 6 months followup 2 patients improved completely, 7 partially and 3 had poor recovery. Clinical recovery correlated with MEP but not with SEP or MRI changes.

Conclusion: The evoked potential and MRI changes in vitamin B₁₂ deficiency neurological syndrome are consistent with focal demyelination of white matter in spinal cord and optic nerve. Myelopathic presentation is commoner and SEP is more frequently abnormal. The outcome at 6 months correlated with MEP changes.

Introduction

Vitamin B₁₂ deficiency results in subacute combined degeneration of spinal cord, optic neuropathy, encephalopathy and peripheral neuropathy (1). The neurological syndromes of vitamin B₁₂ deficiency occurs in pernicious anaemia, malabsorption syndromes, gastric and ileal resection, overgrowth of

bacteria in blind loops, anastomosis, diverticulae, and other conditions resulting in intestinal stasis and fish tape worm infestation. Rarely it may be due to vegetarian diet, nitrous oxide poisoning or genetic defect in methyl melonyl CoA mutase (2, 3). Vegetarianism is common in India and is gaining popularity even in Western countries. Diversity of clinical manifestations, atypical, sometimes fluctuating or remitting course of the disease and irrational use of vitamin B complex render the diagnosis of Vitamin

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B_{12} deficiency syndrome at times difficult. Moreover the haematological abnormalities may be present in only 43.6% – 50% patients (4, 5). The neurological syndromes of vitamin B_{12} deficiency may be the sole presentation especially in the early stage and their diagnosis may require a high index of suspicion. Neurophysiological and MRI studies have provided unique opportunity to evaluate the anatomical and functional changes in these patients. Evoked potential studies have revealed higher frequency of tibial compared to median somatosensory evoked potential changes. Motor pathways are also affected although to a milder degree (6, 7, 8). MRI studies have revealed T2 hyperintensity in the posterior part of cervicodorsal spinal cord (7, 8, 9). These studies however have been carried out in relatively small number of patients. In India, because of socioeconomic reasons and vegetarianism, deficiency disorders continue to occur and often these patients remain undiagnosed for long period. In a tertiary care referral teaching hospital, we managed 17 patients with neurological syndromes due to vitamin B_{12} deficiency during 1998 and 2000. This provided an opportunity for studying the neurophysiological and MRI changes in these patients. We report these findings and discuss these in the light of reported histopathological changes.

Patients and Methods

During 1998-2000, we have managed 17 patients with varying neurological manifestations associated with vitamin B_{12} deficiency. The diagnosis of B_{12} deficiency was based on megaloblastic bone marrow or low serum vitamin B_{12} level (<200 pg/ml) or both. A detailed medical history including dietary history was taken in all the patients. The neurological evaluation included mental status assessment by Mini Mental scale, motor power by 0-5 MRC (Medical Research Council) scale and muscle tone by Ashworth scale. Tendon reflex and plantar response were recorded in all the patients. Pinprick, touch, joint position and vibration senses were tested. Urinary symptoms such as frequency, urgency, precipitancy and hesitancy were also noted.

The investigations included hemoglobin, blood counts, red blood cell indices, white blood cell morphology, serum chemistry, blood glucose, serum

bilirubin, serum protein, albumin, globulin and lactic dehydrogenase testing. Bone marrow was examined in all the patients who gave consent. Serum vitamin B_{12} was estimated by chemiluminescence assay before starting therapy. Spinal MRI was carried out on a 2T scanner operating at 1.5 T. T1 (500/15/3 TR in ms/TE in ms/excitations), proton density (2200-2500/20-1) and T2 weighted (2200-2500/80-90/1) SE images were obtained in sagittal plain with a slice thickness of 3 mm, interslice gap of 0.3 mm and $220/250 \times 250$ matrix. Cranial MRI was possible in one patient only who had behavioural and cognitive changes.

