Clinical/Scientific Notes

G. Pfeffer, MD
H.C.F. Côté, PhD
J.S. Montaner, MD
C.C. Li
M. Jitratkosol, BSc
M.M. Mezei, MD

OPHTHALMOPLEGIA AND PTOSIS: MITOCHONDRIAL TOXICITY IN PATIENTS RECEIVING HIV THERAPY

Mitochondrial toxicity (MT) can occur as a consequence of HIV infection and from treatment with highly active antiretroviral therapy (HAART).[1] Toxicity is additive and manifested by signs including lipodystrophy and lactic acidosis. HIV and HAART are also reported in association with skeletal myopathy and mitochondrial abnormalities on muscle biopsy.[2] This is in contrast to mitochondrial disorders associated with nuclear or mitochondrial DNA (mtDNA) mutations, in which patients may present with syndromic constellations of dysfunction in metabolically active tissues such as the brain and skeletal muscles. Chronic progressive external ophthalmoplegia (CPEO) is a mitochondrial syndrome with gradual onset of ptosis and ophthalmoparesis.[3] Thus far, phenotypes resembling genetic mitochondrial disorders have not been reported in association with acquired mitochondrial toxicity from disease or drugs. We report 3 cases of HIV-infected patients with long exposure to HAART who developed clinical syndromes resembling CPEO.

Case series. See the table for details. The patients were men, between the ages of 52 and 58 years, with long duration of HIV infection (16–24 years) and exposure to HAART (10–15 years). They developed MT manifested by lipodystrophy and also developed ptosis. Two patients had ophthalmoparesis and elevated serum lactate. One patient developed fatigue, migraines, and exertional myalgia, and another had dysphagia and diplopia on lateral gaze without clear ophthalmoparesis on examination. None of the patients had a family history of mitochondrial disease.

During a 3-month period off all antiretroviral agents, patient 1 had marked amelioration of fatigue, headaches, and ptosis. Significant improvement in ptosis and resolution of ophthalmoparesis was demonstrated on examination. This patient started a new antiretroviral regimen without didanosine (ddI) and remained stable with only mild ptosis.

Patient 2 had a period on a ddI-sparing HAART regimen and did not experience improvement. Quadriceps muscle biopsy demonstrated mild nonspecific changes including increased subsarcolemmal staining on oxidative stains and cytochrome *c* oxidase (COX)–negative fibers. Mitochondrial respiratory chain enzyme analysis was unremarkable. Six months later, a levator palpebrae biopsy collected during an oculoplastics procedure for ptosis demonstrated the majority of fibers were ragged-red on modified Gomori trichrome stain, and occasional COX-negative fibers. Genetic analysis revealed a 3.9-kb mtDNA deletion (547–4,443) affecting approximately 40%–60% of mtDNA in both biopsies.

Patient 3 did not return for reassessment; therefore, further investigations or clinical data are not available.

Discussion. CPEO-like syndromes have not been previously reported in association with mitochondrial toxicity in HIV/HAART. Patient 1 did not have a muscle biopsy although his symptoms clearly improved with cessation, followed by alteration of therapy, suggesting that HAART-related MT may have contributed to his syndrome. Patient 2 did not improve upon HAART cessation but had a muscle biopsy diagnostic for mitochondrial disease showing evidence of a 3.9-kb mtDNA deletion in both quadriceps and levator biopsies, which was previously reported with CPEO,[4] suggestive of underlying genetic mitochondrial disease. We therefore suggest that these patients may have had subclinical mitochondrial disease that was unmasked by the additive MT of HIV infection and HAART. Nucleoside analogues such as ddI and stavudine are likely to be implicated, given their well-described time-dependent and dose-dependent MT[5] and partial reversibility.[6] All patients in this series received these agents and in one patient symptoms improved off therapy and did not recur on a regimen that excluded ddI and stavudine.

While other mitochondrial syndromes such as Kearns-Sayre syndrome are characterized by early age at onset,[7] CPEO usually has a later age at onset and is typically benign and slowly progressive.[3] Late-onset CPEO likely occurs when mtDNA abnormalities with low expressivity reach a critical level of heteroplasmy producing phenotypic expression, and this may be accelerated by MT from aging or environmental exposures. HIV infection and HAART likely present more intense MT that may be capable of phenotypically exposing potentially pathogenic

