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Ptosis in human immunodeficiency virus-infected patients under long-term antiretroviral treatment☆

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ABSTRACT

Objective: To present cases of ptosis in HIV-1 patients on long-term antiretroviral therapy (ART) and review the existing literature.
Methods: Five HIV-1-positive patients with slowly progressive bilateral ptosis underwent a comprehensive diagnostic evaluation, including imaging studies, neurophysiological testing, muscle biopsy, and genetic analysis. A literature review was conducted.
Results: On clinical examination, all patients presented with bilateral symmetrical non-fatigable ptosis, three exhibited facial lipoatrophy and two also had mild multidirectional ophthalmoparesis and all had ocular abnormalities in Hess screen test. Additionally, one patient displayed proptosis, three had floppy lower eyelids, and four presented with exotropia. Anti-acetylcholine receptor antibodies were negative in all patients. Brain magnetic resonance imaging (MRI), motor unit potential analysis, and single-fiber electromyography were unremarkable. Orbital MRI revealed introrbital fat expansion in one patient, and limb muscle biopsies were inconclusive in two cases. Blood genetic testing for chronic progressive external ophthalmoplegia was negative in all patients. A total of 30 similar cases have been documented in the literature, with some studies reporting key findings such as muscle histology indicative of mitochondrial myopathy, MRI revealing patchy extraocular muscle hyperintensity, and muscle genetic testing identifying mitochondrial deoxyribonucleic acid (DNA) deletions. Ptosis surgical repair appears to be the most effective treatment.
Conclusion: HIV patients on long-term ART may develop ocular muscle involvement due to mitochondrial dysfunction, with bilateral ptosis being the primary manifestation. Diagnosis is challenging and requires the exclusion of other conditions. Ptosis surgery can significantly improve quality of life.

☆ Case series and review of the literature

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1. Introduction

The introduction of antiretroviral therapy (ART) in the 1990s led to a drastic reduction in morbidity and mortality associated with human immunodeficiency virus (HIV) infection. The main drug classes currently include nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs) [1].

Chronic ART has been associated with several neuromuscular complications, including toxic myopathies, lipodystrophy syndrome, and myositis related to immune reconstitution syndrome [2]. Additionally, a few cases of ART-related ocular myopathy have been reported, though the prevalence and management of these cases remain unclear [3–11].

We aimed to present a series of case reports of HIV-1 patients on long-term ART who developed ptosis, and to conduct a comprehensive literature review on this topic.

2. Materials and methods

We report five patients infected with HIV-1 under long-term ART who developed ptosis, according to the CARE (CAse REport) guidelines [12]. All patients provided informed written consent approval for publication.

Additionally, we conducted a literature review, using Pubmed®, Web of Science® and Google Scholar® tools combining keywords and medical subject headings (MeSH) terms. Two authors (CSS and MdC) independently conducted the review. All peer-reviewed articles published in English were considered. Studies focusing solely on animal models or unrelated conditions were excluded. Our search query was structured as follows: ("HIV" OR "human immunodeficiency virus" OR "antiretroviral treatment" OR "antiretroviral therapy" OR "HAART") AND ("ocular myopathy" OR "ptosis" OR "external ophthalmoplegia"). Data extraction was performed using a standardized form, focusing on patient demographics, HIV status, ART regimens, ocular symptoms, management and treatment outcomes. The titles and abstracts of the retrieved articles were screened. Full-text articles were subsequently reviewed for relevance. The results of the literature review are discussed in detail alongside our case series.

3. Results

3.1. Case series

We present a case series of five adult men with chronic HIV-1 infection who have been under long-duration continuous ART with various regimens since treatment initiation (Table 1).

