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Vitamin B12 deficiency neurological syndromes: correlation of clinical, MRI and cognitive evoked potential

Abstract *Objective* To evaluate cognitive function in B12 deficiency neurological syndromes and response to B12 therapy. *Methods* Patients were diagnosed on the basis of low serum B12 or megaloblastic bone marrow or both. Detailed neurological examination was performed and mental status was evaluated by the Mini Mental State Examination (MMSE). Hemoglobin, RBC indices, blood counts, serum chemistry, HIV, thyroid profile, antiparietal cell antibody and craniospinal MRI were done. Cognitive evoked potential was carried out using the odd ball auditory paradigm and recording was achieved from Fz, Cz and Pz referred to mastoid. P3 latency and amplitude were measured and compared with 33 age and sex matched controls. Three months following B12 therapy, clinical and P3 values were reevaluated and compared with the baseline values. *Results* 36 patients, aged 16–80 years were included; 32 patients were above 40 years of age. Their median education level was 14 years. The presenting syndrome was myeloneurocognitive in 9, myeloneuropathy in 10, myelocognitive in 8, myelopathy in 8 and only cognitive in 1 patient. MMSE was abnormal in 17; between 28–19 in 14 and 18–11 in 3 patients. Cranial MRI carried out in 14 patients revealed multiple white matter hyperintensity in T2 in 3 and cortical atrophy in 1. P3 was unrecordable in 7 and latency was prolonged in 8 out of 33 patients. P3 latency was significantly prolonged in patients compared to controls and both MMSE and P3 latency improved significantly at the 3-month follow-up. *Conclusion* MMSE was abnormal in 47 % and P3 in 45.5 % of patients with B12 deficiency neurological syndromes which improved following treatment. *Significance* There is high incidence of reversible cognitive impairment and P3 abnormalities in B12 deficiency neurological syndromes.

Key words subacute combined degeneration · B12 · dementia · P3 · MRI · outcome

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Introduction

Since its discovery, vitamin B12 deficiency has been reported to result in various neurological syndromes, which include subacute combined degeneration (SCD), peripheral neuropathy, dementia and psychiatric abnormalities [10, 16, 20, 23, 26]. In the West, B12 deficiency neurological syndromes are reported mostly in patients with pernicious anemia, elderly individuals and children with an inherited defect in B12 metabolism [6, 8–10, 31]. Sensory motor dysfunctions in SCD have been documented using nerve conduction and motor- and sensory-evoked potentials [8, 16]. A subclinical visual pathway abnormality has also been reported using visual evoked potential in 60 % of patients with B12 deficiency neurological syndromes [18]. Cognitive impairment has been reported in various early studies but cognitive evoked potential changes and its response to therapy have not been reported. In this communication, we report the cognitive functions in patients with B12 deficiency neurological syndromes and their response to therapy.

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Patients and methods

From 2004 to 2005, 36 patients with B12 deficiency neurological syndromes, who were referred to us, were included in this study. The diagnosis of B12 deficiency was based on low serum B12 (< 211 pg/ml) and or megaloblastic bone marrow. A detailed medical history including dietary habit, daily intake of milk or its product, malabsorption syndrome, addiction, gastrointestinal surgery and hepatic and renal failure were noted. Cognitive function was evaluated by the Mini Mental State Examination (MMSE). Patients were considered cognitively impaired if MMSE was below 29 for 9 years of schooling, below 26 for 5–8 years of schooling and below 22 for 0–4 years of schooling [7]. Visual functions were assessed by field, color and acuity of vision. Presence of optic atrophy and other cranial nerve palsy were noted. Muscle power was assessed by the MRC (Medical Research Council) scale, muscle tone, reflex and sense of joint position, touch and pinprick were also noted.

The laboratory investigations included hemoglobin, RBC indices, leukocyte counts, platelet, RBC morphology and segmented polymorph. Blood sugar (fasting and post prandial), serum bilirubin, transaminases, lactate dehydrogenase, protein, albumin, creatinine, blood urea nitrogen, thyroid profile and HIV serology were measured in all patients. Fasting blood was centrifuged and serum was analyzed for B12 using ADVIA Centaur assay (Bayer Corporation), which is a competitive immunoassay using direct chemiluminescence technology. Antiparietal cell antibody was assessed using the enzyme linked immunosorbent assay. Bone marrow aspirate was obtained by sternal puncture and examined for any abnormality.

