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External ophthalmoplegia in human immunodeficiency virus-infected patients receiving antiretroviral therapy

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Abstract

BACKGROUND—On rare occasions, patients infected with human immunodeficiency virus (HIV) can develop a disorder similar to chronic progressive external ophthalmoplegia (CPEO) while undergoing long-term treatment with antiretroviral therapy. Orbital imaging may help explain the pathogenesis of this abnormality.

METHODS—In this case series, 5 adult patients who presented with a CPEO-like disorder after more than 10 years of antiretroviral therapy and who underwent T1-weighted high-resolution magnetic resonance imaging (MRI) of the orbits and brain were retrospectively identified. Patients also were screened for acetylcholine receptor antibody levels.

RESULTS—All patients had bilateral external ophthalmoplegia and blepharoptosis. Acetylcholine receptor antibody titers were not increased. Brain MRI was unremarkable. Orbital MRI showed patchy bright signal inside the extraocular muscles that had conserved volume.

CONCLUSIONS—Patients with HIV under long-term antiretroviral therapy may develop functional abnormalities of extraocular muscles that are structurally normal in size, that is, changes are similar to those observed in the orbital MRIs of patients with CPEO. This constellation of signs and symptoms suggests a possible role of HIV disease or antiretroviral therapy in the CPEO-like syndrome observed in some HIV-infected individuals.

Among the many ophthalmologic manifestations of human immunodeficiency virus (HIV) infection and the acquired immunodeficiency syndrome (AIDS) are various neuro-ophthalmic symptoms.¹ With the introduction of highly active antiretroviral therapy (HAART) 15 years ago,^{2–4} there has been a substantial decrease in mortality of patients with HIV disease⁵ and a subsequent increase in recognition of previously unknown comorbidities, including iatrogenic syndromes.

Recently, various forms of skeletal muscle dysfunction have been documented in patients with HIV undergoing antiretroviral therapy.⁶ These myopathic conditions have been attributed both to the virus itself (including HIV polymyositis, inclusion-body myositis, vasculitis, and myasthenic syndromes) and to HAART (including myopathies secondary to nucleoside-analogue reverse-transcriptase inhibitors and protease inhibitors).⁶ In addition, there are rare reports of HIV-infected patients presenting with ophthalmoplegia and ptosis.^{7,8} This study describes a series of HIV-infected patients who presented with bilateral external ophthalmoplegia and blepharoptosis. The purpose of the present investigation was

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to characterize the underlying etiology with magnetic resonance imaging (MRI) and to compare the changes seen on MRI to those previously described in chronic progressive external ophthalmoplegia (CPEO).⁹

Methods

This study was approved by the University of California, Los Angeles, Institutional Review Board and complied with all relevant privacy laws and the Health Insurance Portability and Accountability Act. The medical records of consecutive patients with HIV who presented to the Jules Stein Eye Institute between 2006 and 2010 were retrospectively reviewed. All patients who presented with bilateral progressive ptosis and external ophthalmoplegia were included.

All patients had undergone complete ophthalmologic examinations, including ocular motility testing. Ocular alignment was assessed with the use of cover-uncover and alternate prism cover testing at distance (20 feet) in the cardinal gaze positions. Motor alignment at near was assessed at 14 inches. In cases of unilateral or bilateral visual acuity <20/400, Krimsky light reflex testing was performed to evaluate ocular alignment. All motor evaluations were performed with spectacle correction. Ocular ductions were measured using a standard 4-point scale.¹⁰ All patients underwent similar evaluation, which included acetylcholine receptor antibody levels (binding, blocking, and modulating) and electrocardiograms. High-resolution orbital MRI was performed using a 1.5-T Sigma scanner (General Electric, Milwaukee, WI) using surface coils, as described elsewhere.^{9,11}

Results

Five patients identified by record review were included in this study (Table 1). The patients ranged in age from 44 to 62 years, and their duration of HIV infection ranging from 13 to 23 years. All of the patients presented with a chief symptom of bilateral blepharoptosis and symptoms related to diplopia or difficulty with pursuit, eccentric gaze, or strabismus. All patients stated that they had excellent compliance with their medication regimen. Sensorimotor examination of all patients revealed limited versions, ranging from mild limitation to horizontal versions in patient 5 to moderate-to-severe limitation in multiple directions of gaze in the remaining patients (Table 2). Detailed evaluation of eye movements of all 5 patients revealed slow saccades horizontally and vertically. Smooth pursuit was normal in all patients. Although 3 of the 5 patients complained of diplopia (patients 2, 4, and 5), 4 presented with tropias in central gaze (patients 2-5). A composite of the ocular ductions of a representative patient is depicted in Figure 1.

All patients had normal acetylcholine receptor antibody levels (binding, blocking, and modulating) and normal findings on electrocardiogram. None of the patients demonstrated any features of myasthenia gravis, including eyelid twitch, eyelid curtaining, eyelid fatigue, diurnal variation, or improvement with rest. In addition, all patients were seen at multiple times throughout the day, and there was no change in the amount of blepharoptosis or strabismus that was measured. No patients had any improvement of their blepharoptosis with rest or worsening with fatigue.

