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Antiretroviral Therapy-Associated Acute Motor and Sensory Axonal Neuropathy

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Key Words
Acute axonal neuropathy · Guillain-Barré syndrome · HIV infection · Highly active antiretroviral therapy

Abstract
Guillain-Barré syndrome (GBS) has been reported in HIV-infected patients in association with the immune reconstitution syndrome whose symptoms can be mimicked by highly active antiretroviral therapy (HAART)-mediated mitochondrial toxicity. We report a case of a 17-year-old, HIV-infected patient on HAART with a normal CD4 count and undetectable viral load, presenting with acute lower extremity weakness associated with lactatemia. Electromyography/nerve conduction studies revealed absent sensory potentials and decreased compound muscle action potentials, consistent with a diagnosis of acute motor and sensory axonal neuropathy. Lactatemia resolved following cessation of HAART; however, neurological deficits minimally improved over several months in spite of immune modulatory therapy. This case highlights the potential association between HAART, mitochondrial toxicity and acute axonal neuropathies in HIV-infected patients, distinct from the immune reconstitution syndrome.

Introduction

Guillain-Barré syndrome (GBS) is an acute peripheral neuropathy classified into at least four subgroups by electrodiagnostic criteria, pathology, and anti-ganglioside antibody profiles [1]. GBS has been reported in patients with primary HIV infection, although this is not commonly observed [2]. In HIV-infected patients, GBS has been reported in association with the immune reconstitution syndrome, whereby there is a re-emergence of previously anergic lymphocytes upon viral suppression with highly active antiretroviral therapy (HAART) [3–7]. Nucleoside analogue reverse transcriptase

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inhibitors (NRTIs), a key component of HAART, have been related to GBS in HIV-infected individuals in association with the immune reconstitution syndrome [8–10]. Bristol-Myers Squibb reported 22 cases of GBS associated with stavudine therapy, each with lactatemia, resulting in 7 deaths [10]. We report a case of an HIV-infected adolescent presenting with subacute weakness and lactatemia, diagnosed with acute motor and sensory axonal neuropathy (AMSAN) following long-term HAART therapy, distinct from the immune reconstitution syndrome.

Case Report

A 17-year-old female with HIV secondary to a blood transfusion during infancy presented after a fall at home. The patient complained of generalized weakness for 4–5 days prior to admission that resulted in a buttock abscess. Pertinent past medical history includes HIV-associated pulmonary hypertension, cardiomyopathy, sensorineural hearing loss, major depressive disorder, and complex partial epilepsy. Her antiretroviral regimen included stavudine, abacavir, ritonavir, and lopinavir that were administered by a caretaker daily for several years. She underwent frequent follow-up assessments in the HIV clinic, with routine periodic viral load and CD4 lymphocyte monitoring.

On neurological examination, the patient was alert and oriented to person, time and place, with a depressed affect. Cranial nerves 1–12 were intact. There was marked pitting edema of the hands and feet, with greater distal than proximal weakness of the upper (3/5) and lower extremities (2/5) bilaterally. Patellar and Achilles reflexes were 1+ bilaterally. Sensation to pain and temperature and joint position sense were normal. The patient was unable to ambulate independently due to the profound weakness. She received normal saline intravenously for tachycardia, and broad-spectrum antibiotics were initiated for suspected sepsis secondary to her buttock abscess. Laboratory tests revealed a complete blood count of 19.2 with 41 bands, and an elevated serum lactate level (13.5 mmol/l). The patient had a CD4 count of 392 cells/mm^3 and an undetectable viral load (**table 1**). Results from a lumbar puncture were within normal limits for white blood cells, red blood cells, glucose, and protein levels. Cerebrospinal fluid studies were negative for herpesvirus 1/2, Epstein-Barr virus, cytomegalovirus, and *Treponema pallidum*. Magnetic resonance imaging of the brain and spine with and without gadolinium showed normal findings. All antiretroviral medications were discontinued due to the lactatemia, concerning for possible mitochondrial toxicity. Electromyogram (EMG) and nerve conduction studies (NCS) revealed numerous abnormalities, leading to the final diagnosis of AMSAN (**table 2**). First, there were absent sensory nerve action potentials in the medial, ulnar, sural, medial plantar, and superficial peroneal nerves. Second, very low compound muscle action potentials (CMAPs) were recorded at the median, peroneal, and tibial nerves, with absent CMAPs of the ulnar nerve. F wave studies showed prolonged distal latencies, with relative sparing of nerve conduction velocities. Finally, EMG elicited positive sharp waves and fibrillations. The constellation of EMG and NCS findings were consistent with a diagnosis of AMSAN. The patient was empirically treated with intravenous immunoglobulin (0.4 mg/kg/day) for 5 days but failed to show significant improvement in her distal extremity weakness in spite of a normalized lactate level.