Cervicodorsal spinal MRI was carried out using 1.5 T signa GE medical system, USA and T1, T2 and fast spin echo T2 images were obtained in the sagittal and axial views. In some patients cranial MRI was also carried out.

Cognitive evoked potential

For cognitive evoked potential the stimuli were delivered using the auditory oddball paradigm where two types of tones – target (rare) and non-target (frequent) – were used at a rate of 1 Hz which was delivered binaurally. The target tones comprised of 20 % of total stimuli, which appeared randomly. The patient was asked to count the target tones mentally. The stimulus (tone) intensity was kept between 60 and 80 dBSPL depending on the tolerance of the individual. The low-frequency responses extended to below 1 Hz and the high frequency response to above 30 Hz. The sweep time was 1 s. A total of 32 rare epochs were averaged. The recording electrodes were placed at Fz, Cz and Pz referred to linked mastoids. The impedance was kept below 5 KΩ, sweep 100 ms/div with sensitivity 20 μv/div. The P3 responses were averaged twice for reproducibility. The peak latency of N1, P2, N2 and P3 and their peak to peak amplitudes were measured in Fz, Cz and Pz channels averaging the infrequent stimuli [15]. The abnormalities were defined on the basis of mean ± 2.5 SD of controls which were obtained from 33 healthy age (43.61 ± 14.74) and sex matched volunteers. The upper limit of latency of CzP3 was 397.92 (338.30 ± 23.85) ms, FzP3396.53 (338.26 ± 23.31) ms and PzP3418.26 (342.14 ± 30.45) ms. The amplitudes had a wide normal distribution; therefore, it was not considered for defining abnormality.

Patients were treated with vitamin B12 injection 1000 μg daily for 10 days, alternate day for 10 injections, weekly for 1 month then monthly. At 3 months, the patients were evaluated clinically and cognitive evoked potentials were repeated. The functional outcome was defined as complete (independent for activities of daily living), partial (dependent for activities of daily living) and poor (bed ridden) [16].

Statistical analysis

The P3 parameters were compared with the controls and patients with abnormal MMSE with normal MMSE using independent t test. The base line and 3-month MMSE and P3 were compared by paired t test. The correlation of P3 with various clinical, radiological and laboratory parameters were evaluated by using parametric or nonparametric test with the help of SPSS 10 software.

Results

A total of 36 patients with B12 deficiency neurological syndromes were included with 8 being female. The mean age of the patients was 50.6 (16–80) years; 32 patients were above the age of 40 years and 3 between 25 and 40 years. The mean duration of illness was 11.4 (0.25–50) months. Their median education level was 14 (2–17) years. 31 patients were vegetarian and 2 occasional non-vegetarian (< 1/week); only 4 of these patients consumed milk > 500 ml/day. None of the patients was in a retirement home or living alone. None had gastrointestinal surgery, malabsorption or HIV. Two patients had hepatitis and 2 consumed alcohol (100–500 ml/day). One patient had vitiligo but none had thyroid dysfunction or rheumatoid arthritis. The serum vitamin B12 level was low in 30 out of 34 and megaloblastic bone marrow in all 20 patients in whom it was carried out. Four patients with a normal B12 level, however, had megaloblastic bone marrow. Antiparietal cell antibody was present in 50 % of patients.

The presenting syndromes at admission were myeloneuropathy with cognitive impairment in 9, myeloneuropathy in 10, myelocognitive in 8, myelopathy in 8 and only cognitive impairment in one patient. 15 patients complained about memory impairment and 17 had a low MMSE score with regard to their education and age cutoff. Dementia was mild to moderate. The MMSE score was 28–19 in 14 and 18–11 in 3 patients. On the basis of MMSE, the majority of these patients had impaired recall [14] and serial 7s [17] which is a bedside test primarily of attention. Disorientation to time was present in 7 and person in 5, impaired naming in 9, writing in 4 and coping in 2 patients.

Behavioral abnormalities

Behavioral abnormalities in the form of aggression, rigidity of thoughts, anxiety, visual hallucination and delusion were the dominant feature in 5 patients. Paranoid delusion was present in 1 patient, delusion of grandiosity in 2 and delusion of reference in 1. Two patients were treated as schizophrenia due to psychosis, hallucination and flight of ideas. One patient was treated as diffuse Lewy body disease due to hallucination, fluctuating consciousness and associated akinetic rigid

state. All these patients had associated features of myeloneuropathy except one.