Neurophysiological studies

Neurophysiological study included motor evoked potentials to lower limbs, tibial somatosensory evoked potential, visual evoked potential, nerve conduction study of peroneal and sural nerves and concentric needle electromyography (EMG) of distal muscles. Motor evoked potentials were recorded from the lower limbs bilaterally following transcranial electrical stimulation of cerebral cortex and spine. A digitimer D180 stimulator delivering electrical shock up to 750 V with a time constant of 50–100 μ s was used. The stimulating electrode was 1 cm diameter saline soaked felt pad mounted on a plastic handle. For activating tibialis anterior (TA), the anode was kept at the vertex and cathode 7 cm posterior. For lumbar stimulation, the cathode was placed below the spinous process of T12 vertebra and anode proximal to it. Motor evoked potentials were recorded by surface electrode from TA in a belly tendon montage. During the cortical stimulation, the patient was asked to slightly contract the target muscles (10% of maximum force) whereas during the spinal stimulation the patient was asked to relax. Electromyogram signals were filtered through 20Hz – 2KHz at a gain of 0.5 – 1 mv/div. The stimulus intensity was 90-100% for the cortical and 60-70% of maximum output for spinal stimulation. Three responses were obtained and the potential with shortest latency was analysed. Central motor conduction time to tibialis anterior (CMCT-TA) was calculated by subtracting the L1 latency from Cz.

Tibial SEP was carried out by stimulating the posterior tibial nerve below the medial malleolus employing 0.1 ms square wave pulse at 3 Hz sufficient

to produce a painless twitch of the big toe. The recording electrode was placed at the spinous process of first lumbar vertebra and 2 cm caudal to Cz. The reference electrodes were placed at L3 and Fz respectively. The electrode impedance was kept below 5 KΩ and frequency band pass 2-3000 Hz and analysis time 100 ms. Five hundred and twelve responses were twice averaged at a gain of 1-2 μ V/div to ensure reproducibility. The SEP latency of N21, P40 and N21-P40 central sensory conduction time (CSCT) were measured. The results of nerve conduction and evoked potentials were compared with our laboratory's normal values which were obtained from 32 healthy adult volunteers (10). The abnormality was defined as mean \pm 2.5 SD of controls. The upper limit of CMCT-TA is 16.1 (12.1 ± 1.6) ms, tibial CSCT 27.1 (20.1 ± 2.8) ms and VEP 106 (96.9 ± 3.6) ms and lower limit of peroneal nerve conduction velocity 35.5 (46.54 ± 4.4) m/sec and sural nerve conduction velocity 37.4 (50.9 ± 5.4) m/sec. The distal compound muscle action potential of peroneal and sensory nerve action potential of sural did not have a normal distribution therefore the lowest value 1.6mV and 4.8 μ V respectively were considered abnormal (10).

The patients were followed up clinically at 3, 6 and 12 months. The outcome was defined at the end of 6 months into complete, partial (dependence for activities of daily living) and poor (bed ridden state). The neurophysiological and MRI findings were correlated with clinical findings and outcome by χ^2 test.

Results

We evaluated 17 patients who presented with various neurological syndromes due to vitamin B₁₂ deficiency. Their age ranged between 15 and 67 (mean 38.6) years and 3 were females. The duration of symptoms ranged between 1 and 24 (mean 8.6) months and 12 patients were lactovegetarian. None of the patients had history of malabsorption syndrome or gastrointestinal surgery, 3 patients took alcohol occasionally and 1 had hypothyroidism and was on regular thyroxine supplementation.

The presenting syndrome of our patients was of myelopathy in 8, myeloneuropathy in 5; myelopathy with dementia in 3 and neuropathy in 1 patient. Lower limb paresthesia was reported by 13 patients

and 4 had paresthesia in upper limbs as well. Walking difficulty was present in 15 patients which worsened in darkness. Bladder symptoms were reported by 5 patients and included straining, urgency, incontinence in 1 patient each and retention in 2 patients. Dementia was present in 3 which interfered with daily activities in 2 patients. The mini mental state examinations score ranged between 20-30 (mean 27.5). Spastic paraparesis of grade IV was present in 13 and ankle reflex was absent in 4 patients. In two patients, the lower limbs were areflexic with grade IV muscle power. The upper limbs were weak in 2 patients with brisk biceps and triceps reflexes. All the patients had impaired joint position and vibration sense in the lower limbs. Vibration sense was impaired in the upper limbs in 4 patients only. Pinprick and touch sensations were reduced in the lower limbs distally in 3 patients and girdle like sensation in mid waist was reported by 2. One patient had pelvic girdle weakness with generalised areflexia and impaired proprioception in both lower limbs for 6 weeks resembling a subacute inflammatory demyelinating neuropathy.

