

Sensorimotor Neuropathy and Abnormal Vitamin B₁₂ Metabolism in Early HIV Infection

M. Veilleux, O. Paltiel and J. Falutz

ABSTRACT: Distal sensory peripheral neuropathy (DSPN) has been reported in 5 to 75% of patients with human immunodeficiency virus (HIV) infection, particularly in advanced stages of the disease. Twenty HIV seropositive patients were studied prospectively to determine the frequency of DSPN in clinical stage II and III of the HIV infection, and to investigate the role of vitamin B₁₂ deficiency on the frequency of DSPN in HIV patients. All patients had complete blood count, serum vitamin B₁₂ level, anti-intrinsic factor antibody, Schilling test, and electrodiagnostic studies including nerve conduction studies and concentric needle examination in the lower extremities, and sympathetic skin responses. Only 1 patient (5%) had clinical and electrophysiological evidence of possible DSPN. Of the 6 patients with abnormal Schilling test, only one had DSPN based on distal sensory symptoms, abnormal neurological examination and electrodiagnostic studies. Evidence for possible DSPN was present in 5% of patients with early HIV infection and did not appear to be more frequent in patients with concurrent vitamin B₁₂ deficiency.

RÉSUMÉ: Fréquence de la polynévrite sensitivomotrice distale et métabolisme anormal de la vitamine B₁₂ en phase précoce de l'infection par le VIH. Une polynévrite sensitive distale (PSD) a été rapportée chez 5 à 75% des patients atteints d'une infection par le virus de l'immunodéficience humaine (VIH), surtout en phase avancée de la maladie. Nous avons fait une étude prospective de vingt patients séro-positifs pour le VIH afin de déterminer la fréquence de la PSD dans les stades cliniques II et III de l'infection par le VIH et d'investiguer l'influence d'un déficit en vitamine B₁₂ sur la fréquence de la PSD chez ces patients. Tous les patients ont eu une formule sanguine complète, un dosage de la vitamine B₁₂ et des anticorps dirigés contre le facteur intrinsèque, un test de Schilling et des études électrodiagnostiques, incluant des études de la conduction nerveuse et de la discrimination spatiale aux membres inférieurs, et des réponses cutanées sympathiques (RCS). Seulement 1 patient (5%) avait des manifestations cliniques et électrophysiologiques compatibles avec une PSD. Parmi les 6 patients qui avaient un test de Schilling anormal, seulement un avait une PSD documentée par des symptômes sensitifs distaux, un examen neurologique et des études électrodiagnostiques anormales. Des manifestations compatibles avec une PSD étaient présentes chez 5% des patients en phase précoce de l'infection par le VIH et ne semblaient pas être plus fréquentes chez les patients qui avaient une déficience concomitante en vitamine B₁₂.

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The peripheral nervous system is affected in 5 to 75% of human immunodeficiency virus (HIV) sero-positive individuals.¹⁻¹² Distal sensory peripheral neuropathy (DSPN) is the most common form of peripheral neuropathy in HIV-positive patients^{5,11} and occurs particularly in the advanced stages. The pathogenesis remains obscure but toxins, metabolic and nutritional factors, and direct viral invasion of the axon are suspected as causative agents. A recent report suggested a high incidence of vitamin B₁₂ deficiency in HIV seropositive patients with myelopathy and peripheral neuropathy.¹³

Twenty HIV seropositive patients were studied prospectively to determine: 1) the frequency of DSPN in CDC Group II and III of the HIV infection; and 2) the role of vitamin B₁₂ deficiency on the frequency of DSPN in HIV patients.

MATERIALS AND METHODS

Twenty consecutive HIV seropositive patients seen at the Montreal General Hospital AIDS Clinic between January and June 1991 who were in group II and III according to the Center for Disease Control (CDC) HIV disease classification,¹⁴ were

From the Division of Neurology (M.V.), Haematology (O.P.), and the Immunodeficiency Treatment Center (J.F.), Montreal General Hospital and McGill University, Montreal.