None of the patients had optic atrophy or visual abnormality. Lower limb weakness was severe (grade 0-I) in 1, moderate (grade II-III) in 3, mild (grade IV) in 10 and the remaining patients had normal muscle power. Knee reflex was brisk in 28 and reduced in 6 patients. Ankle reflex was absent in 19 patients. Lower limb joint position and vibration was impaired in all except one and 2 patients had horizontal level (C4 and D10 spinal level) of sensory loss.

Twenty patients were anemic (Hb < 12 g/dl) and mean corpuscular volume was increased in 25; 5 of whom had segmented polymorph. Serum albumin was low in 6 and raised lactate dehydrogenase in 14/21patients.

MRI was performed in 24 patients. Spinal MRI revealed T2 hyperintensity of cervicodorsal region and cord atrophy in 11 patients each out of 24 patients. Three patients also had multiple cervical disc protrusion with thecal indentation only. Cranial MRI was also done in 14 patients and revealed multiple T2 hyperintense lesions in 3 (Fig. 1) and diffuse cortical atrophy in 1 patient. One patient, who had an old cerebellar stroke, was hypertensive.

Cognitive evoked potential

Cognitive evoked potential was carried out in 33 patients and it was unrecordable in 7 and had a prolonged CzP3 latency in 8 patients. P3 latency and MMSE were significantly abnormal in patients compared to controls (Table 1); however, amplitudes were not significantly different. Patients with abnormal MMSE had more prolonged P3 latency (417.58 ± 62.31 ms) compared to normal MMSE (369.29 ± 27.16 ms) which is significant (t = 2.49, p = 0.03). Cz P3 amplitude however was not statistically different (t = –0.08, P = 0.93) between abnormal MMSE (14.72 ± 5.90μv) and normal (14.90 ± 5.28μv). CzP3 latency correlated with age (P = 0.04), hemoglobin (0.004), MCV (0.0001), MMSE (P = 0.02) but not with duration of illness (P = 0.94), presenting syndrome (P = 0.07) or antiparietal cell antibody (P = 0.29). Abnormality in cranial MRI in the form of cortical atrophy and white matter changes did not correlate with MMSE (P = 1.00) or P3 abnormality (P = 0.30). Peroneal and sural nerve conductions were measured in 33 patients and were abnormal in 7 patients. P3 abnormality did not correlate with nerve conduction abnormality (P = 0.39).

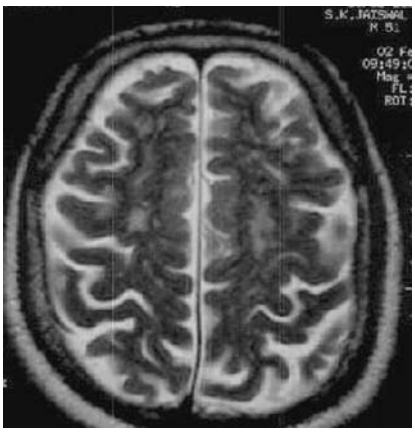

Fig. 1 Cranial MRI, T2 sequence of a patient with B12 deficiency neurological syndrome revealed multiple white matter hyperintensity

Table 1 Comparison of P3 and MMSE changes in patients with B12 deficiency neurological syndromes (SCD) and controls

Parameters	SCD (n = 26)	Normal (n = 33)	P value
CzP3			
Latency ms	391.58 + 51.91	338.30 ± 23.85	0.0001
Amplitude μv	14.82 + 5.46	13.23 ± 6.79	0.33
FzP3			
Latency ms	390.81 ± 48.59	338.26 ± 23.31	0.0001
Amplitude μv	14.14 ± 6.62	13.23 ± 6.79	0.61
PzP3			
Latency ms	393.16 ± 57.03	342.15 ± 30.45	0.0001
Amplitude μv	14.28 ± 4.45	14.27 ± 6.68	0.99
Age	50.56 ± 15.09	43.61 ± 14.74	0.06
MMSE	27.03 ± 4.40	28.94 ± 1.43	0.02

Follow-up

A total of 31 patients were followed up at 3 months; 29 patients had complete and 2 had partial functional recovery. Lower limb power improved in all and joint position in 5 patients; however, reflex abnormality persisted. Behavioral abnormality improved in all. MMSE score improved in all and became normal in 29 patients. The cognitive evoked potential was repeated in 18 patients and was recordable in 17 patients including 3 patients who had an initially unrecordable P3. P3 latency was within the normal range in 15 (Fig. 2) and prolonged in 2 patients. There was a significant improvement in MMSE and P3 latency at the 3-month follow-up compared to base line (Table 2). The details of clinical presentation, hemoglobin level, MMSE score and CzP3 latency are summarized in Table 3.

