Blepharoptosis and External Ophthalmoplegia Associated with Long-Term Antiretroviral Therapy

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Background. Long-term antiretroviral therapy (ART) is associated with lipodystrophy, peripheral neuropathy, lactic acidosis, and myopathy. Blepharoptosis, without prior ART association, is usually caused by age-associated involutional ptosis, but it is also seen in mitochondrial myopathies with external ophthalmoplegia, cardiac conduction disturbances, and neurological impairments.

Methods. Patients presented over a 2-year period. Four patients underwent surgical blepharoptosis repair.

Results. Five human immunodeficiency virus type 1–infected patients (median age, 50 years; range, 46–53 years) who were receiving ART presented with severe blepharoptosis; 2 of these 5 also presented with external ophthalmoplegia. Findings included decreased palpebral fissure height (median, 6.5 mm; normal height, 9 mm), mildly impaired levator function (median, 10 mm; normal, >13 mm), and markedly decreased marginal reflex distance (median, 0.5 mm; normal, 4 mm). A greater advancement of the levator aponeurosis was required during surgical repair, a finding consistent more with myogenic than with involutional blepharoptosis. All patients had severe lipodystrophy, which preceded blepharoptosis by a median interval of 4.7 years (range, 2.8–5.7 years). Four patients also presented with peripheral neuropathy and metabolic abnormalities before the onset of blepharoptosis, and 3 had cardiac conduction disturbances. Patients received ART for a median of 7.8 years (range, 4.9–11.2 years), thymidine analogue–containing ART for a median of 7.1 years (range, 1.2–7.9 years), and protease inhibitor–containing ART for a median of 7.1 years (range, 4.9–8.9 years).

Conclusions. We report the novel findings of blepharoptosis and external ophthalmoplegia in patients who are receiving ART. Ptosis was preceded by lipodystrophy with long-term use of both thymidine-analogue– and protease inhibitor–containing ART. The findings are most consistent with myogenic ptosis in a generalized mitochondrial myopathy syndrome. Clinicians should also be watchful for other potential myopathic ptosis-associated complications, including proximal weakness, dysphagia, deafness, and cardiac conduction disturbances.
dideoxy nucleoside analogues didanosine and zalcitabine [7], as well as to the entire NRTI class and related agents, such as ribavirin and hydroxyurea.

Blepharoptosis and external ophthalmoplegia have not been previously associated with long-term ART in HIV-infected patients. Blepharoptosis—or, more simply, ptosis—is a drooping of the upper eyelid that becomes disabling when vision is obstructed. Blepharoptosis is defined by its etiology, associated levator muscle dysfunction, unilateral or bilateral involvement, associated ophthalmoplegia, and other associated neurological impairments. Blepharoptosis is etiologically classified as myogenic, neurogenic, aponeurotic-involutional, and traumatic/mechanical [18–20]. The most common cause of acquired blepharoptosis is aging-associated aponeurotic-involutional ptosis. Other common causes of ptosis include myasthenia gravis (for neurogenic ptosis) and mitochondrial abnormalities (for myogenic ptosis). Myogenic ptosis is usually congenital, but it can also be acquired (e.g., chronic progressive external ophthalmoplegia). Mitochondrial myopathy syndromes caused by mitochondrial gene depletion are well-established causes of chronic progressive external ophthalmoplegia and ptosis, which have also been associated with cardiac conduction disturbances and other neurological impairments, including neuropathies, deafness, and proximal muscle weakness [21–23]. Blepharoptosis is quantified by the palpebral fissure height (i.e., the distance from the upper to lower eyelid at the papillary axis), levator function (i.e., excursion of the upper eyelid margin from downgaze to upgaze, with the brow stabilized by gentle pressure), and the marginal reflex distance (i.e., the distance from the papillary light reflex to the upper eyelid margin).

