Miller Fisher Variant of Guillain-Barré Syndrome Associated with Lactic Acidosis and Stavudine Therapy

Sanjiv S. Shah,† Tomas Rodriguez,‡ and Joseph P. McGowan†,‡

†Department of Medicine, Bronx-Lebanon Hospital Center, and ‡Albert Einstein College of Medicine, Bronx, New York

We describe the first case of Miller Fisher syndrome (ophthalmoplegia, ataxia, and areflexia) associated with lactic acidosis as an adverse effect of receipt of an antiretroviral regimen containing stavudine. We review this syndrome in the context of recent descriptions of neuromuscular toxicities attributed to nucleoside analogue reverse-transcriptase inhibitor–induced mitochondrial toxicity.

Nucleoside analogue reverse-transcriptase inhibitors (NRTIs) used for the treatment of HIV infection have been associated with symptomatic, sometimes fatal, lactic acidosis [1]. Symptomatic hyperlactatemia has been shown to occur more commonly when antiretroviral regimens contain the NRTIs stavudine and/or didanosine, and it is believed to result from the inhibition of mtDNA γ-polymerase, causing eventual disruption of the electron transport chain [2]. The clinical spectrum of mitochondrial toxicity includes hepatic steatosis and lipoatrophy, and there have been recent reports of neuromuscular compromise manifested by a Guillain-Barré–like syndrome of marked motor weakness associated with hyperlactatemia [3]. We present what is, to our knowledge, the first case of the Miller Fisher variant of Guillain-Barré syndrome associated with lactic acidosis in an HIV-infected patient receiving antiretroviral therapy.

Case report. A 42-year-old woman was admitted to Bronx-Lebanon Hospital Center (Bronx, NY) with a 3-week history of nausea, hyperemesis, and weakness. She denied having fever, cough, headache, abdominal pain, or diarrhea. She had a documented weight loss of 13 kg since her prior outpatient clinic visit 5 weeks earlier.

HIV infection had been diagnosed in 1990, and the patient had a history of CNS toxoplasmosis, cryptococcal meningitis, and lipodystrophy. She had a CD4 cell count of 449 cells/mm³ and an HIV load of <50 copies/mL 3 months before admission to the hospital. Her nadir CD4 cell count was 12 cells/mm³, which occurred ∼5 years before hospitalization. She had been prescribed stavudine, abacavir, lamivudine, and nevirapine for the previous 9 months. Before this regimen, she had received a regimen containing stavudine for 22 months. She had discontinued her antiretroviral therapy 3 days before hospital admission because of vomiting.

Initial physical examination revealed an acutely ill–appearing woman with a temperature of 37.1°C (98.7°F), a pulse of 120 beats/min, and a blood pressure of 120/70 mm Hg lying and 96/60 mm Hg sitting; her average blood pressure during her previous 6 outpatient visits was 118/78 mm Hg. The findings of the remainder of her examination, including a detailed neurologic evaluation, were unremarkable. At the time of admission to the hospital, the patient’s blood urea nitrogen level was 12 mg/dL, and her serum creatinine level was 0.8 mg/dL; 4 months previously, these values were 9 mg/dL and 0.6 mg/dL, respectively. She underwent intravenous fluid resuscitation, and her blood pressure returned to baseline within 24 h, with no orthostatic hypotension; her pulse was 85 beats/min. She had an arterial lactate level of 8.2 mmol/L when she was normotensive and a serum bicarbonate level of 21 mEq/L, with an anion gap of 24. Her arterial lactate level remained elevated (6.5 mmol/L) 3 days later. The findings of abdominal ultrasonography were significant for an enlarged homogenous liver.

The patient complained of diplopia on the fourth hospital day. Neurologic evaluation demonstrated bilateral sixth cranial nerve, partial right third nerve, and left central seventh nerve palsies, as well as symmetrical pupils. On hospital day 8, the patient remained alert and oriented but had complete bilateral ophthalmo-plegia with absent oculocephalic reflexes and no pto-sis. The findings of a retinal examination were unremarkable, and visual fields were full. Limb strength was preserved, lower extremity areflexia was elicited, and dysmetria on bilateral finger-to-nose testing was evident.

Brain MRI, with and without gadolinium contrast, revealed cerebral and cerebellar cortical atrophy, as well as scattered focal lesions and small enhancing spots in both internal capsules, the right external capsule, and both anterior subcapsular areas, without mass effect. CSF evaluation findings, including negative...
results of cryptococcal antigen tests, were unremarkable on 2 occasions. The results of stool examinations were negative for enteric pathogens, including *Campylobacter* species. Miller Fisher syndrome was diagnosed.

On hospital day 9, the patient became febrile and tachypneic, and a new left–lower lobe pulmonary infiltrate was revealed by chest radiography. The patient’s and her family’s wishes were to not allow mechanical ventilation, and the patient died on day 11 of hospitalization. The immediate cause of death was considered to be aspiration pneumonia.