Discussion

In our study cognitive impairment was found in 47.2 % of patients with vitamin B12 deficiency neurological syndrome and 45.5 % had abnormal cognitive evoked potential. Cognitive abnormality has been reported to

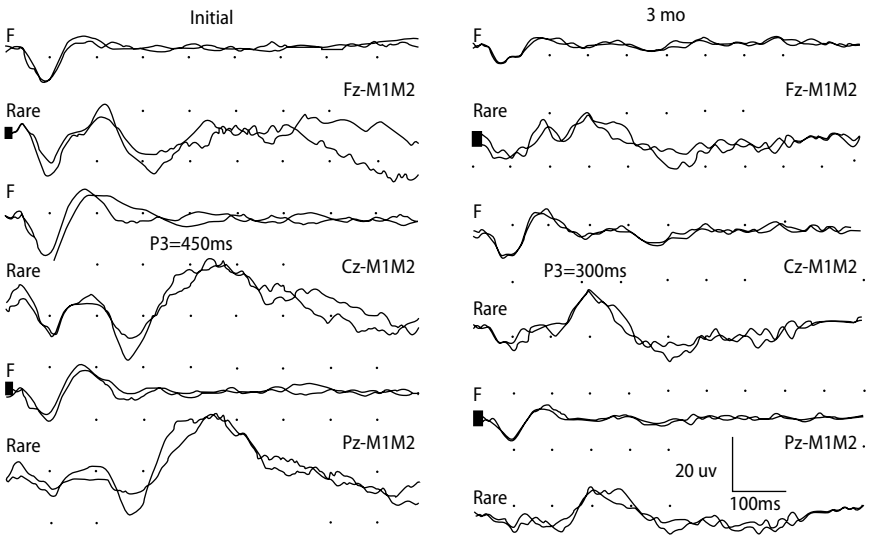

Fig. 2 Cognitive evoked potential of the same patient showing prolonged P3 latency which improved the 3-month B12 therapy. His MMSE score also improved from 23 to 30. *F* frequent stimuli

Table 2 Comparison of baseline and 3 months follow-up P3 and MMSE changes in patients with B12 deficiency neurological syndromes

Parameters	Initial	3 mo	p value
CzP3			
Lat ms	376.38 ± 55.72	329.08 ± 41.84	0.004
Ampl μv	15.26 ± 6.92	16.61 ± 6.64	0.60
FzP3			
Lat ms	372.15 ± 46.11	327.46 ± 33.44	0.004
Ampl μv	14.15 ± 6.20	15.08 ± 8.25	0.71
PzP3			
Lat ms	374.42 ± 65.08	337.67 ± 37.49	0.006
Ampl μv	13.58 ± 5.35	15.45 ± 6.35	0.38
MMSE	28.16 ± 2.98	29.68 ± 1.19	0.006

Lat latency; *Ampl* amplitude

be rare. In a large study of 143 patients with cobalamin deficiency, only 8% of patients had cognitive impairment. The lower frequency of cognitive impairment in the earlier study may be due to different patient populations, inclusion of milder cases, and lack of quantitative mental status evaluation. An elderly population survey however revealed a high prevalence of cobalamin deficiency which was associated with reduced MMSE and behavioral abnormality [6]. In a patient with B12 deficiency due to pernicious anemia, detailed evaluation of cognitive functions using extensive protocol revealed multifocal cognitive impairments affecting, in particular, intellectual function, memory, word retrieval and problem solving skills [13]. Cognitive abnormality in our patients was mostly global with frequent abnormalities in attention as assessed by serial 7s, orientation, naming and recall simulating Alzheimer's disease. The B12 deficiency dementia however can be differentiated from Alzheimer's disease by its rapidity of progression, associated myelo- or myeloneuropathy and improvement of cognitive functions following B12 therapy. Rapidly progressive cognitive impairment, myelopathy and cranial MRI abnormalities found in our patients simulated HIV encephalomyelopathy. The myelopathy in HIV clinically and pathologically simulate subacute combined degeneration as both produce patchy or diffuse vacuolar demyelination affecting posterior and pyramidal tract [4]. Subcortical white matter T2 hyperintensity followed by cortical atrophy has been described in HIV encephalopathy. HIV virus affects oligodendroglia resulting in demyelination, inflammatory changes and astrocytosis [14]. In subacute combined degeneration, small ill-defined often perivascular foci of demyelination within the cerebral white matter have been described. Histopathologically there is fusiform swelling of the myelin sheath and axons in newer foci and fiber degeneration in older foci [1]. Neurons and oligodendroglia are spared but there are astrocytosis and myelinolysis due to the cobalamin dependent enzymatic pathway [12]. Recently increased TNFα and reduction of neurotrophic factors IL6 and EGF have been suggested for CNS damage in subacute combined degeneration [24]. All our patients were negative for HIV and they improved following B12 therapy. The association of B12 deficiency in various neurological diseases such as multiple sclerosis [19], Alzheimer's disease [30] and HIV [4] although postulated have yet to be confirmed in view of a lack of improvement following B12 therapy. Routine measure of cognitive function by MMSE often fails to detect executive cognitive dysfunction; moreover MMSE is education and age dependent [22]. In our study lack of detailed cognitive functions evaluation may miss mild cognitive impairment. MMSE with the clock drawing or short performance test is found to be more sensitive for detecting cognitive dys-