Leber hereditary optic neuropathy presents in persons with predisposing mtDNA mutations as acute central vision loss with sensory neuropathies, ataxia, and altered reflexes [24–26]. Only 10%–30% of persons with these mtDNA mutations develop Leber hereditary optic neuropathy, because an additional precipitating factor (e.g., NRTI use, HIV infection, nutritional factors, metabolic disease, or toxic exposures) is required. Lactic acidosis syndrome and the related HIV-associated neuromuscular weakness syndrome (HANWS) usually present as hyperlactatemia with nausea, vomiting, and abdominal pain [27]. HANWS also typically includes ascending progressive weakness and other neurological impairments that occur with cessation of ART. Chronic progressive external ophthalmoplegia, other myopathy syndromes, and even HANWS have also been associated with external ophthalmoplegia, as opposed to intranuclear ophthalmoplegia seen in patients with multiple sclerosis or isolated cranial neuropathies, such as those of the third, fourth, or sixth cranial nerves.

METHODS

Patients. All patients presented to a single academic practice over a 2-year period. This academic practice treats ∼100 HIV-infected patients who have received ART for a mean duration

Figure 1. Chronological progression of blepharoptosis shown for each patient (Pt) from the times of known HIV infection, first antiretroviral therapy regimen, onset of clinical lipodystrophy, first blepharoptosis repair, and follow-up care. The times of presentation of peripheral neuropathy (*), cardiac conduction abnormality (○), and normal serum lactate level (□) are indicated. Ophthalmologic examination results for the right (OD) and left (OS) sides are presented as palpebral fissure height (PF), levator function (LF), and marginal reflex distance (MRD). y, Year.
Table 1. Characteristics of HIV-infected patients with blepharoptosis and external ophthalmoplegia associated with long-term antiretroviral therapy.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Median (range)</th>
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<tbody>
<tr>
<td>Age, years</td>
<td>50 (46–53)</td>
</tr>
<tr>
<td>No. of years since diagnosis of HIV infection</td>
<td>11.2 (7.8–18.2)</td>
</tr>
<tr>
<td>Duration of antiretroviral therapy, years</td>
<td>7.8 (4.9–11.2)</td>
</tr>
<tr>
<td>Duration of use of components of antiretroviral therapy, years</td>
<td></td>
</tr>
<tr>
<td>Protease inhibitors</td>
<td>7.1 (4.9–8.9)</td>
</tr>
<tr>
<td>Thymidine analogues</td>
<td>7.1 (1.2–7.9)</td>
</tr>
<tr>
<td>Didanosine</td>
<td>7.1 (4.9–8.2)</td>
</tr>
<tr>
<td>Time since onset of lipodystrophy, years</td>
<td>4.7 (2.8–5.7)</td>
</tr>
<tr>
<td>Time since ptosis repair, years</td>
<td>0.4 (0.1–1.5)</td>
</tr>
<tr>
<td>Duration of follow-up for ptosis, years</td>
<td>1.8 (0.7–2.6)</td>
</tr>
<tr>
<td>CD4+ T lymphocyte count, cells/µL</td>
<td></td>
</tr>
<tr>
<td>Nadir</td>
<td>202 (19–440)</td>
</tr>
<tr>
<td>Recent</td>
<td>620 (135–1042)</td>
</tr>
</tbody>
</table>

of 5.4 years (20% have received ART for ≥9 years: D.M.P., unpublished data). The institutional review board approved the chart and laboratory reviews, which provided details about the patients’ medical histories and other associated medical conditions. Ophthalmologic evaluations were conducted after referral from the primary HIV care provider. The presence of lipodystrophy was determined by the primary HIV care provider on the basis of documented body morphologic changes and metabolic abnormalities. All patients provided consent and were evaluated as part of an observational lipodystrophy study protocol with the institutional review board’s approval. The laboratory reviews included all routine chemistry evaluations, including assessment of the anion gap. Patients were receiving suppressive ART (defined as a regimen that led to a viral load <50 copies/mL) at the most recent follow-up visit.

**Blepharoptosis repair.** All surgeries were performed under monitored local anesthesia using standard surgical techniques [18, 28]. During repair, the levator muscle/aponeurosis was advanced incrementally until the desired upper eyelid level and contour was achieved. Specimens were obtained from the orbicularis oculi muscle, the levator muscle/aponeurosis, and preaponeurotic fat.