Spinal MRI was carried out in 11 patients. The spinal MRI revealed T2 hyperintensity which was present in cervicodorsal and only cervical region in 3 patients each. The signal changes extended for a mean of 7 spinal segments (range 6-9). In axial section, the signal changes were present in posterior region of spinal cord (Fig. 1). In 3 patients there was dorsal cord atrophy; in these patients the duration of symptoms was 2, 3 and 6 months respectively. In 2 patients spinal MRI was normal. Cranial MRI was carried out in 1 patient who had cognitive impairment (MMSE = 25) but his MRI was normal. The clinical and MRI findings are summarised in table 1. Hemoglobin was below 12 gm/dl in 12 (range 3.9 – 12.7). hypersegmented neutrophils were present in 2 patients, macrocytosis in 12, and mean MCV was 105.3 (range 94.4 – 114) fl. The bone marrow revealed megaloblastic reaction in 14 out of 16 patients. Serum vitamin B₁₂ level was reduced in 8 patients.

Evoked potential study

Tibial SEPs were abnormal in 12 out of 15 patients (Fig. 2). The abnormalities included unrecordable SEP in 9 patients (17 sides) and N21-P40 conduction

time was prolonged in 4 patients (4 sides). Right to left asymmetry was noted in 4 patients. In three of these patients there was unilateral prolongation and

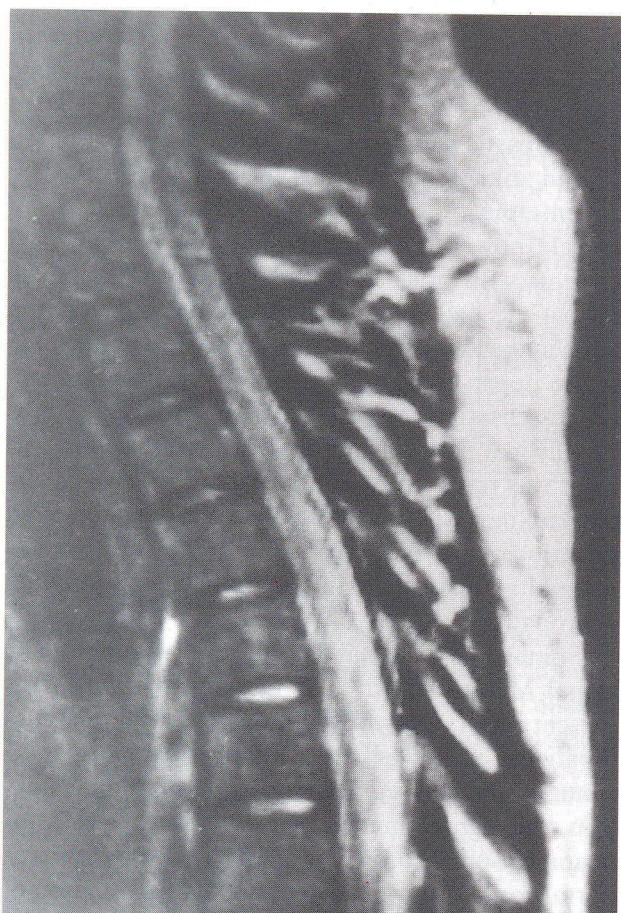


Fig. 1. – Spinal MRI, T2 sequence of a patient with subacute combined degeneration showing hyperintense signal changes in cervicodorsal region in sagittal section (a) which is located mostly in the posterior part of the spinal cord (axial section b).

in one tibial SEP was not recordable on one side and CSCT was prolonged on the other. Central motor conduction time to lower limb was carried out in 12 patients and was abnormal in 8 (Fig. 3); unrecordable in 2 patients (4 sides) and CMCT-TA was prolonged in 6 patients (12 sides). Visual evoked poten-

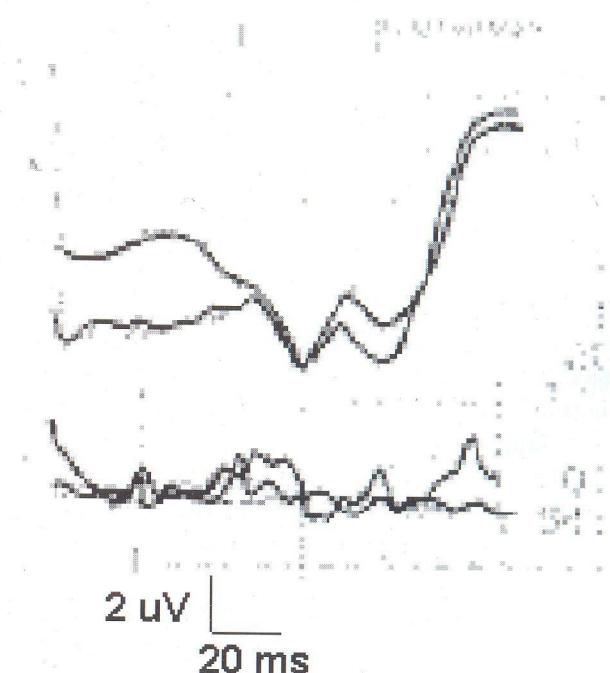


Fig. 2. – Right tibial somatosensory evoked potential of a patient with subacute combined degeneration (patient no 16) showing prolongation of central sensory conduction time (CSCT = 35.6 ms). The CSCT on left side was normal (22.6 ms).