In all patients, the primary symptom was progressive bilateral ptosis without fluctuation. In three patients (patients 1, 2, and 4), the ptosis

Table 1
Clinical and demographical characteristics of the case series The current ART regimen is highlighted in bold. Right/left; MRD1, marginal reflex distance 2 - distance between the lower margin of the upper lid and the light reflex on the cornea; MRD2, marginal reflex distance 2 - distance between the light reflex on the cornea and the upper margin of the lower lid; PFH, palpebral fissure height - vertical distance between the open upper and lower eyelids. *Levator palpebrae superioris* muscle function, distance from the upper eyelid margin in downgaze to upgaze with *frontalis* muscle function neutralized; * No visible corneal light reflex. ABC, abacavir; ART, antiretroviral therapy; ATV, atazanavir; AZT, zidovudine; COBI, cobicistat; DDI, didanosine; DOR, doravirine; DRV, darunavir; DTG, dolutegravir; d4T, stavudine; EFV, efavirenz; FTC, emtricibatine; HIV-1, human immunodeficiency virus type 1; HU, hydroxyurea; IDV, indinavir; INSTIs, integrase strand transfer inhibitors; LPV, lopinavir; N/A, not available; NFV, nelfinavir; NNRTIs, non-nucleoside reverse transcriptase inhibitors; NRTIs, nucleoside reverse transcriptase inhibitors; NVP, nevirapine; OD, *oculus dexter* (right eye); OS, *oculus sinister* (left eye); PI, protease inhibitors; RAL, raltegravir; RPV, rilpivirine; RTV, ritonavir; SQV, saquinavir; 3TC, lamivudine; TDF, tenofovir; VR, values of reference.

		Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age at assessment (years)		60	73	63	59	61
HIV−1 disease duration (years)		30	29	26	17	30
ART drugs (cumulative exposure time, years)	**NRTIs**	**ABC** (17), DDI (11), **3TC** (24), AZT (3)	DDI (1), **3TC** (0.6), TDF (23), AZT (1)	ABC (5), FTC (3), **3TC** (9), TDF (3)	ABC (5), FTC (3), **3TC** (9), TDF (3)	ABC (3), FTC (7), 3TC (4), TDF (7), AZT (3)
	NNRTIs	EFV (13), NVP (2)	**DOR** (0.6)	-	-	EFV (4), NVP (6), **RPV** (9)
	PI	NFV (9), SQV (2)	LPV (28), RTV (28)	ATV (3)	ATV (3)	DRV (5), RTV (3)
	INSTIs	**DTG** (4)	**DTG** (0.6), RAL (17)	**DTG** (9)	**DTG** (9)	**DTG** (5)
	Others	-	-	-	-	COB (1)
Total ART duration (years)		30	29	26	12	27
Clinical symptoms		Bilateral upper eyelid drooping	Bilateral upper eyelid drooping + occasional horizontal binocular double vision	Bilateral upper eyelid drooping + occasional horizontal binocular double vision	Bilateral upper eyelid drooping	Bilateral upper eyelid drooping + occasional exertional myalgia
Ocular symptoms duration (years)		18	8	3	3	10
Clinical findings		Bilateral ptosis + bilateral proptosis + OD exotropia + multidirectional ophthalmoparesis Lipodystrophy	Bilateral ptosis with compensatory *frontalis* hyperactivation + OS exotropia + bilateral floppy lower eyelids (scleral show 2/3 mm)	Bilateral ptosis + *steatoblepharon* + OS exotropia + multidirectional ophthalmoparesis	Bilateral ptosis + OS exotropia (sequelae)	Bilateral ptosis + floppy lower eyelids (scleral show 4/2 mm) Lipodystrophy
Lipodystrophy		Yes	Yes	No	No	Yes
MRD1 (mm), VR 4–5		2/3	-* /1	-/-*	2/-*	-/-*
MRD2 (mm), VR 4–5		14/12	-* /8	-/-*	6/-*	-/-*
PFH (mm), VR~10		16/15	7/9	6/9	8/6	8/9
***Levator palpebrae superioris* muscle function** (mm), VR> 10		14/13	7/9	6/8	N/A	9/10
Hess screen test		Bilateral hypoactivation of the medial rectus (~10º of deviation bilaterally)	Bilateral hypoactivation of the medial rectus (~ 6º/5 º of deviation of OD/OS) and hypoactivation of the right inferior oblique.	Bilateral hypoactivation of the inferior oblique (>15º bilaterally)	N/A	Bilateral hypoactivation of the inferior oblique (<5º bilaterally)