Table Patient characteristics

	Patient 1	Patient 2	Patient 3
Age, y/sex	58/M	54/M	52/M
Duration HIV positive, y	24	16	20
Duration of HAART, y	11	10	15
Current HAART regimen (consecutive months)	ddI (113), indinavir (113), ritonavir (56)	ddI (44), 3TC (44), lopinavir/ritonavir (44), atazanavir (27), nevirapine (44)	ABA (26 as of 02/08), 3TC (140), darunavir (3), ritonavir (3), etravirine (3), raltegravir (3)
Past HIV medications (cumulative exposure in months)	AZT (22), 3TC (8), d4T (88)	AZT (5), 3TC (105), ddI (79), d4T (60), ABA (2), TDF (27), saquinavir (2), indinavir (33), nevirapine (75), enfuvirtide (12)	AZT (18), 3TC (177), ddI (106), d4T (72), ABA (101), nevirapine (101), delavirdine (18), efavirenz (39), indinavir (26), saquinavir (15), nelfinavir (9), lopinavir (103), ritonavir (11), tenofovir (81)
Symptoms	Gradually progressive bilateral ptosis over 2 y; intermittent diplopia; fatigue; exertional myalgia; migraine headaches	Gradually progressive bilateral ptosis; diplopia at extremes of lateral gaze; dysphagia	Gradually progressive bilateral ptosis over 10 years; vertical diplopia in last year
Signs	Ptosis; multidirectional ophthalmoparesis; lipodystrophy	Ptosis; lipodystrophy	Ptosis; multidirectional ophthalmoparesis; lipodystrophy
Lactate (ref 0.5–2.1 mEq/L)	3.1 (had been mildly elevated [2.3–3.1] for several months)	2.4 (had been at the upper limit of normal [2.0–2.1] for several months)	2.1 (No prior lactate data)
Muscle biopsy	None	Quadriceps biopsy: inconclusive, mitochondrial enzymes unremarkable; levator palpebrae biopsy: abundant RRF, COX-negative fibers	None
Genetic studies	None	Large mtDNA deletion (548–4,444); no other mutations from whole mtDNA genome sequencing	None
Improvement off therapy	Patient had 3 months off all ARVs: resolution of ophthalmoparesis, fatigue, and headaches; mild ptosis as residua	ddI was changed to enfuvirtide with no effect	N/A

HAART = highly active antiretroviral therapy; ddI = didanosine; 3TC = lamivudine; AZT = zidovudine; ABA = abacavir; d4T = stavudine; RRF = red ragged fibers; COX = cytochrome *c* oxidase; ARV = antiretrovirals; N/A = not applicable.

mtDNA abnormalities. HIV-negative individuals with late-onset CPEO may have equally important sources of MT that have not yet been identified.

CPEO-like syndromes may occasionally occur in patients with long duration of HIV infection and exposure to HAART. These syndromes may be from accumulated mitochondrial toxicity or toxicity superimposed upon a preexisting subclinical genetic mitochondrial disorder. Improvement may occur by withdrawing offending agents or by use of alternative drug regimens. Patients with HIV with long disease duration and exposure to HAART may provide a model for future study of mitochondrial toxicity and mtDNA heteroplasmy in CPEO. Attempts should be made to identify other sources of mitochondrial toxicity in HIV-negative patients with late-onset CPEO and suspicion should be heightened for a CPEO-like syndrome in long-term HAART-treated HIV survivors.

From the Division of Neurology (G.P., M.M.M.) and Department of Pathology & Laboratory Medicine (H.C.F.C., C.C.L., M.J.), University of British Columbia; and British Columbia Centre for Excellence in HIV/AIDS (J.S.M.), Vancouver, Canada.

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Address correspondence and reprint requests to Dr. Michelle M. Mezei, Adult Metabolic Diseases Clinic, Vancouver General Hospital, 4th Floor, 2775 Laurel St., Vancouver, BC, V5Z 1M9, Canada; mezei@interchange.ubc.ca

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James T.H. Teo, MA, MRCP, MPhil
Orlando B. Swayne, MA, MRCP, MPhil
Eli Silber, MD, FCP

CEREBELLAR ATAXIA AFTER MALARIA

In May 2008, a 54-year-old man was admitted to a London hospital, having been transferred out of Ghana, for generalized tremors, loss of coordination, and impaired balance for the previous 3 days.

Ten days previously, he had presented to a clinic in Ghana with fever, and falciparum malaria parasites were detected on blood film. He was treated with a 3-day course of Coartem® (artemether-lumefantrine combination). On day 3, his blood film was negative but as he remained symptomatic he was given an additional course of Coartem and Fansidar® (pyrimethamine-sulfadoxine combination). The following day he was apyrexial and well enough to return to work. On day 6, he had slight difficulty using his keyboard due to hand tremor and coordination difficulties. By day 9, he had developed arm and leg tremors and was unable to walk. Repeat blood films at this point were negative. He was started on diazepam and thiamine and transferred to London. The patient was a white man born in the United States who had lived in Ghana for 2.5 years and worked as a mining engineer at a gold mine. He drank about 50 mL scotch whiskey a day.