Three months after discharge, the patient had minor improvements in strength of her distal upper extremities (4/5) when compared to distal lower extremities (2/5), and was still unable to ambulate independently.

Discussion

The classical GBS variants follow an infectious prodrome, resulting in an augmented immune response which cross-reacts with axolemmal or Schwann cell antigens, leading to peripheral nerve damage via molecular mimicry [1]. GBS may occur in HIV-infected patients at the time of seroconversion or, more commonly, in the setting of the immune reconstitution syndrome [3–5, 7]. The immune recovery phase, evidenced by an increase in the CD4 lymphocyte count and a decrease in the HIV viral load, is presumptively

responsible for the neuroimmune-mediated attack. While other cases of GBS associated with lactic acidosis related to HAART have been reported [8, 11], this is the first case of GBS, AMSAN in particular, occurring in the absence of the immune reconstitution syndrome. Although impossible to prove conclusively, the most likely mechanism of AMSAN in our patient was HAART-associated mitochondrial toxicity. This is evidenced by an acute lactatemia, in the absence of any other etiology, which resolved upon cessation of antiretroviral therapies. The confounding buttock abscess observed on examination would be another potential source of lactatemia; however, the abrupt cessation of HAART showed immediate and sustained decrease in the serum lactate level, consistent with a hypothesis of a HAART-related phenomenon. Given the patient's tremendous amount of comorbities, including cardiomyopathy, sensorineural hearing loss, and pulmonary hyptertension, an underlying previous undiagnosed mitochondrial cytopathy could also explain the patient's symptomatology. However, mitochondrial DNA testing was performed at admission which was unrevealing. A pre-existing or acquired mitochondrial cytopathy cannot be completely ruled out since the entire nuclear and mitochondrial genomes were not sequenced. Given the numerous reports of HAART-related mitochondrial toxicity in HIV-infected patients, we believe a subset of patients may have HIV- or drug-induced mitochondrial toxicity as opposed to an underlying mitochondrial cytopathy prior to diagnosis.

HAART-related mitochondrial toxicity has been associated with lactatemia and death, particularly in the case of stavudine [10]. Chronic stavudine use, in addition to lactatemia, has been associated with Miller Fisher syndrome in one case report [8]. It is hypothesized that NRTIs, in particular zidovudine, induce myotoxicity via oxidative stress, inhibition of the mitochondrial machinery, and L-carnitine deficiency [9]. NRTIs may alter the function of the mitochondrial enzyme DNA polymerase gamma, leading to dysfunction or depletion in addition to HIV-induced mitochondrial toxicity [12]. Stavudine has been hypothesized to mimic GBS via the inhibition of the mitochondrial polymerase gamma enzyme [13]. Other HAARTs are likely to affect the mitochondrial machinery via similar mechanisms, as opposed to altering the nuclear to mitochondrial DNA ratios, which has been shown to be an ineffective marker of HAART-associated mitochondrial toxicity [14].

One possible treatment of HAART-associated GBS is stabilization of the mitochondria via carnitine therapy. Unfortunately, in our patient, total and free carnitine levels were not measured and vitamin/cofactor therapies were not utilized. These would have been reasonable therapeutic options as the patient responded only minimally to intravenous immunoglobulin treatment, supporting a role of therapy-induced mitochondrial toxicity in addition to an immune-mediated pathophysiology. To further support a neuroimmune mechanism of the disease, IgG anti-ganglioside antibodies to GM1, GM1b, and GD1a may have been useful in the disease classification. Plasmaphoresis, a common therapeutic modality for AMSAN, was not attempted in our patient because of her higher procedural risk secondary to severe HIV-related chronic pulmonary hypertension and cardiomyopathy.