**Microscopic evaluation.** The fresh tissue specimens were collected from the surgical site and fixed in 3.0% glutaraldehyde in sodium phosphate buffer, 0.1 M (pH, 7.4). The specimens were then cut into 1–2-mm³ pieces and rinsed in the phosphate buffer. They were postfixed in 1% osmium tetroxide in the phosphate buffer, dehydrated in an ethanol gradient, and then embedded in Spurr resin [29]. Ultra-thin (80-nm) sections were cut on a Leica Ultracut S ultramicrotome (Leica Microsystems), picked up on copper grids (3 mm), and stained with uranyl acetate and lead citrate. They were observed with a JEOL1200EX II transmission electron microscope (JEOL) and documented on Kodak S0-163 electron image film (Eastman Kodak). For light microscopic examination of the levator and orbicularis muscle specimens, the osmium postfixed, Spurr-embedded samples were cut (into 1-µm sections) and were stained with toluidine blue on glass slides.

**RESULTS**

**Case Reports**

**Patient 1.** Patient 1, a 53-year-old, Asian, homosexual man presented with blepharoptosis and external ophthalmoplegia after an 11.6-year history of known HIV infection. He began receiving triple-class ART 5.3 years into HIV infection, when he presented with *Pneumocystis* pneumonia and Kaposi sarcoma, with a nadir CD4+ T lymphocyte count of 19 cells/µL. After 15 months, stavudine was replaced by lamivudine because of bilateral lower extremity sensory peripheral neuropathy, which subsequently resolved. After having received ART for 19 months, the patient presented with lipodystrophy, with facial and peripheral lipoatrophy and intra-abdominal obesity. He presented with ptosis after 6.3 years of ART. Examination revealed that the patient had bilateral upper eyelid ptosis and decreased levator function. His ocular motility examination demonstrated limitation, with variable strabismus. Evaluations for myasthenia gravis and thyroid eye disease with acetylcholine receptor antibody, chest CT, electromyography, and thyroid screening yielded normal findings. After 6 months of evaluation, the patient underwent bilateral ptosis repair, which was later repeated because of residual ptosis. No further progression was noted during subsequent follow-up. Most recently, he was found to have new asymptomatic sinus bradycardia (54 beats/min) with otherwise normal electrocardiography findings, and his recent CD4+ T lymphocyte count was 451 cells/µL.

**Patient 2.** Patient 2 was a 51-year-old, white, homosexual man who presented with ptosis ≥9 years after HIV infection.
Figure 2. Antiretroviral therapy and related medications presented for each patient (Pt) from preceding ptosis diagnosis to last follow-up visit. Red, nucleos(t)ide reverse-transcriptase inhibitors; green, nonnucleoside reverse-transcriptase inhibitors; blue, protease inhibitors; purple, other medications. Agents preceded by an “r-” are ritonavir boosted. ADF, adefovir; ATZ, atazanavir; d4T, stavudine; ddl, didanosine; EFV, efavirenz; rAPV, amprenavir or fosamprenavir; HU, hydroxyurea; IDV, indinavir; LPV, lopinavir; NFV, nelfinavir; NVP, nevirapine; rIF, ribavirin and pegylated IFN; 3TC, lamivudine; TDF, tenofovir. *Two weeks of initial zidovudine treatment are not shown.

had been diagnosed. He has never had an opportunistic infection, and his pre-ART nadir CD4+ T lymphocyte count was 440 cells/μL. He started taking an ART regimen that contained a PI 4 years after receiving the diagnosis of HIV infection. His pre–HIV infection rheumatoid arthritis symptoms returned with commencement of ART, and his allergic rhinitis and asthma persisted. He has a 20–pack year history of smoking, which he stopped at the time that HIV infection was diagnosed. After 2 years of ART, he developed lipodystrophy that included hypertriglyceridemia, hypercholesterolemia, facial and peripheral lipodystrophy, dorsocervical fat accumulation, and intra-abdominal obesity. After 4 years of ART, he developed bilateral lower-extremity peripheral sensory neuropathy; thus, lamivudine replaced stavudine in the regimen, with subsequent resolution. He developed upper eyelid ptosis after almost 5 years of ART. Examination revealed bilateral ptosis. Motility examination, levator function, and acetylcholine receptor antibody screening yielded normal findings. Ptosis progressed during >2 years of follow-up, but the patient has not undergone surgical repair. His recent CD4+ T lymphocyte count was 665 cells/μL.

