ORIGINAL ARTICLE

Comparison of clinical and electrodiagnostic features in B12 deficiency neurological syndromes with and without antiparietal cell antibodies

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Background and aims: This study was undertaken to compare the clinical and electrodiagnostic (Edx) features in autoimmune and nutritional vitamin B12 deficiency neurological syndromes.

Methods: Consecutive patients with vitamin B12 deficiency neurological syndromes were evaluated and blood counts, red blood cell indices, serum chemistry, thyroid function, HIV serology, antiparietal cell antibody (APCA), serum B12, bone marrow and spinal MRI assessed. EDx studies included nerve conduction, tibial somatosensory (SEP) and motor evoked potential (MEP) to the tibialis anterior, and visual evoked potential (VEP). The results were compared between APCA positive and negative groups.

Results: 57 patients aged 17–80 years (mean 45.3) were studied; 48 were vegetarians. The presenting clinical syndromes were myeloneuropathy in 25, myelopathy in 14, myeloneuroencephalopathy in 13, myeloencephalopathy in four and behavioural abnormality only in one patient. Spinal MRI in 47 patients revealed posterior spinal cord hyperintensity in 21 and cord atrophy in six. Nerve conduction was abnormal in 15%, MEP in 56.6%, SEP in 87.3% and VEP in 63.6% of patients. At 3 months, 31 patients had complete, 11 partial and three poor recovery. APCA was positive in 49% of patients. There was no difference in clinical, MRI or Edx findings or outcome between the APCA positive and negative groups.

Conclusion: APCA was positive in 49% of patients with B12 deficiency neurological syndrome but their clinical, MRI and Edx changes were not different from the APCA negative group. Neurological manifestations may be caused by B12 deficiency itself rather than the underlying cause.

Vitamin B12 deficiency is common in vegetarians, especially in Hindus and Jains who exclude animal protein from their diet for religious or social reasons. Lower levels of serum B12 have been reported in vegetarians compared with non-vegetarians in India.¹ Vitamin B12 deficiency can also occur as a result of autoimmune diseases, parasitic diseases, drugs, gastrointestinal surgery, malabsorption and genetic defects, such as transcobalamin II polymorphism.² Pernicious anaemia is an autoimmune disorder in which the gastric mucosa is atrophic, with loss of parietal cells resulting in intrinsic factor deficiency. In the absence of intrinsic factor, less than 1% of dietary vitamin B12 is absorbed. In the nervous system, vitamin B12 acts as a coenzyme in the methyl melonyl CoA mutase reaction which is necessary for myelin synthesis. Vitamin B12 deficiency therefore results in defective myelin synthesis leading to diverse central and peripheral nervous system dysfunctions. Pernicious anaemia may be associated with a number of autoimmune disorders, such as myxoedema, thyrotoxicosis, Hashimoto's thyroiditis, Addison's disease and vitiligo. Untreated vitamin B12 deficiency due to autoimmune or nutritional causes results in macrocytic anaemia, subacute combined degeneration of the spinal cord, encephalopathy and neuropathy in various combinations and permutations.^{3–6}

The different causes of B12 deficiency (that is, nutritional deficiency or autoimmunity) may have different clinical, laboratory and prognostic features because of the effect of autoimmune conditions or the effect of the associated antineuronal autoantibodies. A Medline search using the key words "pernicious anaemia", "antiparietal cell antibody", "nutritional deficiency" and "subacute combined degeneration" did not reveal any study comparing the clinical, laboratory findings and prognosis of vitamin B12 deficiency of autoimmune or nutritional aetiology. We have prospectively

evaluated patients with B12 deficiency neurological syndrome and compared their clinical, radiological and electrodiagnostic (Edx) findings, and outcome, in terms of the presence or absence of antiparietal cell antibodies (APCA).

Subjects and methods

Consecutive patients with B12 deficiency neurological syndromes during the period 1998–2005 were included in the study. The diagnosis of B12 deficiency neurological syndrome was based on low serum B12 levels (<211 pg/ml) and/or megaloblastic bone marrow. Patients were subjected to a detailed clinical history, with recording of family history, drug exposures, dietary intake by food frequency questionnaire, addictions, gastrointestinal surgery, jaundice and chronic diarrhoea. History of autoimmune disorders, in particular thyroid dysfunction, vitiligo, rheumatoid arthritis and myasthenia gravis were noted. The presence of anaemia, jaundice or hepatosplenomegaly was also recorded. Mental status was evaluated using the minimal state examination (MMSE). Muscle power, tone, tendon reflex, coordination and sensations to pinprick, joint position and vibration were tested.