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enrolled in the study. All patients had general medical and neurological history and examination, extensive blood workup including complete blood count, serum vitamin B₁₂ level, anti-intrinsic factor antibody, Schilling test, and CD4 count, and were referred to the EMG Laboratory for electrophysiological testing. All recruited subjects were homosexual or bisexual. Age, duration of HIV infection, and current medications were recorded in all cases. Patients previously exposed to known neurotoxins such as alcohol and didanosine, with a medical condition known to be associated with a peripheral neuropathy, or with a family history of peripheral neuropathy were excluded.

A diagnosis of distal sensorimotor peripheral neuropathy was made according to the criteria for HIV-1 associated sensory neuropathy.¹⁵ Since none of the patients had cerebrospinal fluid studies, one could only diagnose possible DSPN based on sensory symptoms in the hands and feet, hypoactive or absent ankle reflexes, reduced distal sensation to light touch, pinprick or vibration in the legs with stocking distribution, and abnormalities on electrodiagnostic testing.

HIV status was tested by enzyme-linked immunosorbent assay (ELISA) and confirmed by immunofluorescence assay (IFA). Vitamin B₁₂ level assay was performed by mechanized radio-immunoassay using the ARIA II system (Becton-Dickinson) and considered abnormal if less than 132 pmol/L. Schilling test was performed using 0.5 µCi of cyanocobalamin-Co⁵⁷ (Frosst, Kirkland, Quebec). A less than 10% absorption of orally administered vitamin B₁₂ was considered abnormal. Finally, CD4 counts were measured using a whole blood lysis technique, defining CD4 and CD8 subsets of CD3 (T cells), CD19 (B cells) and CD56 (NK cells).

Peroneal and tibial motor, sural and superficial peroneal nerve conduction studies (NCS) were done in a standard fashion using surface recording electrodes.¹⁶ In 11 patients, medial plantar nerve conduction studies were also performed. Results on motor and sensory nerve conduction studies were compared with normal controls. Needle examination of the anterior tibialis, medial gastrocnemius, abductor hallucis and vastus lateralis muscles was performed in all patients using a standard concentric EMG electrode. Spontaneous activity and motor unit potentials were analyzed subjectively. Sympathetic skin responses (SSR) were obtained on stimulation of the right median nerve at the elbow by recording from the left palm and sole as described by Shahani et al.¹⁷ The study was performed in a quiet, semi-dark room at a temperature of 20-22 degrees Celsius. Electrical stimuli and recording were performed on a Dantec 2000 or Nomad using a sweep speed of 500/millisecond, low-frequency filter of 5 Hz, high-frequency filter of 2 kHz, and sensitivity of 100 µV. Only the absence of SSR from the palm or sole was considered abnormal.

Comparisons of the age, estimated duration of seropositivity, CD4 count were made between the groups with and without abnormal vitamin B₁₂ metabolism using unpaired Student's t-test.

RESULTS

All patients were male and the mean age was 36.7 years (range: 28-46). The mean estimated known duration of HIV seropositivity was 3.5 years (range 0.2-8). At the time of the study, six patients were on no medication and 14 were receiving zidovudine (AZT). None had been on didanosine prior to the

study. Only one patient fulfilled all criteria for possible HIV-associated DSPN.

Clinical findings

One patient complained of tingling sensation in his hands and feet. On neurological examination, he had absent ankle jerks, reduced pinprick and light sensation in the feet up to the ankles and reduced vibration sensation in the toes. Nerve conduction showed no response on superficial peroneal and medial plantar nerve stimulation but normal sural nerve response, concentric needle electrode examination (CNEE) and SSR in the legs. Another patient described a mild burning sensation on the anterior-lateral aspect of the thigh, and neurological examination was normal except for a reduced pinprick and light touch sensation in the distribution of the right lateral femoral cutaneous nerve distribution. His electrodiagnostic studies were normal.

Electrophysiological studies

Peroneal and tibial motor, and sural nerve conductivity was normal in all patients and was not significantly different from age-matched controls. Superficial peroneal NCS were normal in all but 1 patient who had clinical evidence for DSPN and had no response on superficial peroneal and medial plantar nerve stimulation. Concentric needle electrode examination of distal leg muscles showed normal insertional activity and motor unit potentials on voluntary muscle activation in our patients. SSR were present in the hand and foot in all patients except in an asymptomatic patient who had a normal neurological examination, normal NCS and CNEE.