Conclusion

Clinicians should be aware that GBS variants can occur in both adult and pediatric HIV patients on chronic HAART in the absence of an immune reconstitution syndrome.

Both mitochondrial toxicity (evidenced by elevated serum lactate) and neuroimmune mechanisms may play a role in disease pathogenesis.

Table 1. Laboratory values

	Results	Normal values
Hematology		
WBC, K/mcl	19.2	4.19–9.43
Bands, %	41	0–1
Segs, %	30	45–76
Lymphocytes, %	15	14–41
Monocytes, %	9	4–8
Hemoglobin, g/dl	10.1	10.8–13.3
Platelets, K/mcl	309	194–345
CD4, cells/mm^3	392	500–1,500
HIV viral load, copies/ml	0	0
Chemistry		
Na, mmol/l	131	133–143
K+, mmol/l	3.9	3.3–4.7
Cl–, mmol/l	91	97–107
Blood urea nitrogen, mg/dl	4	7–21
Creatinine, mg/dl	0.5	0.5–1.1
Albumin, g/dl	3.6	3.8–5.6
Alkaline phosphatase, u/l	94	82–169
Direct bilirubin, mg/dl	2.74	<0.4
Total bilirubin, mg/dl	3.8	<0.8
Aspartate aminotransferase, u/l	46	0–26
Alanine aminotransferase, u/l	14	19–49
Lactate, mmol/l	13.5	1–2.4
Pyruvate, mg/dl	1.67	0.3–1.5
Coagulation		
PT, s	16.5	11.5–13.8
PTT, s	30	22.3–34.4
INR	1.4	0.8–1.1
Cerebrospinal fluid		
WBC, /μl	1	0–6
RBC, /μl	1	0
Protein, mg/dl	31	15–45
Glucose, mg/dl	93	41–84
CMV PCR	negative	
EBV	negative	
HSV-1, HSV-2	negative	
VDRL	non reactive	
Other		
Valproic acid, mg/μl	56	50–100
Ammonia, μmol/l	24	29–54
Thyroid-stimulating hormone, μu/ml	3.40	0.51–4.91
B12, pg/ml	1,892	210–911
Free T4, ng/dl	1.94	1.1–1.6
RPR	NR	NR

Table 2. Summary of electromyogram and nerve conduction studies

Nerve, location	Amplitude mV	Distance cm	Latency ms	Conduction velocity, m/s
Motor nerve conduction studies				
Ulnar, wrist	0	7		
Ulnar, below elbow	0	20		
Ulnar, above elbow	0	10		
Median, wrist		0.1	6	4.40
Median, elbow	0.1	20	7.90	57.1
Peroneal, ankle	0.3	6	5.00	
Peroneal, fibula	0.4	30	13.10	37.0
Peroneal, knee	0.2	8	15.45	34.0
Tibial, knee	0.3	30	14.90	

Nerve, location	Distance cm	Response
Sensory nerve conduction studies		
Median, wrist	13	None
Ulnar, wrist	11	None
Sural, calf	12	None
Superior peroneal, lateral	12	None
Medial plantar, sole	14	None

Nerve	Spontaneous					MUAP			Recruitment
	IA	FIB	PSW	FASC	HFD	AMP	DUR	PPP	
Electromyogram studies									
Tibialis anterior	3+	3+	3+	0	0	0	0	0	None
Gastrocnemius	3+	3+	3+	0	0	0	0	0	None
Vastus lateralis	3+	3+	3+	0	0	0	0	0	None
Biceps	1+	1+	1+	0	0	0	0	1+	Reduced
Deltoid	1+	0	0	0	0	0	0	0	Reduced
First dorsal interosseus	3+	3+	2+	0	0	0	0	0	None

MUAP = Motor unit action potential; IA = insertional activity; FIB = fibrillations; PSW = positive sharp waves; FASC = fasciculations; HFD = high-frequency discharges; AMP = amplitude; DUR = duration; PPP = polyphasic potentials.

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