Patient 3. Patient 3 was a 46-year-old, white, homosexual male who had received a diagnosis of HIV infection 13.2 years prior to his presentation with ptosis. He had an extensive history of ART, which he began receiving 2 years after HIV infection had been diagnosed, when his CD4+ T lymphocyte count reached its nadir of 315 cells/μL. After 2 weeks receiving zidovudine, followed by 2 weeks “off” zidovudine, he began receiving a 1-year course of didanosine monotherapy, followed by another year of additional lamivudine dual-drug therapy. His regimen was then switched to an almost 3-year course of PI-containing ART. Hydroxyurea, didanosine, nevirapine, and adefovir were added to his regimen. After 1 year, the adefovir component was stopped, and the patient continued to receive hydroxyurea and triple-class ART, which he is currently taking.

The patient’s history of opportunistic infections includes Kaposi sarcoma, the onset of which occurred when he commenced his first treatment regimen and which persisted for ∼3 years. He had a 20–pack year history of cigarette smoking and continues to smoke 1 pack per day. After 5.5 years of ART, he first presented with lipodystrophy, with metabolic features of hypertriglyceridemia and hypercholesterolemia and body morphologic changes of peripheral and facial lipodystrophy, gynecomastia, and intra-abdominal obesity. His serum lactate level was normal. Five years after lipodystrophy was diagnosed, the patient presented with lipodystrophy, with metabolic features of hypertriglyceridemia and hypercholesterolemia and body morphologic changes of peripheral and facial lipodystrophy, gynecomastia, and intra-abdominal obesity. His serum lactate level was normal. Five years after lipodystrophy was diagnosed, the patient presented with bilateral lower-extremity peripheral sensory neuropathy, which manifested as decreased heel reflex and decreased vibratory sensation. At the same time, he presented with atypical chest pain and a new, incomplete right–bundle branch block (QRS, 108 milliseconds). Bilateral blepharoptosis occurred 5.7 years after lipodystrophy. He underwent bilateral surgical repair 3 months after the diagnosis. Subsequent follow-up did not demonstrate progression of ptosis, and his recent CD4+ T lymphocyte count was 1042 cells/μL.

Patient 4. Patient 4 was a 50-year-old, white, heterosexual woman with a remote history of injection drug use who pre-
AIDS

Figure 3.  A, Photographs of patients (Pt) 1–5 before ptosis, during ptosis, and after repair. B, Photographs of external ophthalmoplegia in patient 5 in 4 gazes, with upper eyelids retracted by the examiner. NA, not available.

AIDS presented with ptosis 11.2 years after diagnosis of HIV and hepatitis C virus coinfection. After 3 years of known HIV infection, PI-containing ART was commenced at a nadir CD4+ T lymphocyte count of 202 cells/μL. After 11 months—and after nephrolithiasis had occurred—nelfinavir replaced indinavir in the regimen, and the patient stopped smoking (after a 22–pack year history of smoking). During the first years of ART, she also was given treatment for thyrotoxicosis associated with a toxic multinodular goiter, which required thyroidectomy; chronic obstructive pulmonary disease; hypertension; Legionella pneumonia; and multidermatomal herpes zoster. After 2.7 years of ART, she developed lipodystrophy with hypertriglyceridemia, hypercholesterolemia, facial and peripheral lipatrophy, and intra-abdominal obesity. She subsequently presented with a new left–bundle branch block (QRS, 124 milliseconds) and worsened paroxysmal supraventricular tachycardia, although the serum lactate level was normal 4 months later. Three months later, stavudine replaced didanosine in the ART regimen, and the patient commenced a course of pegylated IFN and ribavirin therapy for hepatitis C virus infection. Four months later, bilateral blepharoptosis was diagnosed. Didanosine replaced stavudine after she ceased hepatitis treatment. Ptosis markedly worsened, requiring bilateral ptosis repair after 18 months of observation. During the preoperative evaluation, the patient’s prior bundle branch block was noted to have resolved, and her recent CD4+ T lymphocyte count was 620 cells/μL.