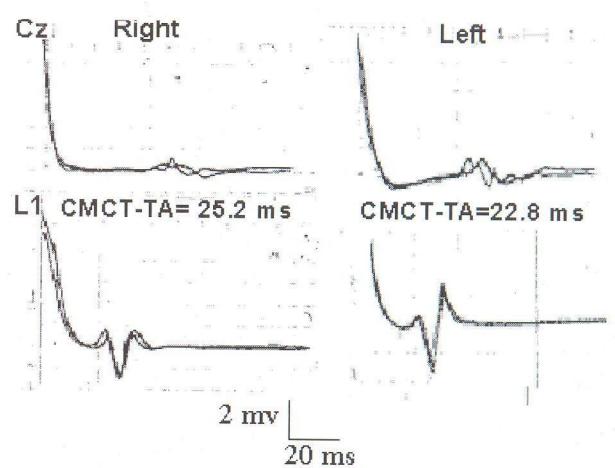


Fig. 3. – Central motor conduction study in a patient with subacute combined degeneration (patient no 17) showing prolongation of central motor conduction time to both lower limbs.

Table 1. - Clinical and MRI features in patients with vitamin B_{12} deficiency neurological syndrome

S. No	Age/sex	Duration of symptoms (mo)	Dementia	Myelopathy	Neuropathy
1	32/M	24	+	+	-
2	15/F	2	-	+	+
3	30/M	9	-	+	-
4	22/F	6	+	+	+
5	37/M	24	-	+	-
6	43/M	4	-	+	+
7	35/F	4	-	+	-
8	35/M	24	-	+	+
9	67/M	3	-	+	+
10	37/F	24	-	+	-
11	50/M	6	-	+	-
12	64/M	3	+	+	-
13	50/M	1.5	-	-	+
14	30/M	1	-	+	-
15	53/M	2	-	+	-
16	20/M	2	-	+	-
17	47/M	3	-	+	+

Table 2. - Evoked potential changes in patients with vitamin B_{12} deficiency neurological syndrome

Pt. No	B_{12} (μ g/ml)	Megaloblastic bone marrow	CMCT (ms)	CSCT (ms)	VEP (ms)	MRI
1	72.5	+	NR/NR	NR/NR	92.0/92.0	Cervicodorsal T ₂ hyperintensity
2	330	+	ND	NR/NR	98.0/104.0	Dorsal cord atrophy
3	163	N	ND	16.4/21.6	92.0/92.0	Normal
4	0	+	NR/NR	NR/NR	120.0/120.0	Dorsal cord atrophy
5	ND	+	24.4/24.8	31.0/24.0	100.0/104.0	Not done
6	445	+	16.4/18.6	NR/28.0	96.0/110.0	Not done
7	0	N	16.4/21.8	23.6/26.0	118.0/118.0	Cervical T ₂ hyperintensity
8	0	N	11.2/14.8	NR/NR	100.0/102.0	Normal
9	336.3	+	25.6/22.4	NR/NR	132.0/136.0	Not done
10	200	+	ND	31.0/26.0	96.0/90.0	Cervicodorsal T ₂ hyperintensity
11	ND	+	13.6/11.6	24.0/15.0	ND	Not done
12	ND	+	22.0/26.0	NR/NR	ND	Not done
13	0	-	ND	ND	ND	Not done
14	200	+	ND	ND	ND	Cervicodorsal T ₂ hyperintensity
15	140	+	7.2/11.2	35.6/22.8	110.0/110.0	Cervical T ₂ hyperintensity
16	90	+	14.8/16.0	NR/NR	96.0/96.0	Cervical T ₂ hyperintensity
17	90	+	22.8/21.6	NR/NR	112.0/108.0	Dorsal cord atrophy

NR = not recordable, ND = not done.