occasionally obstructed the visual field. Two patients (patients 2 and 3) had occasional horizontal binocular diplopia. The duration of symptoms ranged from 3 to 18 years. There were no bulbar, respiratory or limb symptoms. There was no relevant family history or consanguinity. In terms of medical history, three patients (patients 1, 2, and 3) had diabetes mellitus type 2, and four had dyslipidaemia (patients 1, 2, 3, and 5). Patient 4 displayed a history of glaucoma aggravated by amaurosis and exotropia of the left eye, both occurring before the onset of ptosis.

On physical examination, 3 patients (1, 2, and 5) presented with facial lipoatrophy that had developed several years prior to the onset of ocular symptoms. Except for patient 4, blepharoptosis was relatively symmetrical (Fig. 1). Margin reflex distance (MRD) 1, palpebral fissure height, and levator muscle function were reduced in all patients (Table 1), except for patient 1, who exhibited bilateral axial proptosis, more pronounced on the right side (ocular protrusion measured at 25 mm in the right eye and 22 mm in the left eye on Hertel exophthalmometry; normal range approximately 16.7–21.7 mm) [13]. Pupillary reflexes and fundoscopy were normal, and visual acuity was within the normal range for all patients. Patients 1, 2, 3, and 4 exhibited unilateral exotropia in the primary position of gaze (in patient 4, this was secondary to glaucoma and amaurosis). Patients 2 and 5 displayed floppy lower eyelids with increased scleral show (Table 1), while patient 3 presented with bilateral dermatochalasis. Patients 1 and 3 exhibited mild multidirectional ophthalmoparesis, but no diplopia was observed during the examination. Hess screen test was performed in four patients, two of them had hypoactivation of medial rectus (patients 1 and 2) and inferior oblique muscles (patients 3 and 5) (Fig. 2). All patients exhibited normal muscle tone, strength, and muscle bulk, with negative fatigue tests and no evidence of fasciculations or myotonia. Deep tendon reflexes were normal, and Hoffmann's and Babinski's signs were absent. Sensory examination, as well as gait and coordination testing were unremarkable.

Blood workup, including thyroid function, autoimmunity panel, and anti-thyroid antibodies, were unremarkable in all patients. Creatinine kinase (CK) levels were normal, except for patient 3 who had a higher value (400 UI/L, normal <180 UI/L). Antibodies against acetylcholine receptor (AchR), anti-muscle-specific kinase (MuSK) and anti-low-density lipoprotein receptor-related protein 4 (LRP4) were negative in all. Motor unit potentials quantification on electromyography (EMG) of right *biceps brachialis* and *tibialis anterior* was normal in all. Bilateral single-fiber EMG of the *orbicularis oculi* was within normal limits in all subjects.

Brain magnetic resonance imaging (MRI) was normal and orbital MRI did not reveal changes in the morphology or volume of the extraocular muscles. However, in patient 1 there was a mild expansion of intraorbital fat bilaterally, with a more pronounced focal increase between the lateral rectus muscle and the optic nerve in the right orbit (Fig. 3). Muscle biopsy was performed in patients 2 and 3 (deltoid muscle in both patients and *vastus lateralis* in patient 3), revealing a slightly increased variability of muscle fibers size, and presence of few ragged red fibers. These findings were considered discrete, non-specific myopathic changes. Additionally, patients 2 and 3 underwent a functional analysis of the mitochondrial respiratory enzyme chain, and the results were within the average range. Blood genetic testing for chronic progressive external ophthalmoplegia (next-generation sequencing panel testing 51 genes), was performed in all subjects, but no pathogenic variant was found. A trial of pyridostigmine and prednisolone was tried in three patients (2, 3, 5) without any improvement.