In London, he was unable to stand due to severe truncal ataxia. He did not have a rest tremor but had severe postural limb tremor and a suggestion of myoclonus in the right outstretched arm. Coordination was significantly impaired with a marked symmetric intention tremor and dysmetria. He had no nystagmus or ophthalmoplegia but there was some saccadic intrusion into smooth pursuit. Cranial nerve examination was otherwise unremarkable. Power was preserved throughout. His reflexes were depressed and his plantars were flexor. Sensory examination in the upper and lower limbs (including joint position sense) was normal (see a video of the examination on the *Neurology*® Web site at www.neurology.org).

Routine blood tests were unremarkable, with normal thyroid function, vitamin B_{12}, and vitamin E levels. Urine mercury was normal. Serology showed strong reactivity against *Plasmodium falciparum* antigen, but the blood film was negative. Antineuronal antibodies (anti-Purkinje-cell antibodies, Anti-Hu, Anti-Yo, and Anti-Ri) were negative. He had a weakly positive antinuclear antibody, but was negative for anti-dsDNA. Lumbar puncture was performed within 10 days of onset and CSF parameters were unremarkable (<1 leukocyte/cm^3, 4 erythrocytes/cm^3, protein 0.40 g/L, no organisms and no oligoclonal bands). MRI scan with gadolinium enhancement was unremarkable (figure e-1A). A diagnosis of delayed cerebellar ataxia associated with malaria was made. Within 5 weeks of conservative management, the patient was able to walk unaided.

A tremor analysis was performed to document the characteristics of the tremors as no formal study is described in the literature using surface electromyography to derive information about tremor frequency. There was an 11.5-Hz tremor in the biceps with the arms held vertically, decreasing to 9.5 Hz when held horizontally (figure e-1B). This falls within the range of enhanced physiologic tremor and the frequency change with posture suggests that it relates to peripheral mechanical factors. In addition, there was a 5-Hz tremor which did not change frequency in different arm postures. This combination of tremors was also detectable in the hand muscles during pincer grip (figure e-1C). While standing, there was marked 3-Hz tremor in both gastrocnemii, indicating a slow sway (figure e-1D), which was coherent between sides. This is consistent with a cerebellar axial postural tremor.[1,2]

Discussion. Delayed cerebellar ataxia after malaria is recognized in patients without cerebral malaria, suggesting a distinct entity from cerebral malaria.[5,6] The frequency of this is unknown and MRI appearances or movement characteristics have not been reported in the literature. There has been some debate as to whether it is due to artemether-based anti-malarials[4] or to the infection itself.[3] However, in the largest case series of 74 patients,[6] none was treated with artemether. Other postinfectious cerebellar syndromes are shown in the table.

Supplemental data at www.neurology.org

Table Postinfectious cerebellar syndromes

Infections/organisms	Course
Varicella zoster virus	~1–2 weeks after infection onset. Usually resolves completely within 1 month. Rarely can also lead to meningoencephalitis and cerebellitis with lasting neurologic sequelae.
Epstein-Barr virus	~1–2 weeks after infection onset. Usually resolves completely within 1 month.
Mumps (and vaccine)	~1–2 weeks after infection onset. Usually resolves completely within 1 month.
Measles (and vaccine)	~1–2 weeks after infection onset. Usually resolves completely within 1 month.
Mycoplasma pneumoniae	~1–2 weeks after infection onset. Usually resolves completely within 1 month.
Typhoid fever	~1–2 weeks after infection onset. Usually resolves completely within 1 month.
Malaria	~1–2 weeks after infection onset. Usually resolves completely within 1 month.

Although anti-Purkinje cell antibodies have been shown to be absent in patients with this delayed cerebellar ataxia,[7] this does not exclude an unidentified antibody or autoimmune process. If the cerebellar ataxia is linked to malaria itself, the transience and delayed onset suggests that this syndrome may result from functional inactivation of the cerebellum or cerebellar outflow tracts through an autoimmune-mediated process.

The questions behind the etiology of this delayed cerebellar syndrome should not mask the importance of recognizing this condition in patients with malaria. The prognosis is good, with recovery occurring in the order of weeks with conservative management.

From the Sobell Department of Motor Neuroscience (J.T.H.T., O.B.S.), Institute of Neurology; and Department of Neurology (O.B.S., E.S.), King's College Hospital, London, UK.

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Address correspondence and reprint requests to Dr. Eli Silber, Department of Neurology, Kings College Hospital, Denmark Hill, London SE5 9RS, UK; esilber@doctors.org.uk

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