Ascending paralysis associated with HIV infection

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We present two patients with a high viral load of HIV-1 who developed symptoms of ascending paralysis leading to respiratory failure and autonomic instability. One patient had symptom improvement with highly active antiretroviral therapy (HAART) and a subsequent decrease in viral load. The other patient improved with intravenous immunoglobulin therapy and did not show much improvement on HAART alone. There are several proposed mechanisms for peripheral neuropathies seen in HIV-infected patients, including a direct action of HIV on the nerve by neurotropic strains or formation of autoantibodies against nerve elements. The comparison of the response to different therapies in these two cases highlights the importance of understanding different pathophysiologies, as the treatment modality may differ.

About 34 million people are affected with HIV worldwide as of 2010, including more than 1.1 million in the United States (1). The immune impairment manifests clinically in multiple organ systems including the nervous system. Since the introduction of highly active antiretroviral therapy (HAART), HIV has evolved into a chronic condition with an increase in related complications (2). Neurologic complications occur in more than 40% of patients with HIV infection, and the prevalence of neuropathologic findings at autopsy is about 80% (3, 4). Central and peripheral nervous system involvement in HIV-infected patients occurs due to various causes, including opportunistic infections, immune reconstitution, a side effect of antiretroviral medication, or the effect of the virus (5). The variations might be due to a difference in age, disease stage, treatment history, timing of the study (i.e., pre- or post-HAART era), and the diagnostic criteria used in different studies. We present two cases of ascending paralysis in HIV-positive patients. Not only was the autoimmune nature of Guillain-Barré syndrome (GBS) in the setting of an immunocompromised patient remarkable, but more importantly the improvement seen in both patients required different treatment approaches.

CASE 1

A 33-year-old white man presented with a 1-day history of bilateral lower-extremity weakness, numbness, and a tingling sensation that started in his feet and progressed to his knees

Table 1. Blood work

Blood laboratory test	Patient 1	Patient 2
CD4 count (cells/ μ L)	526	22
HIV PCR (copies/mL)	2,095,380	59,200
Rapid plasma reagin	Negative	Negative
Human herpesvirus 6 PCR	Negative	N/A
Herpes simplex virus PCR	Negative	Negative
Varicella-zoster virus IgM	Negative	N/A
Lyme antibody	Negative	N/A
Monospot	Negative	N/A
Cytomegalovirus PCR	N/A	Positive
Toxoplasma IgG and IgM	N/A	Negative
Thyroid-stimulating hormone	Normal	Normal
Folic acid	Normal	Normal
Vitamin B12	Normal	Normal
Serum protein electrophoresis	Negative	Negative
Ganglioside antibody panel	Negative	N/A
Heavy metal screen	Negative	Negative

PCR indicates polymerase chain reaction; Ig, immunoglobulin.

and very soon involved his fingertips bilaterally. The patient was diagnosed with HIV 1 week earlier during evaluation of a flulike illness including fever, chills, and maculopapular rash with diarrhea. His HIV viral load was 2,095,380 copies/mL, with a CD4 count of 526 cells/ μ L (*Table 1*). Baseline genotype testing done at that time showed no drug resistance. His past medical history was unremarkable. Examination disclosed intact cognition, intact cranial nerves, decreased sensation in the lower extremities bilaterally up to the knees, along with decreased sensation on the palmar aspect of the hands bilaterally. Muscle strength was slightly decreased bilaterally in the

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Table 2. Initial cerebrospinal fluid data

Laboratory test	Patient 1	Patient 2
Protein (mg/dL)	109	331
Glucose (mg/dL)	52	54
White blood cells (cells/ μ L)	35 (89% lymphocyte)	8 (52% lymphocyte)
Red blood cells (cells/ μ L)	N/A	4000
Gram stain	Negative	Negative
IgG synthesis	Elevated	N/A
Oligoclonal bands	Negative	Negative
Adenovirus	Negative	N/A
Epstein-Barr virus IgM	Negative	Negative
Varicella zoster virus PCR	Negative	Negative
Herpes simplex virus PCR	N/A	Negative
Cocksackie A/B PCR	Negative	Negative
Cytomegalovirus PCR	Negative	Negative
Cryptococcal antigen	Negative	Negative
West Nile antibody	Negative	Negative
Cytology	Negative	Negative
Venereal Disease Research Laboratory	Negative	Negative
Bacterial culture	Negative	Negative
HIV PCR (copies/mL)	N/A	2142
Mycoplasma IgG	1:4	N/A
Mycoplasma IgM	Negative	N/A