Blood counts, haemoglobin, general blood picture, red blood cell indices and segmented polymorphs were recorded. Serum albumin, lactate dehydrogenase, bilirubin, transaminases, fasting and postprandial blood sugar, thyroid profile and HIV serology were carried out in all patients.

Spinal MRI was performed using a 1.5 T Signa GE medical system. T1 (500/15/3 = TR in ms/TE in ms/excitation), T2

Abbreviations: APCA, antiparietal cell antibody; CMCT-TA, central motor conduction time to the tibialis anterior; Edx, electrodiagnostic; MEP, motor evoked potential; MMSE, minimal state examination; SEP, somatosensory evoked potential; VEP, visual evoked potential

Figure 1 Spinal MRI, T2 sequence, axial section showing hyperintense signal changes in the cervical spinal cord. The patient had quadriplegia and cognitive impairment which improved completely following B12 treatment.

(2200–2500/80–90/1) and PD (2200–2500/20/1) images were obtained in axial and sagittal sections. In some patients cranial MRI was also carried out. The presence of abnormal signal alterations, their location and cortical atrophy were noted.

Electrodiagnostic studies included nerve conduction study of sural and common peroneal nerves, bilateral tibial somatosensory (SEP) and motor evoked potential (MEP) to the tibialis anterior and pattern reversal visual evoked potential (VEP). The recordings were made using surface electrodes employing standard techniques. The results of Edx values were compared with our normal laboratory values.⁷

Serum B12 levels were estimated by chemiluminescence assay and APCA by ELISA. As soon as the diagnosis was confirmed, patients were treated with cyanocobalamin or hydroxycobalamin 1000 µg intramuscularly daily for 10 days followed by weekly for one month and then monthly administration. Outcome was defined on the basis of activities of daily living at 3 months. Complete recovery was defined as independence, partial recovery as dependence for everyday activities and poor recovery as bed ridden state.³

Clinical, laboratory, MRI and Edx changes in patients with and without APCA were compared by χ^2 test, Fisher's exact test and *t* test using SPSS version 10 software.

RESULTS

There were 57 patients with vitamin B12 deficiency neurological syndromes. Age ranged from 17 to 80 years (mean 45.3) years and 17 were females. The majority were vegetarian (*n* = 48); of these, five were vegans and 36 consumed less than 500 ml of milk or milk products daily. Nine patients consumed alcohol in moderation and four were smokers. Duration of illness ranged from 10 days to 60 (mean 11) months. Presenting symptoms included behavioural abnormality in 14, forgetfulness in 19, paresthesia in 44 and walking difficulty in 48 patients. Paresthesia was restricted to the legs in 38 patients and involved the upper limbs also in six patients. Walking difficulty was mainly due to sensory ataxia leading to a bedridden state in 14 and dependency for everyday activities in 20 patients. The frequency of these symptoms was not different between the APCA positive and negative groups.

The presenting neurological syndromes included myeloneuropathy in 25, myelopathy in 14, myeloneuroencephalopathy in 13, myeloencephalopathy in four and behavioural change only in one patient. On MMSE, mild to moderate cognitive impairment was noted in 27 patients (11–28, mean 24.4). Cognitive impairment was associated with behavioural

Table 1 Clinical, laboratory and evoked potential changes in patients with B12 deficiency neurological syndromes with and without antiparietal cell antibodies