Based on the clinical presentation and extensive negative investigations, a diagnosis of ocular myopathy secondary to long-term ART was made. Patient 5 recently underwent bilateral ptosis repair with levator resection at an external facility, resulting in clinical and functional improvement (Fig. 1). Unfortunately, we did not have access to a muscle sample from this procedure. The remaining patients are still awaiting surgical repair.

Fig. 1. Photographs of patients in primary position of gaze. L, left, R, right.

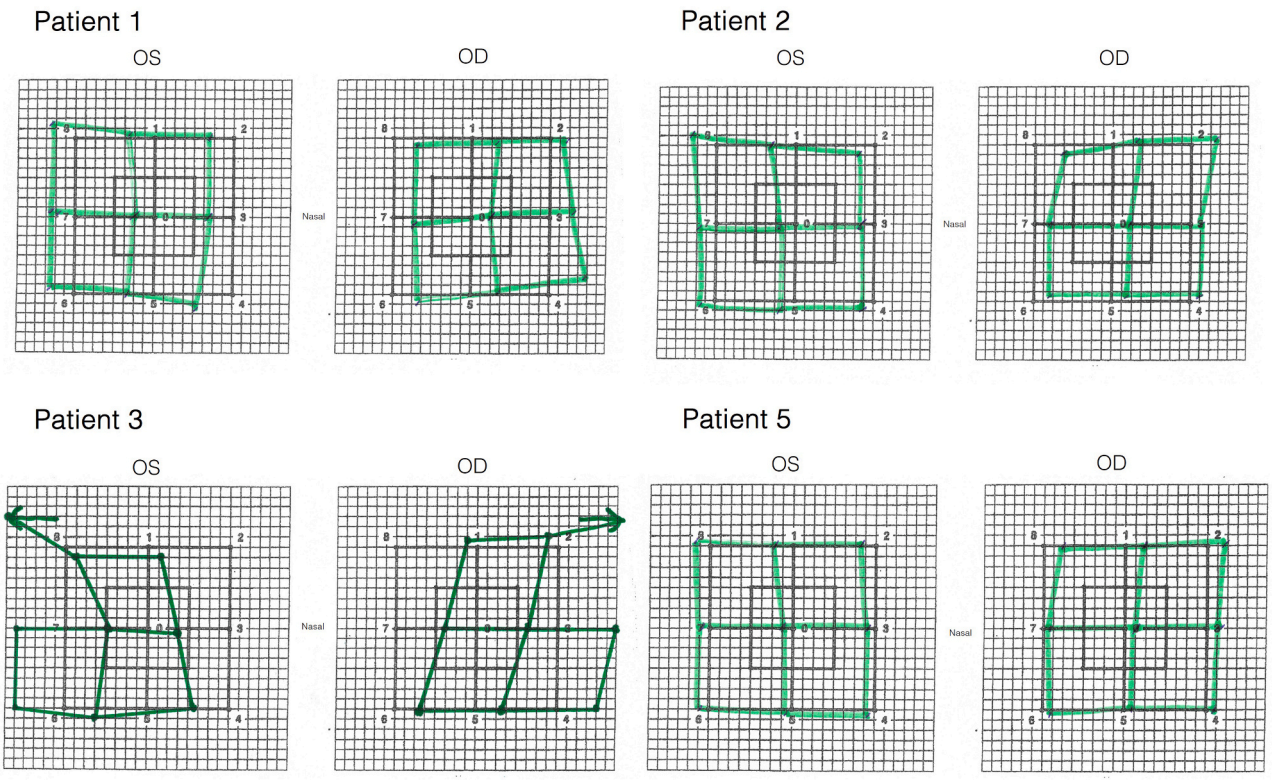

Fig. 2. Hess screen test results (not available for patient 4). OD, *oculus dexter* (right eye); OS, *oculus sinister* (left eye).