Neuropathologic examination at autopsy revealed brain stem encephalitis, which was most marked in the medulla. The encephalitis was confined to the grey matter and spared the white matter, with focal chromatolysis of neuronal cell bodies and the presence of T cells and macrophages. The involved areas included the medial and inferior vestibular nuclei, the dorsal vagal nucleus bilaterally, and, on one side, the nucleus of the solitary tract and the spinal trigeminal nucleus. Neuronal death was observed in the nucleus superior to the medial longitudinal fasciculus and was associated with macrophage and lymphocytic infiltration bilaterally, which may have extended from the medullary lesion. Significant demyelination of the cranial nerves was not observed.

**Discussion.** Miller Fisher syndrome is a rare clinical variant of Guillain-Barré syndrome; it accounts for 5%–10% of cases and is manifested by the triad of signs of ophthalmoplegia, ataxia, and areflexia, all of which were present in our patient [4]. A Guillain-Barré syndrome–like syndrome has recently been described in patients with lactic acidosis related to the use of NRTIs—particularly stavudine—with or without concomitant use of didanosine [3]. Miller Fisher syndrome has been reported in only 2 HIV-infected patients previously [5, 6]. This is the first report of Miller Fisher syndrome in an HIV-infected patient that has been associated with stavudine-related lactic acidosis.

Controversy exists regarding the pathogenesis of Miller Fisher syndrome. It has been thought to be essentially a peripheral neuropathy similar to Guillain-Barré syndrome. However, before Miller Fisher described this syndrome, Bickerstaff and Cloake [7] reported a study of patients with altered sensorium and ophthalmoplegia attributable to brain stem encephalitis. Both syndromes may represent a complex of inflammatory nerve dysfunction, with or without brain stem encephalitis, and “overlap” syndromes have been described [8–10]. In cases of Miller Fisher syndrome, brain MRI with gadolinium administration has revealed enhancement of the third, sixth, and seventh nerves and, in some cases, evidence of brain stem encephalitis [11]. Patchy demyelination of peripheral nerves, which may only be apparent by electron microscopy, also has been described [12]. A strong association has been found between the presence of an antibody directed against the GQ1b ganglioside of peripheral nerves and the finding of ophthalmoplegia in Miller Fisher syndrome and, to a lesser extent, with Bickerstaff’s encephalitis [9, 13]. Anti-GQ1b antibody has been shown to cross-react with the lipopolysaccharide of *Campylobacter jejuni*, which may be a cause of precipitating infection [13]. Our patient did not complain of a diarrheal illness, and stool cultures did not yield *Campylobacter* species. Anti-GQ1b antibodies were not recovered in this case.

A recent report by the US Food and Drug Administration described 25 cases of NRTI-associated lactic acidosis complicated by neuromuscular toxicity consistent with Guillain-Barré syndrome [3]. Twenty-two of the affected patients had been using regimens that contained stavudine. Twelve of the patients were female, and 7 died (including 6 women). Risk factors associated with the development of NRTI-related lactic acidosis include length of exposure to the drug, age, female sex, obesity, and use of stavudine or didanosine [14]. Our patient had many of these risk factors, including female sex, stavudine use, obesity (the BMI before onset of acute illness was 31.7), and prior evidence of lipodystrophy. In several case-control studies, non-alcoholic steatohepatitis (NASH) has been found to be more common in obese individuals, particularly female patients [15]. Fatty liver disease has been described in NRTI-induced lactic acidosis [16]. Similar pathogenic mechanisms, including a possible role for the proinflammatory cytokine TNF-α as a mediator, may be involved in both NASH and lactic acidosis associated with antiretroviral therapy [17].

Inherited abnormalities in the mtDNA or nuclear DNA of genes involved in the respiratory cascade have been associated with neurodegenerative syndromes known as “mitochondrial encephalomyopathies” [18, 19]. These syndromes are generally progressively debilitating. Progressive external opthalmoplegia/supranuclear palsy associated with possible mitochondrial genetic defects and dysfunction has been described elsewhere [18, 19]. Peripheral nerve damage associated with mitochondrial dysfunction is most often axonal and may be demyelinating [19]. Although these syndromes develop as a result of inherited mitochondrial dysfunction, similar presentations might develop more acutely in acquired mitochondrial dysfunction or depletion, as has been described in association with the use of NRTIs [20]. In our patient, the association between lactic acidosis, extensive NRTI exposure, the finding of scattered focal lesions on the T2-weighted MRI without enhancement of the cranial nerves, and lack of evidence of demyelination of the examined dorsal root ganglia support the possible association with acquired mitochondrial dysfunction as the etiology of the neurologic observed abnormalities. Clinicians should be aware that Miller Fisher syndrome may be associated with NRTI-related lactic acidosis.
References