	APCA negative (<i>n</i> = 29)	APCA positive (<i>n</i> = 28)	<i>p</i> Value
Age (y)	44.5 (15)	45 (17.5)	0.92
Male	21	19	0.77
Vegetarian	26	22	0.35
Alcoholic	2	7	0.07
Smoking	3	0	0.32
Duration of symptoms (months)	16.0 (24.8)	9.68 (13.1)	0.24
Presenting syndrome			
M/MN/MNC/MC/C	9/11/8/1/0	5/14/5/3/1	0.38
Abnormal MMSE	12	15	0.59
Haemoglobin (<12 g/dl)	21	22	0.76
Mean corpuscular volume (>96 fl)	17	23	0.08
Leucopenia	3	2	0.67
Thrombocytopenia	7	4	0.50
Serum albumin	3.87 (0.59)	3.94 (0.42)	0.48
MRI cord atrophy/hyperintensity/normal	5/12/8	1/9/12	0.16
Outcome			
Complete/partial/poor	12/7/2	19/4/1	0.28
CMCT-TA			
NR/prolonged/normal	0/12/13	2/16/10	0.25
Tibial CSCT			
NR/prolonged/normal	13/11/3	17/7/4	0.46
VEP			
NR/prolonged/normal	18/9	17/11	0.78
Sural conduction			
NR/slow/normal	0/2/14	1/2/14	0.62
Peroneal conduction			
Abnormal/normal	1/16	2/17	1.00

APCA, antiparietal cell antibody; C, cognitive; CMCT-TA, central motor conduction time to the tibialis anterior; CSCT, central sensory conduction time; M, myelopathy; MC, myelocognitive; MN, myeloneuropathy; MNC, myeloneurocognitive; NR, not recordable; VEP, visual evoked potential.

abnormalities in 33% of patients. The behavioural abnormalities included irritability in 10, hallucination in five, depression in four, obsession, aggression and anxiety in two each and delusion in one patient. All patients had lower limb spasticity; 15 had severe (MRC grade II–III) and 19 mild (grade IV) weakness. Ankle reflex was absent in 32 patients. Joint position and vibration sense were impaired in all except one who had only behavioural abnormality. Hypothyroidism and vitiligo were present in one patient each who were APCA positive. Anaemia was present in 43 patients (haemoglobin <12 g/dl), mean corpuscular volume was elevated (>96 fl) in 40 patients and segmented polymorphs were found in seven patients. Leucopenia was present in five and thrombocytopenia in seven patients. Low serum albumin was present in 15%, mild elevation of bilirubin in 18% and lactate dehydrogenase in 60% of patients. Serum B12 levels between APCA positive (132.18 (40.74) pg/ml) and negative (110.23 (53.13) pg/ml) groups were not significantly different ($p = 0.27$).

MRI findings

Spinal MRI was carried out in 47 patients which revealed posterior spinal cord hyperintensity in the cervicodorsal region in 21 and cord atrophy in six patients (fig 1).

Neurophysiological findings

Sural nerve conduction was unrecordable in one patient and conduction velocity was slowed in four of 33 patients. Peroneal nerve conduction was abnormal in three of 36 patients. Central motor conduction time to the tibialis anterior (CMCT-TA) was carried out in 53 patients and the majority of patients showed prolonged CMCT-TA (28 patients); in only two patients it was unrecordable. Tibial central sensory conduction time was carried out in 55 patients and in majority it was abnormal, being unrecordable in 30 and prolonged in 18 patients. VEP revealed prolongation of P100 latency in 35 patients.

At 3 months, 31 patients had complete, 11 partial and three poor recovery. APCA were present in 28 and absent in 29 patients. There was no difference in clinical, neurological, MRI or Edx parameters between the APCA positive and negative groups. Also, there was no difference in therapeutic response between the two groups (table 1). In the APCA positive group, one patient each had hypothyroidism and vitiligo.

DISCUSSION

In our study of B12 deficiency neurological syndromes, myelopathy was present in 93%, encephalopathy in 48% and neuropathy in 44% of patients, in various combinations and permutations. Combined syndromes occurred in nearly all patients and pure syndromes occurred as an exception (2%). Similar results have been reported in a previous study involving 143 patients with 153 episodes of cobalamin deficiency in which myelopathy was reported in 88% and encephalopathy in 15%; 14% of patients had symptoms only without corresponding neurological signs.⁶ Higher frequency and severity of neurological involvement in our study may have been due to selection criteria. We selected patients with neurological deficits who had low serum B12 levels or megaloblastic bone marrow, in contrast with the study of Heaton *et al* in which patients with B12 deficiency, even without neurological signs, were also included.⁶ In spite of these differences, a high frequency of proprioceptive impairment was noted in both of these studies.