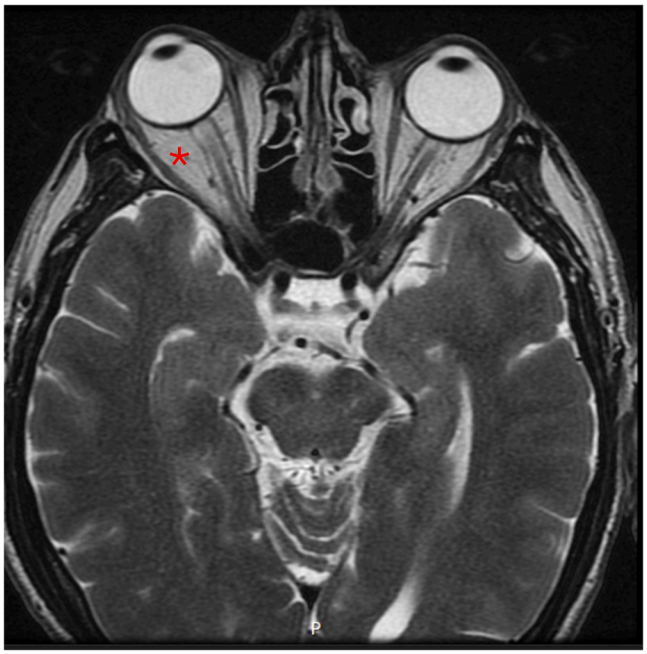

Fig. 3. Orbital MRI (axial T2) of patient 4 demonstrates bilateral exophthalmos with increased orbital fat, particularly between the lateral rectus and optic nerve on the right side, resulting in a more pronounced protrusion of that eye (*). MRI, magnetic resonance imaging.

3.2. Literature review

Our literature review yielded a total of 58 articles from the electronic search, with nine articles meeting the inclusion criteria. All were case reports or case series published between 2008 and 2017 [3–11]. Table 2 summarizes the studies' results.

4. Discussion

4.1. Epidemiology and demographical features

Ptosis, with or without concomitant ophthalmoparesis, associated with ART appears to be an uncommon occurrence, with only 30 cases documented in the literature to date [3–11]. Given that approximately 29.8 million people were receiving ART globally in 2022 [14], it is likely that ART-associated ocular myopathy is underreported. This may be due to its slow, progressive nature, often presenting initially as only ptosis, and its prevalence in older adults, where symptoms can be mistakenly attributed to aging. It appears to be more prevalent in middle-aged men. In the literature, 93.3 % (28/30) of cases were males, with a median age of 52 years (range 44–77 years) [3–11].

4.2. Clinical features

As in our cases, previously reported patients had a long history of ART and experienced a gradual onset of bilateral blepharoptosis, with a median symptom duration of 13 years (range 2–24 years). Additionally, 12 patients (40.0 %) also presented with external ophthalmoparesis [3, 5,9,11], and 5 patients (16.7 %) reported diplopia [5,9]. Lipodystrophy was present in three (60.0 %) of our patients and in nearly half (13, 43.3 %) of the patients in previous reports [3–7]. It is, therefore, a common feature that typically appears before the onset of ocular symptoms and is part of the *spectrum* of metabolic disturbances found in these patients. Other clinical features described in the literature include cardiac conduction abnormalities and dysphagia [3,5]. One of our patients, as well as a patient reported by Pfeffer et al., presented with exertional myalgias [5]. Jones *et al.* also reported fine pigmentary retinopathy in one patient [11]. Additionally, other ocular abnormalities, including proptosis and lower eyelid involvement, were present in our

Table 2
Summary of the previous study results. ART, antiretroviral treatment; COX, cyclooxygenase; EMG, electromyography; HIV, human immunodeficiency virus; IQR, interquartile range; m, months; MRI, magnetic resonance imaging; N/A, not available.

