

SHORT REPORT

Peripheral neuropathy in patients with HIV infection: consider dual pathology

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Sex Transm Infect 2002;78:462-463

Two HIV infected patients presented with peripheral neuropathy, in one patient this was originally ascribed to HIV associated mononeuritis multiplex and in the other to stavudine. Investigations confirmed these diagnoses and in both cases genetic analysis identified a second hereditary aetiology: in the first patient hereditary neuropathy with liability to pressure palsies and in the second hereditary motor and sensory neuropathy.

The peripheral nervous system is the most frequently affected area of the neuraxis in patients with HIV infection. Up to 35% of HIV infected individuals will develop a peripheral neuropathy due to HIV itself, which is mainly sensory; a similar presentation may occur secondary to drugs such as zalcitabine, didanosine, and stavudine.¹ A mainly motor neuropathy may occur, caused by Guillain-Barre syndrome, and rarely a mixed sensorimotor neuropathy is seen as part of the diffuse inflammatory lymphocytosis syndrome (DILS).² Mononeuritis multiplex due to an associated vasculitis may be caused by HIV and cytomegalovirus. The former typically affects patients with symptomatic HIV disease who have not developed AIDS, whereas the latter occurs within the context of severe immunosuppression.¹

Hereditary motor and sensory neuropathies are a heterogeneous group of neurological diseases.³ Hereditary motor and sensory neuropathy (HMSN), also called Charcot-Marie-Tooth (CMT) 1a is usually caused by a 1.5 Mb duplication at chromosome 17p11.2 which includes the peripheral myelin protein (PMP) 22 gene; rarely HMSN 1a is due to point mutations in PMP 22.³ Hereditary neuropathy with liability to pressure palsies (HNPP) is due to a deletion of the same 1.5 Mb region or very rarely to point mutation in PMP 22.⁴

In this report we describe two patients presenting with peripheral neurological symptoms which were originally ascribed to HIV infection and its treatment. In one the possibility of another pathological process was only apparent after neurophysiological studies and in the other after a detailed neurological examination by an experienced neurologist.

CASE REPORTS

Case 1

In January 2000 a 49 year old white man developed sudden onset right foot drop with sensory symptoms in the distribution of the common peroneal nerve which gradually improved over 4 weeks. Eight months later he developed numbness and tingling over the outer aspect of the left foot, in the distribution of the left sural nerve; these symptoms resolved spontaneously over 2 weeks. In October 2000, the patient reported impaired sensation and weakness of the left hand in the distribution of the median nerve. General inquiry was unremarkable, he denied weight loss or dry eyes/mouth; alcohol intake was 10 units per week. There was no family history of neurological disorder.

The patient was found to be HIV positive in 1985 and began combination antiretroviral therapy in 1998 with stavudine, lamivudine and zidovudine: the latter drug was changed to efavirenz, because of intolerance in June 1999. On this regimen CD4 count = 440 cells $\times 10^6/l$ and HIV viral load was undetectable, but the patient developed a mild peripheral sensory neuropathy, which was ascribed to stavudine.

Examination in November 2000 showed impaired sensation in left sural nerve territory and in the left hand, weakness of abductor pollicis brevis, and opponens pollicis brevis with impaired sensation in median nerve territory. Knee jerks were depressed and ankle jerks were absent; plantar reflexes were flexor. There was no pes cavus. General examination was unremarkable. The patient was thought clinically to have mononeuritis multiplex. Investigations showed a normal full blood count, erythrocyte sedimentation rate (ESR), red cell folate and serum B12, urea and electrolytes and random blood glucose. A CD4 lymphocyte count = 680 (normal = 270-1350) cells $\times 10^6/l$, CD8 count = 2155 (normal = 9-990) cells $\times 10^6/l$, CD4:CD8 = 0.32 (normal = 0.38-3.39). Syphilis serology, hepatitis Bs Ag, ANCA, ANA, rheumatoid latex, and autoantibody screen were negative. Nerve conduction studies and an electromyogram (EMG) revealed a sensorimotor (predominantly sensory) peripheral neuropathy with some demyelinating features. Biopsy of left quadriceps was normal and a left sural nerve biopsy showed an infiltrate of CD8 positive lymphocytes in a perivascular distribution, suggesting the diagnosis of a vascular inflammatory neuropathy, such as DILS. In addition, there was a mixed demyelinating and axonal neuropathy. A teased nerve fibre preparation showed numerous tomaculous bodies, characteristic of HNPP.