Vitamin B₁₂ metabolism

None of our 20 patients had evidence of megaloblastic anemia on complete blood count. Eight patients had a serum vitamin B₁₂

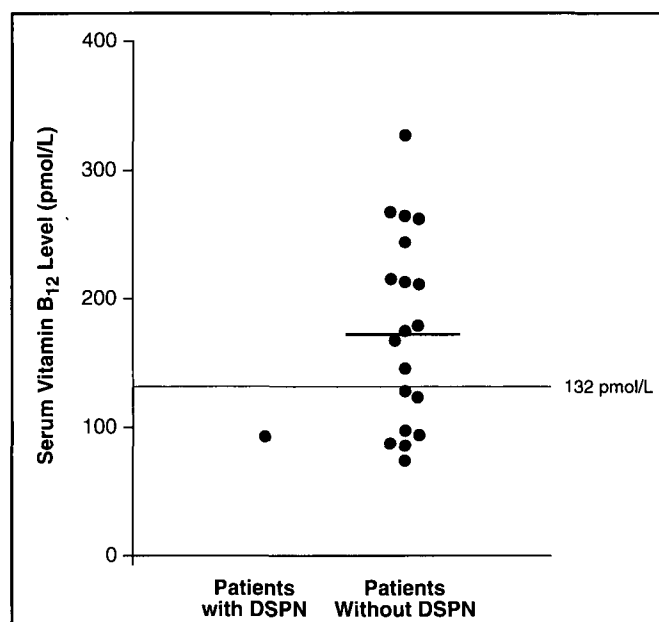


Figure: Serum vitamin B₁₂ in patients with and without DSPN. Serum vitamin B₁₂ level in patients without DSPN (mean ± SD: 178 ± 78 pmol/L) was frequently subnormal.

level less than 132 pmol/L, and of these 8 patients, 4 had an abnormal Schilling test. Only one patient with reduced vitamin B₁₂ level and abnormal Schilling test had clinical and electrophysiological evidence of DSPN. Patients with and without DSPN had similar vitamin B₁₂ levels (Figure). Two patients with a low Schilling test had normal serum vitamin B₁₂, neurological examination and electrophysiological testing. Six patients (29%) had an abnormal Schilling test and their mean serum vitamin B₁₂ (mean ± SD: 130.2 ± 50.9) was not significantly lower as compared to patients with normal Schilling test (mean ± SD: 194.5 ± 76.1; two-tailed P value of 0.07). Anti-intrinsic factor antibodies were not detected in any patient.

HIV infection and vitamin B₁₂ absorption

Patients with a Schilling test less than 10% had a significantly lower CD4 count (mean ± SD: 175/cc³ ± 128) as compared to patients with normal Schilling test (mean 374.2 ± 178; unpaired t test, *p* < 0.02). Patients with a CD4 count of less than 200/cc³ did not have a lower vitamin B₁₂ absorption on the Schilling test (mean ± SD: 12.4 ± 11.9) as compared to those with CD4 count greater than 200/cc (mean ± SD: 16.4 ± 8.1; unpaired t test, *p* = 0.38). Estimated duration of HIV seropositivity was not significantly longer in patients with a low Schilling test.

DISCUSSION

Evidence of peripheral nerve involvement is present in 5 to 75% of patients with HIV infection. Neuropathies associated with HIV seroconversion include acquired inflammatory demyelinating polyneuropathy (AIDP) and ganglioneuropathy. Neuropathies previously reported with asymptomatic HIV infection include AIDP, chronic inflammatory demyelinating polyneuropathy (CIDP), and DSPN.^{9,18-20} Finally, in advanced stages of HIV infection, patients may present with DSPN, AIDP, CIDP, progressive polyradiculopathy, or mononeuritis multiplex.

The distal sensory polyneuropathy is an axonal, predominantly sensory neuropathy characterized clinically by painful dysesthesias, loss of all sensation in a glove and stocking distribution, and areflexia. Cerebrospinal fluid protein may be slightly elevated but white blood cells are typically absent.^{5,20} Nerve biopsies have demonstrated axonal loss of both myelinated and smaller unmyelinated fibers.¹⁸ The course of this neuropathy is usually slowly progressive over the duration of the illness, with management of pain being the biggest concern.