tials were carried out in 13 patients and P100 latency was prolonged in 7 patients and in 2 there was unilateral prolongation (Fig. 4). The details of evoked potential changes are summarised in table 2. Peroneal nerve conduction was abnormal in 5 patients; unrecordable in 1, slowing of conduction velocity in 2 and reduced distal compound muscle action poten-

tial in 4 patients. Sural nerve conduction velocity was abnormal in 8, being unrecordable in 2 and the remaining had marginal slowing of nerve conduction velocity. The amplitudes of sensory nerve action potential was reduced in 6 patients. In the patient with subacute neuropathy all sensory nerve conductions (sural, median, ulnar) were unrecordable although

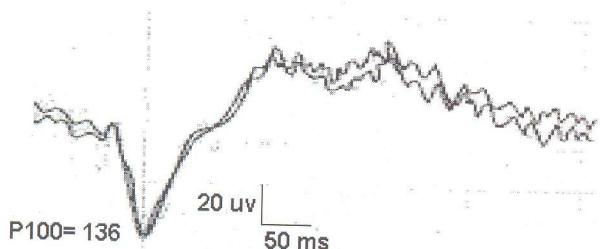


Fig. 4. – Visual evoked potential in a patient with subacute combined degeneration showing prolongation of P100 latency (136 ms).

motor conductions were normal. The clinical, radiological and evoked potential findings in vegetarian (5) and non vegetarian patients are compared in table 3. The differences between these groups are not significant, except central motor conduction time was less frequently abnormal in non vegetarians.

The SEP changes did not correlate with the duration of illness ($X^2 = 2.29$, df = 2, NS), MRI changes ($X^2 = 5.83$, df = 4, NS) and hemoglobin level ($X^2 = 0.54$, df = 2, NS). The MEP changes also did not correlate with MRI changes ($X^2 = 5.80$, df = 4, NS) and duration of illness ($X^2 = 2.54$, df = 2, NS), but inversely correlated with hemoglobin level ($X^2 = 14.28$, df = 2, $P < 0.01$). The recovery of patients was related to MEP changes ($X^2 = 14.28$, df = 4, $P < 0.01$) but not with SEP ($X^2 = 6.37$, df = 4, NS) or MRI changes ($X^2 = 5.71$, df = 4, NS).

Discussion

In our study of vitamin B₁₂ deficiency neurological syndromes, myelopathy was the commonest clinical manifestation, SEP was most frequently abnormal (80%) followed by MEP (67%) and nerve conduction (47%). Spinal MRI revealed T2 hyperintensity in 6 and cord atrophy in 3 patients. In an earlier study, tibial SEP was abnormal in all 7 and MEP in 2 out of 7 patients, however, these authors did not undertake VEP studies (6). The evoked potential changes are consistent with the reported autopsy findings in vitamin B₁₂ deficiency neurological syndromes. The brunt of the disease falls on the fasciculus cuneatus resulting in demyelinating lesions which coalesce with the adjacent new lesions and at later stage may result in diffuse changes. The lateral columns are also regularly affected (11). The vulnerability of posterior column especially fasciculus cuneatus manifested with proprioceptive disturbances in the lower extremities in all the patients whereas only 4 patients had vibration sense impairment in the upper extremities. The tibial SEP changes were also more pronounced being unrecordable in 9 patients and CSCT was prolonged in 4 patients (4 sides).

Central motor conduction was abnormal in 8 out of 12 patients; unrecordable in 2 and CMCT was prolonged in 6 patients (16 sides). Unrecordable central motor conduction could suggest severe conduction

Table 3. – Comparison of clinical radiological, neurophysiological findings in vegetarians and non vegetarians with B₁₂ deficiency syndrome

Parameters	Vegetarian (n = 12)	Non vegetarian (n = 5)
Myelopathy		
MRC (mean)	4.5	4.4
Mean Ashworth score	1.2	1.4
Bladder Inv	2	1
Cognitive impairment	4	2
ADL score (mean)		11/6
Tibial SEP		
NR	5	4
Prolonged	3	1
Normal	4	0
MEP		
NR	1	1
Prolonged	5	0
Normal	6	0

NR = not recordable, SEP = somatosensory evoked potential, MEP = motor evoked potential, ADL = activities of daily living.

block or anterior horn cell involvement. Prolongation of CMCT was also mild to moderate (less than twice the upper limit of normal) which could as well be due to desynchronisation of descending volleys in the motor pathways (10, 12). The CMCT changes are consistent with the reported demyelination of lateral column in vitamin B₁₂ deficiency. Histopathologically pyramidal pathways are regularly involved at cervicodorsal region (11). 13 of our patients had spastic paraparesis with mild weakness. The upper limbs were also weak in 2 patients only suggesting major brunt of the disease affecting dorsal cord.