Case 2

A 29 year old black African woman was found to be HIV antibody positive when she presented in April 2001 with *Pneumocystis carinii* pneumonia and disseminated *Mycobacterium avium intracellulare* infection (treated with rifabutin, clarithromycin, and ethambutol). At this time she began antiretroviral therapy with lamivudine, stavudine, and zidovudine. In January 2002, stavudine was discontinued because of worsening painful peripheral neuropathy and zidovudine was substituted. The patient denied any family history of neurological disease and was not taking any alternative/complementary therapy. The patient was admitted to hospital in February 2002 with a further deterioration in symptoms. Examination revealed bilateral wasting of the first dorsal interossei, weakness of the small muscles of the hand, reduced joint position sense in the feet and ankles, dysaesthesiae up to the knees, absent ankle jerks, and pes cavus.

Investigations showed normal results for full blood count, serum B12 and red cell folate, liver function tests, calcium and phosphate and blood glucose. The CD4 count = 120 cells $\times 10^6/l$ and HIV viral load was undetectable. An autoantibody screen was negative, as was serology for hepatitis B and syphilis. Serum C3 and C4 and arterial blood gases were normal. The resting venous lactate was 7.4 (normal 0.5-2.2) mmol/l.

This returned to normal over 6 days after antiretroviral therapy was stopped. Nerve conduction studies and an EMG showed evidence of a mixed sensory and motor demyelinating neuropathy, which is not the typical finding in either HIV related sensory neuropathy or neuropathy due to antiretroviral therapy.

Genetic studies

Genetic analysis was carried out on peripheral blood by polymerase chain reaction analysis of five microsatellite markers within a 1.5 Mb region of chromosome 17p11.2, the site which undergoes rearrangement in hereditary neuropathies.^{3,4}

Case 1

A homozygous/heterozygous genotype was identified at all five loci which was confirmed by dosage analysis, strongly supporting the presence of a deletion at this locus and confirming the diagnosis of HNPP.

Case 2

The presence of three alleles at all five loci indicated duplication of chromosome 17p11.2 and confirmed HMSN 1a.

DISCUSSION

In both patients, the presentation with peripheral neurological symptoms and signs were originally ascribed to HIV infection, or as a treatment side effect. In case 1 a combined muscle and nerve biopsy was performed, looking for evidence of vasculitis as the combined approach has a much higher sensitivity for histological abnormalities when compared to nerve biopsy alone.³ The histological appearances of the nerve biopsy showing a heavy CD8 positive lymphocyte perivascular infiltrate, together with the peripheral blood CD8 lymphocytosis pointed to an inflammatory vascular disorder, such as DILS.^{2,6} The diagnosis of HNPP was confirmed by histology of the sural nerve biopsy and by genetic analysis.

In the second case the presentation was thought originally to be due to stavudine induced peripheral neuropathy.^{7,8} Clinical examination raised the possibility of an underlying hereditary neuropathy. Until she developed a painful peripheral neuropathy the patient had no neurological symptomatology. Despite the absence of a family history the patient's sister underwent neurophysiological testing and was found to have HMSN 1a.

These cases demonstrate that Ocam's razor, which expounds the theory of diagnostic parsimony, may not apply in the immunosuppressed HIV infected patient presenting with peripheral neurological symptoms, as more than one diagnosis may co-exist. They also suggest that patients with "bad"

nerves due to any aetiology are more likely to develop complications. For example, in case 1, nerve damage from minor pressure was more likely because of the underlying axonal neuropathy.

ACKNOWLEDGEMENTS

We thank Dr Mike Groves and Dr Jean Jacobs for interpretation of the nerve biopsy.

Source of income: nil.

Conflict of interest: none declared.

CONTRIBUTORS

RFM proposed the project and wrote the first and final drafts of the manuscript. SB, STS, and HM were responsible for patient care, critically reviewed drafts of the manuscript, and carried out a literature review.

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Accepted for publication 16 August 2002

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