Table 3 Clinical, Mini Mental State Examination (MMSE) and CzP3 latency before and 3 months after the treatment of the patients with B12 deficiency neurological syndromes

Serial Number	Age Years	Clinical syndromes	Hemoglobin g/dl	Initial CzP3L ms	Follow-up CzP3L ms	Initial MMSE	Follow-up MMSE
1	80	Myeloneurocognitive	11.1	523	.	21	.
2	73	Myeloneuropathy	13.3	389	.	27	27
3	69	Myeloneurocognitive	11.8	NR	.	29	29
4	68	Myeloneurocognitive	9.8	396	.	13	.
5	67	Myelopathy	12.1	380	374	30	30
6	67	Myelocognitive	9.8	450	.	28	.
7	62	Myeloneuropathy	11.3	NR	336	28	30
8	62	Myelopathy	11.5	364	340	30	30
9	61	Myelopathy	12	367	.	30	30
10	60	Myeloneuropathy	11	358	347	29	30
11	58	Myeloneuropathy	12.9	.	.	28	30
12	58	Myeloneurocognitive	9.2	402	268	30	30
13	58	Myelocognitive	13.8	325	333	30	30
14	57	Myeloneurocognitive	6	NR	NR	23	24
15	57	Cognitive	15.7	NR	.	17	.
16	55	Myeloneuropathy	10.5	392	.	30	30
17	55	Myeloneuropathy	9.5	412	348	30	30
18	53	Myeloneurocognitive	11	526	430	27	30
19	53	Myelopathy	13.2	396	.	21	.
20	51	Myelocognitive	14.1	NR	408	30	30
21	51	Myelocognitive	14.1	.	387	29	30
22	50	Myeloneurocognitive	13	309	297	27	30
23	50	Myelopathy	9.7	441	.	28	30
24	49	Myelocognitive	13.5	388	.	30	30
25	45	Myeloneurocognitive	11.9	.	.	30	30
26	43	Myeloneuropathy	10.5	404	297	23	30
27	42	Myelocognitive	9.2	430	.	23	30
28	40	Myelopathy	9	391	290	30	30
29	40	Myelocognitive	7.8	375	.	30	30
30	35	Myelocognitive	12.3	389	.	28	30
31	33	Myelopathy	12.2	330	323	30	30
32	31	Myelopathy	14.4	334	327	30	30
33	27	Myeloneurocognitive	8.2	NR	.	17	30
34	25	Myeloneuropathy	12.3	NR	311	30	30
35	20	Myeloneuropathy	11	352	.	30	30
36	16	Myeloneuropathy	12.2	358	304	27	30

NR not recordable; *L* latency

function [3, 25]. Use of age and education-specific cut off scores, however improves the sensitivity of MMSE to 82 % with no loss of specificity [27]. We have also used age and education cut off.