PCR indicates polymerase chain reaction; Ig, immunoglobulin.

deltoids. Patellar, Achilles, and biceps deep tendon reflexes were absent, with only the triceps jerk detected at presentation. Cerebrospinal fluid (CSF) analysis in the emergency department showed elevated proteins with mild lymphocytic pleocytosis (*Table 2*). Based on his presentation and CSF findings, he was started on intravenous immunoglobulin (IVIG) the day of admission for possible acute inflammatory demyelinating polyneuropathy (AIDP). Within the first few days of admission, he was also started on HAART with Truvada, raltegravir, darunavir, and ritonavir. The CSF was positive for mycoplasma IgG antibodies (1:4 titer) with negative IgM. However, the test for serum mycoplasma IgM was positive, and hence the patient was started on levofloxacin. The results of magnetic resonance imaging (MRI) of the brain and cervical spine without contrast were unremarkable.

The patient's ascending paralysis worsened over the next 3 days with paresthesias, loss of all deep tendon reflexes, and involvement of cranial nerves. He completed a full course of IVIG of 2 g/kg over 3 days but continued to deteriorate and was started on a five-cycle regimen of plasmapheresis on day 5. Despite aggressive daily plasmapheresis for three cycles, he continued to worsen with autonomic instability, flaccid quadriplegia, and respiratory failure requiring endotracheal intubation and mechanical ventilation 8 days after admis-

sion. Four days after intubation, the patient fairly quickly recovered his respiratory muscle strength and was extubated. A repeat HIV viral load test after 1 week of HAART showed only 3590 copies/mL.

A nerve conduction study (NCS) and electromyogram (EMG) performed 15 days after presentation showed evidence of an acquired sensory and motor peripheral neuropathy with mixed axonal and demyelinating features. There was also diffuse early denervation indicating secondary axonal loss. The relative paucity of denervation seen on the EMG/NCS exam likely reflected the short time lapse since the onset of symptoms.

The patient continued to gradually regain his muscular function and was transferred to a skilled nursing facility for continuing physical therapy. After a 4-week stay at the facility, his muscle strength was close to baseline, and he was discharged home.

CASE 2

A 37-year-old white man with a history of HIV/AIDS with a last CD4 count of 22 cells/ μ L (*Table 1*) presented to the emergency department with 4 weeks of progressively worsening ascending weakness, tingling, and numbness of his lower extremities, with gradual involvement of his upper extremities. He had a history of recurrent lower-extremity weakness and decreased sensation that had required previous hospitalizations. His past medical history was significant for anemia, several episodes of gastritis, asthma, past hepatitis B infection, and anxiety. His family history was not significant for any neurological diseases. Examination disclosed a cognitively intact man with intact cranial nerves. There was a lack of sensation to light touch in the feet and numbness in the hand bilaterally. Grip strength was weak in both hands with trace finger abduction. Elbow flexion and extension was 3/5 and shoulder flexion was 2/5. Reflexes were absent in both upper and lower extremities. MRI scans of the brain and spine were unremarkable. CSF evaluation revealed classic albuminocytologic dissociation without any signs of active infection (*Table 2*).

NCS and EMG tests 20 days after hospitalization showed diffuse sensory motor polyneuropathy with both demyelinating and axonal features. The patient was started on HAART with Stribild (elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil fumarate) and given 2 days of IVIG. Soon after starting IVIG, the patient showed clinical improvement. He was transferred for rehabilitation after a 1-week hospital stay for aggressive physical therapy. Since his initial presentation about a year ago, he has been rehospitalized twice with similar symptoms despite being on continual HAART, during which his viral load has been very low (varying from <20 copies/mL up to 1510 copies/mL). His symptoms continue to respond to treatment with IVIG. Repeated CSF evaluations reveal cytoalbuminologic dissociation at varying degrees (white cells range from 2 to 8 / μ L, and protein ranges from 114 to 331 mg/dL). Although the patient started out with AIDP with axonal features, he now carries the diagnosis of chronic inflammatory demyelinating polyneuropathy (CIDP).

DISCUSSION

These two cases of HIV illustrate very similar clinical presentations with very different pathophysiologies and long-term outcomes. The CSF and HIV status findings dictated very different treatment regimens. In case 1, the patient had aseptic meningitis with multiple possible etiologies (HIV, mycoplasma, seroconversion) and improved only after his HIV RNA titers came down in a monophasic pattern of illness. In the second case, the patient did not have meningitis but rather had what is now known to be CIDP with recurrent symptoms responding very well to IVIG.