Two patients had electromyography, which did not reveal any abnormalities consistent with myasthenia gravis. The remaining 3 patients did not undergo electromyography because there were no clinical features of fatigue on clinical examination and no clinical history of diurnal variation.

None of the patients had a pigmentary retinopathy that suggested Kearns-Sayre or other mitochondrial pathologic processes. None of the patients endorsed shortness of breath or

dysphagia on review of systems. In addition, there was no family history of ocular motility diseases for any patient. In all 5 patients, T1-weighted high-resolution MRI images of the brain and orbits revealed a bright patchy signal in all four rectus muscles bilaterally, with conserved extraocular muscle volume (Figures 2 and 3).

Discussion

In the aforementioned series, 5 patients presented with CPEO-like signs, including bilateral progressive blepharoptosis and external ophthalmoplegia and a complete lack of fatigueability or other findings consistent with myasthenia gravis. The orbital MRI in these cases revealed a bright signal on high-resolution T1-weighted MRI with preserved extraocular muscle volume, in the absence of orbital inflammation, a finding previously seen only in patients with CPEO.⁹ Although neuro-ophthalmic disorders are a well-recognized category of morbidity in HIV-infected individuals,¹ in a large cohort of HIV-infected subjects, the most common neuro-ophthalmic diagnoses included optic neuropathy, cranial nerve palsies, and visual field defects.¹² Although slowed saccades were commonly described as well, CPEO was not listed as a neuro-ophthalmic finding in this population.¹²

There have recently been a few case reports of HIV-infected patients presenting with CPEO-like signs after long-term use of HAART therapy.^{7,8} In 2008 Dinges and colleagues⁸ described 5 HIV-infected patients who presented with severe blepharoptosis in association with variable ophthalmoplegia and lipoatrophy. Although no definitive etiology was noted, the authors felt that the underlying etiology may have been related to mitochondrial toxicity from thymidine analogue-containing nucleoside reverse-transcriptase inhibitors. In 2009 Pfeffer and colleagues⁷ described 3 similar cases of HIV-infected patients on long-term HAART who presented with ophthalmoplegia and blepharoptosis. One of their patients had resolution of symptoms during a short trial off HAART medications. These authors attributed their patients' presentations to mitochondrial toxicity from HAART. Neither of the aforementioned case series documented their patients' phenotypes with orbital imaging, as in the present study.

In addition to the possible role of antiretroviral therapy posited by previous authors in the etiology of our patients' presentations, HIV disease itself may also be a cause of this phenotype. Nonocular skeletal myopathy in patients with HIV disease has been previously described and has been attributed to a variety of factors, including polymyositis, inclusion-body myositis, nemaline myopathy, diffuse infiltrative lymphocytosis, HIV-wasting syndrome, and vasculitis.^{6,13,14} Drug-induced myositis has been described in HIV-infected patients on HAART in various types of skeletal muscle.^{6,15} The multidrug combination of HAART includes nucleoside reverse-transcriptase inhibitors and protease inhibitors, both of which are known causes of skeletal myopathy.¹⁴ Protease inhibitors cause skeletal myopathy by inhibiting native proteases that degrade transcription factors crucially involved in lipid homeostasis, leading to insulin resistance and fatty acid accumulation in skeletal muscle. Nucleoside reverse-transcriptase inhibitors cause skeletal myopathy by interference with mitochondrial DNA polymerase gamma, the key enzyme required for mitochondrial DNA replication.⁶ Long-term inhibition of this enzyme may cause skeletal mitochondrial myopathy with ragged-red fibers and cytochrome-C oxidase-deficient muscle fibers seen on muscle biopsy, as well as associated hyperlactatemia and mitochondrial DNA depletion.¹⁴ Interestingly, mutations in the same mitochondrial DNA polymerase gamma have been demonstrated in patients with CPEO.¹⁶ The striking clinical similarities between our patients and those with CPEO suggest that reverse-transcriptase-induced mitochondrial DNA polymerase gamma inhibition may underlie their external ophthalmoplegia similarly to CPEO patients whose phenotype is caused by malfunctioning of the same mitochondrial DNA polymerase. This hypothesis is made more likely in light of the absence of retinal and

cardiac findings, which are often seen in association with CPEO syndromes, and the patients' failure to meet criteria for the diagnosis of ocular myasthenia gravis (negative diagnostic testing, lack of fatigueability or recovery of affected muscles after a period of rest).¹⁷

Typically, CPEO presents with insidious onset of progressive symmetric ptosis and decreased versions. Genetic testing may reveal sporadic mitochondrial DNA deletions.⁹ Recently, high-resolution orbital MRI in a series of patients with CPEO demonstrated that all had an abnormal "spongiform" bright signal on T1-weighted imaging,⁹ with conserved muscle volume similar to the patchy bright signal seen on our images. According to Ortube and colleagues,⁹ this abnormal signal has not been seen in any other ophthalmologic subjects whose extraocular muscle size was preserved and who were free of orbital inflammation, but it has been seen in thyroid eye disease (in association with extraocular muscle enlargement) and congenital fibrosis of the extraocular muscles (in association with small muscles). The abnormal patchy signal in association with normal extraocular muscle size is an identical finding in the current patients treated with antiretroviral therapy.