Janssen et al.²¹ reported that 7% of patients with no signs or symptoms of advanced HIV-1 infection had paresthesias in the limbs. According to Simpson,²⁰ clinical symptoms and signs of DSPN may be elicited in 18% of AIDS patients whereas electrophysiological abnormalities suggestive of DSPN are present in 35% of patients.¹² Although 32% of patients in CDC group II/III had an abnormal neurological examination, McAllister et al.²² found no significant difference on nerve conduction studies of the lower extremities when comparing HIV-seropositive patients with age-matched seronegative patients. Finally, Gastaut et al.¹ reported evidence of peripheral nerve involvement on clinical examination, nerve conduction studies and nerve biopsies in up to 89% of HIV-infected (CDC group II, III and IV) patients. In our series of 20 patients with CDC stage II and III of HIV infection, only one patient (5%) had clinical and electrophysiological evidence for a mild predominantly sensory DSPN, and he fulfilled

the criteria for a possible DSPN as defined by the American Academy of Neurology AIDS Task Force. An additional patient had absent SSR in the foot but was clinically asymptomatic. Although abnormal for the patient's age and suggestive of a subclinical small fiber neuropathy, this finding was not considered sufficient evidence for DSPN.

Our low rate of DSPN in early HIV infection as compared to some studies could be explained among others by our small sample size, selection bias, or the lack of sensitivity of the electrophysiological testing. However, Janssen²¹ and McAllister²² also reported a low frequency of clinical or electrophysiological abnormalities (less than 7%) in a larger group of early HIV patients. Furthermore, we used strict exclusion criteria in order not to include patients with conditions that can cause a peripheral neuropathy. Finally, the use of quantitative sensory testing might have helped to identify cases with preclinical nerve dysfunction.

According to several groups, up to 50% of HIV seropositive patients have low serum vitamin B₁₂ concentrations.²³ Harriman et al.²⁴ found low vitamin B₁₂ levels in 7% of patients with asymptomatic HIV infection and 15% of patients with AIDS. In the latter series, they attributed low vitamin B₁₂ levels to malabsorption and suggested low vitamin B₁₂ level was an early manifestation of HIV-1 infection. An unexpectedly high prevalence (20%) of abnormal vitamin B₁₂ metabolism was first noted by Kiebertz¹³ in a population of HIV-infected patients referred for neurological evaluation. However in a recent series of 40 seropositive patients including CDC stage II, III and IV,²³ none of them had a megaloblastic anemia, a reduced serum vitamin B₁₂, or an elevated CSF methylmalonic acid level. Although CSF methylmalonic acid or serum homocysteine levels were not obtained in our series, none of our patients had a megaloblastic anemia and of the 8 cases with low serum vitamin B₁₂ level, only 4 had an abnormal Schilling test hence lending support to the notion that a low vitamin B₁₂ level cannot reliably identify all cases where significant cobalamin deficiency is present. In fact, a normal vitamin B₁₂ can be seen in cases where further evaluation demonstrates a true deficiency irregardless of the absence of hematological abnormalities. Finally, of the 4 patients with abnormal Schilling tests, only 1 had clinical and electrophysiological evidence for a mild DSPN. Our findings suggest that although impaired vitamin B₁₂ metabolism is not uncommon in our small group of HIV-infected patients, it is rarely associated with clinical symptoms and signs of DSPN. Finally, abnormal results on the Schilling test are more associated with a greater degree of immunosuppression (low CD4 count) than a reduced serum vitamin B₁₂.

The frequency of distal sensorimotor polyneuropathy in CDC Group II and III of HIV-1 infection was only 5% based on abnormal clinical history, neurological examination and electrodiagnostic studies. In the early stages of HIV-1 infection, patients with impaired vitamin B₁₂ metabolism did not have a higher incidence of DSPN. Patients with impaired vitamin B₁₂ absorption on the Schilling test were more likely to have a low CD4 count and therefore, a greater degree of immunosuppression.

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