Spinal MRI frequently shows posterior hyperintensity and cord atrophy [2, 16], but there is paucity of cranial MRI study in B12 deficiency syndromes and cranial involvement has been thought to be rare [10]. White matter changes simulating leukoencephalopathy have been reported in children with an inherited cobalamin related co-enzyme defect [5, 21]. MRI abnormality suggestive of delayed myelination has also been reported in infants with nutritional cobalamin deficiency [29]. Spinal MRI changes in our study were consistent with earlier reports [2, 16]. Cranial MRI revealed subcortical white matter hyperintensity in T2 in 3 and cortical atrophy in one out of 14 patients. These changes are also described in elderly, hypertensive and diabetic individuals. None of these four patients were hypertensive or diabetic and 3 were below 60 years of age. Being able to show the reversibility of MRI changes following therapy however would have been helpful, but were not carried out due to financial reasons.

In a large study on cobalamin deficiency, cognitive impairment was found in 17 out of 153 episodes which was characterized by global dementia in 8 and predominant recent memory loss with reduced attention in 9. Five of these episodes were associated with behavioral abnormalities in the form of depression in 2, agitation in 2 and hypomimia in 1 [10]. In our study behavioral abnormalities were also present in 5 patients. Various psychiatric abnormalities have been reported in earlier

studies but detailed cognitive function and neurological evaluations have not been done [11].

The role of the cognitive evoked potential has been evaluated in various types of dementia and has been found to be useful in monitoring the effect of therapy [28]. P3 latency in our study was prolonged in patients compared to controls and patients with abnormal MMSE had greater prolongation than normal MMSE. After B12 therapy all patients had a normal MMSE at the 3-month follow-up except 2. This was associated with the corresponding improvement in P3 latency. The mechanism of improvement in memory functions is not clearly understood but may be related to improvement in the cobalamin dependent metabolic pathway. The P3 latency correlated with age, duration of illness, MMSE, Hb and MCV. Effect of age in P3 latency was reported in an earlier study [17]. We have therefore selected an age matched control and serial follow-up study to reduce the influence of age. B12 deficiency commonly occurs in middle aged and elderly individuals, which may be due to impaired absorptive and metabolic functions of B12 with age and compromised CNS function in the elderly. Increased duration of illness, reduced hemoglobin and increased MCV not only suggest more severe deficit but also may contribute reduced cellular oxygenation.

It can be concluded from this study that mild to moderate reversible cognitive impairment occurred in 47.2 % of patients and P3 was helpful in documenting and monitoring the therapeutic response. Associated myelo- or myeloneuropathy was the rule and cognitive functions improved following B12 therapy. Abnormal P3 may help to discriminate cognitive impairment attributable to B12 deficiency from coincident causes of cognitive decline, though this would need to be tested in future work.