The present study has several limitations. First, this is a retrospective review and is therefore subject to selection and referral bias. In addition, the evaluation was not standardized for all patients, and none of the patients underwent muscle biopsy. During the time period when the patients presented edrophonium was not readily available to us and genetic tests for CPEO were also not readily available to our patients. However, we feel that it would be unlikely that a relatively large number of HIV-infected patients on similar antiretroviral therapy regimens for more than a decade would all present with an unrelated syndrome.

As mortality from HIV infection continues to decrease, medication-induced morbidities may become more prevalent. In our cases of external ophthalmoplegia after long-term treatment of HIV with antiretroviral therapy, the etiology may have been due to either long-term HIV infection or its treatment with medications. HIV-infected patients should be monitored for this possible disease sequelae or medication complication. If HIV associated CPEO-like disease is suspected, orbital imaging may aid the clinical evaluation. Future studies will be necessary to examine the role that age, disease duration, treatment duration, and mitochondrial and genetic factors play in determining an individual patient's susceptibility.

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FIG 1.
A, Patient 1, showing bilateral blepharoptosis and limited versions in all directions. B,
Patient 2, similarly showing bilateral blepharoptosis and limited versions in all directions.

FIG 2.

Patient 1. Coronal T1-weighted MRI showing abnormal bright signal in multiple extraocular muscles in the retro-orbital (A), middle (B) and deep (C) orbit. *IR*, inferior rectus; *LR*, lateral rectus; *MR*, medial rectus; *SR*, superior rectus; *SO*, superior oblique.

FIG 3.

Patient 3. A, Axial T1-weighted MRI showing abnormal bright signal in the medial and lateral rectus muscles in the deep orbit. B, Coronal T1-weighted MRI of the same patient revealing abnormal bright signal deep in both inferior, medial, and superior rectus muscles. C, Coronal T1-weighted MRI showing abnormal bright signal in the anterior portions of all four rectus muscles bilaterally. *IR*, inferior rectus; *LR*, lateral rectus; *MR*, medial rectus; *SR*, superior rectus; *SO*, superior oblique.

Table 1
Demographic features of HIV-infected individuals presenting with CPEO-like symptoms

Case	Age, years	Sex	CD4 count + T-lymphocyte, cells/mm ³	HIV infection, years	Antiretroviral medications	Other medications
1	62	M	280	20	Emtricitabine (nRTI), didanosine (nRTI), nevirapine (non-nRTI), ritonavir (PI)	Atorvastatin, acyclovir, gemfibrozil, atenolol, enalapril, trimethoprim-sulfate
2	45	M	800	23	didanosine (nRTI), lamivudine (nRTI), nevirapine (non-nRTI)	carafate, coenzyme Q10, tamsulosin, acyclovir, ketoconazole, pravachol, fenofibrate, bupropion, levofloxacin, baclofen
3	44	M	Unknown	19	etravirine (non-nRTI), darunavir (PI), ritonavir (PI), raltegravir (HIV integrase strand transfer inhibitor)	acyclovir, bystolic, crestor
4	54	M	1043	13	emtricitabine/tenofovir (nRTI), efavirenz (non-nRTI)	gabapentin, tramadol, duloxetine, clonidine, valgangciclovir, alfuzosin, escitalopram
5	59	F	434	20	Abacavir sulfate (nRTI), lamivudine (nRTI), indinavir (PI)	lisinopril

CPEO, chronic progressive external ophthalmoplegia; F, female; HIV, human immunodeficiency virus; M, male; nRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

Table 2

Clinical features of HIV-infected individuals presenting with CPEO-like symptoms

Case	MRD ₁ , mm (OD; OS)	Ocular ductions	Primary position ocular alignment, PD		
			Distance	Near	Other features
1	0.5; 0	Moderate-to-severe limitation, all directions	Orthotropic		
2	0.5; 0.5	Marked limitation to supraduction and infraduction bilaterally	12, ET	2, ET	No EMG findings suggesting MG
3	1.0; 0.5	Moderate-to-severe limitation of versions, all directions	4, ET	6, ET	History of blepharoplasty
4	2.0; 2.0	Moderate-to-severe limitation of versions, all directions	20, XT	20, XT	No EMG findings suggesting MG
5	3.0; 2.0	Mild limitation of horizontal versions bilaterally	16, HT; 12, ET	8, HT	

CPEO, chronic progressive external ophthalmoplegia; EMG, electromyogram; ET, esotropia; HT, hypertropia; MG, myasthenia gravis; MRD₁, margin reflex distance 1 (distance from upper eyelid to light reflex centered on the pupil); OD, right eye; OS, left eye; PD, prism diopters; XT, exotropia.