Common occurrence of cognitive impairment in our study (48%) may have been a result of the use of MMSE for screening for cognitive impairment which identified an additional 18% of patients above the 30% who complained of forgetfulness. Cognitive impairment in our study was associated with behavioural abnormalities in 33% of patients in the form of

irritability, hallucinations, depression, obsession, aggression, anxiety and delusion. Such neurobehavioural disturbances due to vitamin B12 deficiency have been reported in previous studies. The reported psychiatric symptoms in vitamin B12 deficiency include slow cerebration, confusion, memory changes, delirium, hallucinations, depression, acute psychosis, reversible mania and schizophreniform state.⁸ In 146 patients with neuropsychiatric abnormalities caused by cobalamin deficiency, 28% did not have anaemia or macrocytosis.⁹ In our study, anaemia and macrocytosis were also absent in 23% and 26% of patients, respectively. In a study of 16 patients with cobalamin deficiency, 13 with longstanding dementia did not improve, highlighting the importance of early diagnosis and treatment.¹⁰

The high frequency of proprioceptive impairment was confirmed by tibial SEP abnormalities in 87% of patients in the present study; the literature reports values of 80–100%.^{3–5} A low frequency of SEP abnormalities in B12 deficiency in other studies may be attributed to evaluation of median SEP.⁶ High frequency of tibial SEP abnormalities is consistent with involvement of the posterior column in the cervicodorsal region at autopsy as well as MRI studies. The brunt of the disease falls on the fasciculus cuneatus, resulting in degeneration.¹¹ Neurophysiological changes in subacute combined degeneration take the form of patchy involvement of white matter which affects the spinal cord in particular, throughout its length, resulting in spongiform changes.^{12–13} Generally the largest diameter fibres are affected predominantly, resulting in slowing of conduction.

The pyramidal pathways are however affected to a much lesser degree compared with the posterior columns; hence the SEP was unrecordable in 50% patients, and in the remaining patients central sensory conduction time was prolonged. In most of our patients there was mild weakness with varying degrees of spasticity. Central motor conduction to the tibialis anterior was recordable in all and was prolonged in 53% of patients in our study. In the study of Hammar *et al*, 29% of patients had abnormal central motor conduction time.⁵

Clinically apparent visual impairment is uncommon in vitamin B12 deficiency and was found in only one patient in the present study as well as in a previous study.⁶ VEP studies revealed prolongation of P100 latency in 63.6% of patients. In an earlier study on B12 deficiency, VEP abnormalities were noted in 77% of patients.¹⁰ Vitamin B12 deficiency results in demyelination and subsequent atrophy of the optic nerve with compensatory proliferation of glia, affecting the papillomacular bundle in particular.¹⁴

In vitamin B12 deficiency, the neurological deficits are inversely related to the haematocrit and haemoglobin level.^{6–15} In our study, we found low haemoglobin levels in two thirds of our patients which may be due to underlying malnutrition as was evidenced by low serum albumin in 15% of patients.

In the patients with vitamin B12 deficiency neurological syndromes, comparison of the APCA positive and negative groups did not reveal any significant difference in the clinical, Edx or MRI findings, or outcome. In the APCA positive group, there was one patient each with vitiligo and hypothyroidism, highlighting the autoimmune association. APCA is an indirect marker of autoimmune dysfunction and it is positive in only 2% of the normal population. APCA may also be present in atrophic gastritis, gastric ulcer, thyroid disease and diabetes¹⁶; however, upper gastrointestinal endoscopy was not carried out in our patients.

In an experimental model of cobalamin deficiency in total gastrectomy rats and in rats rendered cobalamin deficient by diet, the morphological and biochemical changes were similar. However, the time required to produce these changes was much longer in the latter group.¹⁷ It is therefore conceivable that

morphological and biochemical alterations are linked to cobalamin deficiency rather than its cause.² In our study, the presence of APCA in 49% of patients suggests a possible role for nutritional factors, especially in vegetarians. Further studies are needed to evaluate the underlying cause of vitamin B12 deficiency in the APCA negative group. The clinical, neurophysiological, radiological and therapeutic responses however were similar between the APCA positive and negative groups.

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