Vitamin B₁₂ deficiency is known to affect the visual pathways although VEP studies are few. There is demyelination and subsequent atrophy of optic nerve with compensatory proliferation of the glia especially affecting papillo-macular bundle (13). Middle aged pipe smokers, less commonly cigar and cigarette smokers develop tobacco – amblyopia. None of our patients had any visual symptom, nor there were any field defects, however, P100 latency on visual evoked potential was prolonged in 7 out of 13 patients. The prolongation of P100 latency is consistent with demyelinating changes. In experimental animals with vitamin B₁₂ deficiency, vegetarian diet has resulted in cage paralysis due to funicular spinal disease (11, 12) which involved the demyelination of both central and peripheral nervous system. In such experiments, although the spinal symptoms were prominent but vision was also affected (14). Histologically detectable lesions were found in the monkeys kept for more than 2 years on vegetarian diet resulted in degeneration of optic nerve in the region of papillomacular bundle, with the myelin sheath being more severely affected than axons. Similar changes could be demonstrated in the region of chiasma and lateral geniculate bodies without any evidence of dying back process (15). Prolongation of P100 latency in our patients may be consistent with demyelination in optic nerve.

Three of our patients had distal sensory loss with absent ankle reflex suggesting of sensory motor neuropathy. The nerve conduction studies were consistent with axonopathy with normal or mild slowing of nerve conduction and reduced or absent sensory or motor nerve action potential. In B₁₂ deficiency, the histology and electron microscopy studies have revealed primary axonal degeneration in peripheral nerve specimen which correlated with slight fall in motor conduction velocity distally (6, 16). In most

of our patients the nerve conduction studies were consistent with axonopathy, however, one patient clinically presented with subacute form of neuropathy with proximal weakness, paresthesia and proprioceptive sensory loss with generalised areflexia. His motor nerve conduction velocity was normal but sensory nerve action potential of sural, median and ulnar nerves were not recordable. In vitamin B₁₂ deficiency, primary sensory demyelinating neuropathy has been reported in 5 patients and all improved following B₁₂ administration (17). Our patient also recovered completely following 2 months of B₁₂ therapy.

In metabolic and toxic conditions, the abnormalities in central and peripheral conductions are usually symmetrical. In our study, there was definite asymmetry in SEP in 4 and VEP in 2 patients. The asymmetry in evoked potential has not been reported in earlier studies. The histological studies have revealed foci of demyelination in white matter in early stage which coalesce older with new lesions (11). Multifocal pattern of myelin and axonal loss has been demonstrated in histopathological study (18). Moreover the early proprioceptive and pyramidal symptoms may be asymmetrical (11). Funicular demyelinating foci may disappear spontaneously or even leaving a nonspecific gliotic scar.

Presence of spinal cord and optic nerve involvement with occasional remission due to commonly used vitamin B complex therapy may be confused with multiple sclerosis. In the tropical countries, multiple sclerosis commonly manifests with spino optic form (19, 20). The neurological syndromes of B₁₂ deficiency may also develop independent of hematological changes (21, 22). In such patients, however, vitamin B₁₂ deficiency should be carefully excluded.

The outcome of the patients in our study were not related to duration of illness, SEP, VEP and MRI changes. It is possible that posterior columns are affected first and are the prime target of vitamin B₁₂ deficiency whereas lateral columns likely to involve later which may explain better recovery of the patients with normal MEP. Motor evoked potentials hence may be useful in predicting the recovery of vitamin B₁₂ deficiency myelopathy.

The radiological abnormalities in our study comprised of T2 hyperintensity which was mainly in cervicothoracic region of spinal cord and more marked in posterior region. This is consistent with the vulnerability of this region of spinal cord in vitamin

B_{12} deficiency. Cord atrophy was seen in 3 patients which may suggest more advanced disease however it was not correlated with duration of illness. Posterior hyperintensity on T2 in the cervicodorsal spinal cord has been reported in various study (6, 8). Most of these studies are however isolated case reports and have not included evoked potential study.

Majority of our patients were non vegetarians (12) highlighting the commonness of vitamin B_{12} deficiency syndromes in vegetarians. On comparing the clinical picture, MRI and neurophysiological findings and their recovery, there was no significant difference except central motor conduction time was less frequently abnormal in non vegetarians. It can be concluded that vitamin B_{12} deficiency is commoner in vegetarians compared to nonvegetarian. Among the neurophysiological tests, somatosensory evoked potentials are most frequently abnormal and the changes are rather persistent whereas MEP are useful in predicting the outcome.

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