Patient 5. Patient 5 was a 47-year-old, white, homosexual man who presented with ptosis and ophthalmoplegia after an 18-year history of known HIV infection and a 7.8-year history of ART. He began taking triple-class ART after 10.4 years of known HIV infection. He also began therapy for diabetes when he presented for HIV care. His ART regimen was intensified with the addition of hydroxyurea after 6 months, because of insufficient virologic response. Hydroxyurea was discontinued 6 months later, after viral suppression, because of continued down-trending in the CD4+ T lymphocyte count to a nadir of 89 cells/μL. He had a brief period of nonadherence to ART associated with depression. Eight months after starting efavirenz, he received a diagnosis of gynecomastia, which was briefly treated with tamoxifen. His regimen was changed to dual-PI ART. After 4.3 years of ART, lipodystrophy was diagnosed in
the context of prior diabetes, hypercholesterolemia, prior gynecomastia, intra-abdominal obesity, and peripheral lipodystrophy. Three months later, nonalcoholic steatohepatitis was diagnosed on the basis of examination of a liver biopsy specimen, and the patient developed bilateral lower extremity peripheral neuropathy. Before his seventh year of ART, the patient again had a period of nonadherence to ART (duration, ~9 months) associated with depression and presumed hepatic encephalopathy; during this time, the patient had a normal serum lactate level. He later reinitiated treatment with a dual-PI ART regimen. At 7.8 years after commencing his first ART regimen, the patient presented with bilateral upper eyelid ptosis and decreased extraocular muscle movements. One month later, he underwent bilateral ptosis repair. No further progression of ptosis has been noted during follow-up, and he has an uptrending recent CD4+ T lymphocyte count of 135 cells/µL.

Case Summary

Five HIV-infected patients (median age, 50 years; range, 46–53 years) presented with ptosis to a single HIV-care provider, and 2 of these patients presented with addition external ophthalmoplegia (figure 1 and table 1). HIV infection had been diagnosed a long time before the patients presented with ptosis (median interval, 11.2 years; range, 7.8–18.2 years). All patients received long-term ART for a substantial duration (median duration, 7.8 years; range, 4.9–11.2 years). All patients received ART that included a thymidine analogue (median duration, 7.1 years; range, 1.2–7.9 years), and 4 patients received thymidine-containing ART for >4 years (figure 2). All patients received PI-containing ART (median duration, 7.1 years; range, 4.9–8.9 years). All patients had body morphology changes of lipodystrophy, including both lipatrophy and fat accumulation; 4 patients also experienced other metabolic abnormalities. The development of lipodystrophy occurred well before the onset of ptosis (median interval, 4.7 years; range, 2.8–5.7 years). Laboratory review failed to find a single incidence of an elevated anion gap or of other indications of acidosis, and 3 patients were specifically demonstrated to have normal blood lactate levels. Four patients presented with peripheral sensory neuropathy before blepharoptosis. Three patients developed cardiac conduction disturbances, with 2 bundle branch abnormalities and 1 case of sinus bradycardia. Associated chronic viral infections were present in most patients: 2 had Kaposi sarcoma, and 1 had hepatitis C virus infection and experienced an episode of disseminated herpes zoster. Two patients also had other inflammatory conditions, including rheumatoid arthritis (patient 2) and diabetes mellitus and nonalcoholic steatohepatitis (patient 5). Three patients also had long histories of tobacco use.