HIV can be neuroinvasive, neurotropic, and neurovirulent. Many peripheral neuropathic syndromes have been reported in the context of HIV infection, including HIV-associated distal sensory neuropathy, neurotoxic nucleoside neuropathy, and inflammatory demyelinating neuropathy. HIV-associated distal sensory polyneuropathy (also called predominantly sensory neuropathy, or distal symmetrical peripheral neuropathy) is the most common neurological problem in AIDS, with variable incidences in different reports ranging from 19% to 66% (6, 7). The risk factors for HIV-associated distal sensory polyneuropathy are older age, history of alcohol abuse, advanced HIV disease, prior use of a neurotoxic antiretroviral drug, and diabetes mellitus (8, 9). Inflammatory demyelinating neuropathy, on the other hand, is less common and can occur at various stages of the disease, requiring different therapeutic approaches.

Both patients presented with an ascending paralysis typically described with clinical GBS. GBS generally follows an infectious prodrome, resulting in an augmented immune response, which cross-reacts with axolemmal or Schwann cell antigens, leading to peripheral nerve damage believed to be due to molecular mimicry. The clinical features of GBS are progressive, ascending, fairly symmetric muscle weakness, typically with absent reflexes. The severity of symptoms can vary from mild to profound weakness of all extremities and involving respiratory muscles, resulting in respiratory failure requiring intubation. Respiratory failure requiring ventilator support occurs in 10% to 30% of the cases (10). Symptoms can also include tachycardia, urinary retention, labile blood pressure, arrhythmias, and paresthesias more commonly seen on fingertips and feet and can include autonomic instability in severe cases. The hallmark laboratory finding is albuminocytologic dissociation on the CSF with a near normal white blood cell count seen in up to 66% of patients (11). Treatment for GBS typically involves IVIG or plasmapheresis, which have been shown to have similar outcomes. In our first patient, intrathecal IgG synthesis was dramatically elevated, suggesting an ongoing immune-mediated process, which did not improve until his viral load came down. Notably, he recovered very rapidly (walking within a week after tetraplegia). This was much faster than could be expected in typical GBS patients who have significant changes, both demyelinating and axonal, on NCS/EMG.

GBS in an HIV/AIDS patient was first described in 1985 (12). GBS may occur in HIV-infected patients at the time of seroconversion, even with normal CD4 counts, and can be the presenting symptom or seen in the setting of the immune

reconstitution syndrome (13–16). Nucleoside analogue reverse transcriptase inhibitors (NRTIs), a backbone component of HAART, have also been related to GBS in HIV-infected individuals in association with the immune reconstitution syndrome. Twenty-two cases of GBS associated with stavudine (NRTI) therapy have been reported (17–19).

Several mechanisms have been proposed regarding GBS in HIV-infected patients. Proposed mechanisms include a direct action of HIV on the nerve by neurotropic strains or formation of autoantibodies against myelin secondary to the abnormal immunoregulation caused by the HIV infection (20). In the setting of immune reconstitution syndrome, there is a reemergence of previously anergic lymphocytes upon viral suppression with HAART (13–16). Cell-mediated immunity is known to play a major role in the pathogenesis of GBS. The clinical features of GBS in HIV-infected patients are similar to those in HIV-negative people. However, HIV GBS may be associated with more frequent recurrent episodes and progression to CIDP (21).

In our first case, the onset of rapidly progressive ascending paralysis coincided with the acute retroviral syndrome of HIV. This patient continued to worsen despite IVIG therapy and plasma exchange and only improved with the initiation of HAART and reduction in the viral load. We have not found any previous reports specifically addressing the efficacy of either IVIG or plasmapheresis in the setting of acute retroviral syndrome, but previously reported cases and our first case suggest that antiretroviral treatment is preferable especially if CSF findings show the presence of meningeal inflammation. In our second case, the patient with chronic HIV infection had clinical symptoms consistent with AIDP and ultimately CIDP with modest recovery only seen with IVIG. IVIG has been shown to speed the course of recovery in patients with GBS and HIV seropositivity. Reports of efficacy range from ineffective or mild benefit to a great response (22). In the first case, mycoplasma tested positive and in the second case cytomegalovirus was positive. Both cytomegalovirus and mycoplasma have been implicated in ascending paralysis. It is fairly common to have several potential causes for similar presentations in HIV patients with neurological complications, which exemplifies the complexity of HIV patients.

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