References

1. Adams RD, Kubik CS (1944) Subacute degeneration of the brain in pernicious anemia. New Engl J Med 23:1–9
2. Bassi SS, Bulundwe KK, Greeff GP, Labuscagne JH, Gledhill RF (1999) MRI of the spinal cord in myelopathy complicating vitamin B12 deficiency: two additional cases and a review of the literature. Neuroradiology 41: 271–274
3. Brodaty H, Moore CM (1997) The Clock Drawing Test for dementia of the Alzheimer's type: A comparison of three scoring methods in a memory disorders clinic. Int J Geriatr Psychiatry 12:619–627
4. Di Rocco A, Bottiglieri T, Werner P, Geraci A, Simpson D, Godbold J, Morgello S (2002) Abnormal cobalamin-dependent transmethylation in AIDS-associated myelopathy. Neurology 58:730–735
5. Enns GM, Barkovich AJ, Rosenblatt DS, Frederick DR, Weisiger K, Ohnstad C, Packman S (1999) Progressive neurological deterioration and MRI changes in cblC methylmalonic acidaemia treated with hydroxocobalamin. J Inherit Metab Dis 22:599–607
6. Gadoth N, Figlin E, Chetrit A, Sela BA, Seligsohn U (2006) The neurology of cobalamin deficiency in an elderly population in Israel. J Neurol 253: 45–50
7. Grun RM, Anthony JC, Basset SS, Fulstein MF (1993) Population based norms for the minimental state examination by age and education level. JAMA 269:2386–2391
8. Hammar B, Glocker FX, Schumacher M, Deuschi G, Lueking CH (1998) Subacute combined degeneration of the spinal cord electrophysiological and magnetic resonance imaging findings. J Neurol Neurosurg Psychiat 65: 822–828
9. Haurani FI (2001) Cobalamins and folates as seen through inborn errors of metabolism: a review and perspective. Vitam Horm 60:353–381
10. Healton EB, Savage DG, Brust JCM, Garrett TJ, Lindenbaum J (1991) Neurologic aspects of cobalamin deficiency. Medicine 70:229–245
11. Hector M, Burton JR (1988) What are the psychiatric manifestations of vitamin B12 deficiency? J Am Geriatr Soc 36:1105–1112
12. Kunze K, Leitenmaier K (1976) Vitamin B12 deficiency and subacute combined degeneration of the spinal cord (funicular spinal disease). In: Vinken PJ, Bruyn GW, Klawans HL (eds) Metabolic and deficiency diseases of the nervous system (part II). In: Vinken PJ, Bruyn GW (eds) Handbook of Clinical Neurology. vol. 28. Elsevier, Amsterdam, pp 141–198
13. Larner AJ, Janssen JC, Cipolotti L, Rossor MN (1999) Cognitive profile in dementia associated with vitamin B12 deficiency due to pernicious anaemia. J Neurol 246:317–319
14. McArthur JC, Brew BJ, Nath A (2005) Neurological complication of HIV infection. Lancet Neurol 4:543–555
15. Misra UK, Kalita J, Babu GN, Dwivedi KD (1997) Clinical psychometry and P3 in patients on phenytoin monotherapy. Electromyogr Clin Neurophysiol 37:123–127
16. Misra UK, Kalita J, Das A (2003) Vitamin B12 deficiency neurological syndromes: A clinical, MRI and electrodiagnostic study. Electromyogr Clin Neurophysiol 43:57–64
17. Oken BS, Kaye JA (1992) Electrophysiologic function in the healthy, extremely old. Neurology 42:519–526
18. Pandey S, Kalita J, Misra UK (2004) A sequential study of visual evoked potential in patients with vitamin B12 deficiency neurological syndrome. Clin Neurophysiol 115:914–918
19. Reynolds EH, Linnell JC, Faludy JE (1991) Multiple sclerosis associated with vitamin B12 deficiency. Arch Neurol 48:808–881
20. Roos D (1978) Neurological complications in patients with impaired vitamin B12 absorption following partial gastrectomy. Acta Neurol Scand 59 (S 69):1–77
21. Rossi A, Cerone R, Biancheri R, Gatti R, Schiaffino MC, Fonda C, Zammarchi E, Tortori-Donati P (2001) Early-onset combined methylmalonic aciduria and homocystinuria: neuroradiologic findings. Am J Neuroradiol 22:554–563
22. Royall DR, Mahurin RK (1994) EXIT25, QED, and DSM-IV: very early Alzheimer's disease. J Neuropsychiatry Clin Neurosci 6:62–64
23. Savage DG, Lindenbaum J (1995) Neurological complications of acquired cobalamin deficiency: clinical aspects. Bailliere's Clin Haematol 8:657–678
24. Scalabrino G, Corsi MM, Veber D, Buccellato FR, Pravettoni G, Manfridi A, Magni P (2002) Cobalamin (vitamin B(12)) positively regulates interleukin-6 levels in rat cerebrospinal fluid. J Neuroimmunol127:37–43

25. Schramm U, Berger G, Muller R, Kratzsch T, Peters J, Frolich L (2002) Psychometric properties of Clock Drawing Test and MMSE or Short Performance Test (SKT) in dementia screening in a memory clinic population. Int J Geriatr Psychiatry 17: 254–260
26. Shevell MI, Matiaszuk N, Ledley FD, Rosenblatt DS (1993) Varying neurological phenotypes among muto and mut- patients with methylmalonylCoA mutase deficiency. Am J Med Genet 45:619–624
27. Tangalos EG, Smith GE, Ivnik RJ, Petersen RC, Kokmen E, Kurland LT, Offord KP, Parisi JE (1996) The Mini-Mental State Examination in general medical practice: clinical utility and acceptance. Mayo Clin Proc 71:829–837
28. Umbricht D, Javitt D, Novak G, et al. (1999) Effects of resperidone- an auditory event related potentials in schizophrenia. Int J Neuropsychopharmacol 2:299–304
29. Von Schenck U, Bender-Gotze C, Koletzko B (1997) Persistence of neurological damage induced by dietary vitamin B-12 deficiency in infancy. Arch Dis Child 77:137–139
30. Wang H-X (2002) Vitamin B12, folate and Alzheimer's disease. Drug Dev Res 56:111–122
31. Watkins D, Rosenblatt DS (2001) Cobalamin and inborn errors of cobalamin absorption and metabolism. Endocrinologist 11:98–104