The patients’ palpebral fissures (figures 1 and 3) showed narrowing to a median of 6.5 mm. Levator function appeared to be mildly impaired (median, 10 mm). The marginal reflex distance of the upper eyelid was markedly decreased (median, 0.5 mm). Four patients successfully underwent bilateral blepharoptosis repair. The surgeon noted that the levator aponeurosis was not stretched or dehisced, and it needed to be advanced more than is normally required in acquired aponeurotic-involutional ptosis. Patient 1 required reoperation to attain sufficient clinical response. The successful surgical response persisted for the 4 patients during the postoperative follow-up period.

Electron and light microscopy analyses of blepharoptosis repair specimens obtained from patients 1, 3, and 4 revealed normal orbicularis oculi and levator muscle histology and normal preaponeurotic adipose tissue. Specifically, there were no microscopic mitochondrial abnormalities, including no evidence of ragged red fibers or inflammatory cellular infiltrates in the levator and orbicularis muscle specimens (figure 4; online only).

DISCUSSION

Although we could attempt to identify a single component of ART as a causative agent, these patients were exposed to all components of ART implicated in the development of lipodystrophy. Most notably, these patients all received PI-containing ART for many years before they developed lipodystrophy and ptosis. All patients also received thymidine analogue–containing ART for many years and didanosine-containing ART for >1 year. Severe lipodystrophy that included lipatrophy and fat accumulation preceded ptosis in all cases. Episodes of peripheral sensory neuropathy preceded ptosis in 4 cases, cardiac conduction disturbances accompanied ptosis in 3 cases, and encephalopathy was present in 1 case. A similar constellation of associated symptoms is seen in myogenic ptosis syndromes associated with well-established mitochondrial pathology. We found no evidence of mitochondrial abnormalities by microscopic examination of surgical specimens, and routine chemistry and lactic acid blood studies also yielded normal findings. The normality of blood chemistry findings and ultrastructural features is typical in myogenic ptosis syndromes, which usually require more-complex methods to find evidence of pathology [21–23]. The absence of ragged red fibers and

Figure 4. Representative microscopic images of normal surgical repair specimens of levator muscle from patients (Pt) 1, 3, and 4 obtained by transmission electron microscopy (EM; original magnification, ×3000) and light microscopy (LM; original magnification, ×1650). Samples were stained with toluidine blue. No morphological or microscopic abnormalities were seen.
mitochondrial morphological changes may reflect the relative low sensitivity of microscopy for assessing mitochondrial dysfunction. Myasthenia gravis, a neurogenic ptosis syndrome, was thoroughly excluded as a diagnosis for the first 2 subjects. Further diagnostic evaluation for the 3 other subjects was not pursued because of the unique presentation of this myogenic ptosis syndrome.

The ptosis in 4 patients responded well to surgical repair. The increased need for the advancement of the levator aponeurosis during the procedure and the decrease in the patients’ levator function is more typical of myogenic ptosis, as opposed to more common involutional ptosis. The external ophthalmoplegia seen in 2 patients is also frequently associated with myogenic ptosis [21–23].

The potential contribution of other inflammatory factors (e.g., concomitant chronic viral infection, autoimmunity, and chronic HIV infection) should also be considered. Smoking is thought to worsen eye diseases in mitochondrial encephalomyopathies and to cause the presentation and exacerbation of Leber hereditary optic neuropathy. Also, use of a nicotine patch and tobacco use have worsened or caused ptosis in patients with myasthenia gravis [30, 31]. Thus, both prior and ongoing tobacco use may also contribute to this ptosis syndrome.

In conclusion, we report the novel findings of blepharoptosis and external ophthalmoplegia as adverse outcomes in HIV-infected patients who are receiving long-term ART. In all cases, ptosis was preceded by lipodystrophy and involved the use of both thymidine analogue–containing ART and PI-containing ART. The successful surgical repair of ptosis required greater advancement of the levator aponeurosis/muscle, suggesting a myogenic cause. Clinicians should be aware of this potential adverse HIV-associated treatment effect and watchful for other potential myopathic ptosis-associated complications, including proximal weakness, dysphagia, deafness, neuropathy, and cardiac conduction disturbances.

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