Study	**n** (male, n)	**Age at assessment**, median (range)	**HIV disease duration**, median (range)	**ART total duration** (years), median (range)	**Bilateral blepharoptosis duration**, median (range)	**Other clinical findings** (n)	**Lab workup** (n)	**EMG** (n)	**MRI** (n)	**Neuropathology** (n)	**Genetic testing** (n)	**Management** (n)
Dinges *et al.* [3]	5 (4)	51 (46–53)	11.6 (11.2–18.2)	6.3 (3.2)	7.8 (4.9–11.2)	Ocular: External ophthalmoplegia (5) Others: peripheral neuropathy (4); lipodystrophy (5); sinus bradycardia (1); right–bundle branch block (1)	Anti-AchR: negative (2) Thyroid function: normal (1) Serum lactate: normal (1)	EMG normal (1)	N/A	*Orbicularis oculi* and *levator palpebrae* superioris muscle: normal (3)	N/A	Surgical repair with no further progression of ptosis (3)
Stack *et al.* [4]	1 (1)	47	17	N/A	5	Lipodystrophy (1)	N/A	N/A	N/A	N/A	N/A	Surgical repair (1) with partial improvement
Pfeffer *et al.* [5]	3 (3)	54 (52–58)	20 (16–24)	11 (10–15)	6 (2–10)	Ocular: Diplopia (1), multidirecional ophthalmoparesis (2) Others: exertional myalgia, migraines (1), dysphagia (1); lipodystrophy (3)	Serum lactate: mildly elevated (3)	N/A	N/A	Quadriceps muscle: inconclusive; normal mitochondrial respiratory chain enzyme analysis (1) *Levator palpebrae superioris* muscle: red ragged fibers and COX-negative (1)	*Levator palpebrae superioris* muscle: 3.9-kb mtDNA deletion (1)	ART was stopped for 3 m with clinical improvement (1) Regiment switch w/ no effect (1)
Silkiss *et al.* [6]	2 (2)	55 (53–57)	16 (15–17)	N/A	N/A	Lipodystrophy (2)	N/A	N/A	N/A	*Levator palpebrae superioris* muscle: findings suggestive of mitochondrial myopathy (2)	N/A	Surgical repair (2)
Blanco *et al.* [7]	2 (2)	46.5 (44–49)	14.5 (11–18)	12.0 (10–14)	3 (2–4)	Lipodystrophy (2)	Myasthenia gravis, thyroid disease or paraneoplasic syndromes excluded	N/A	N/A	N/A	N/A	Regiment switch w/partial improvement (2) Surgical repair (2)
Moscato et *al.* [8]	10 (10)	53.5 (42–77)	23.5 (21–26)	4.5 (3–6)	19 (17–21)	-	N/A	N/A	N/A	*Levator palpebrae superioris* muscle: myopathy with associated epimysial fibrosis	N/A	Surgical repair with improvement (9)
Pineles *et al.* [9]	5 (4)	53.5 (44–62)	21.5 (20–23)	21.5 (13–23)	N/A	Diplopia (3), strabismus (?), multidirectional external ophthalmoparesis (4)	Anti-AchR: negative (5)	Single fiber EMG: normal (2)	Brain MRI: normal (5) Orbital MRI: patchy bright signal in extraocular muscles w/ conserved volume (5)	N/A	N/A	N/A
Chapman *et al.* [10]	1 (1)	51	N/A	19	N/A	-	N/A	N/A	N/A	*Levator palpebrae superioris* muscle: normal	*Levator palpebrae superioris*: multiple	Surgical repair with

(*continued on next page*)

Table 2 (*continued*)

Study	n (male, n)	Age at assessment, median (range)	HIV disease duration, median (range)	ART total duration (years), median (range)	Bilateral blepharoptosis duration, median (range)	Other clinical findings (n)	Lab workup (n)	EMG (n)	MRI (n)	Neuropathology (n)	Genetic testing (n)	Management (n)
											deletions in mitochondrial DNA	improvement (1)
Jones et al. [11]	1 (1)	54	28	N/A	10	Diplopia, left exotropia, multidirectional external ophthalmoparesis Others: fine pigmentary retinopathy	Anti-AchR: negative (1)	EMG: normal	Orbit MRI: normal	*Lateral rectus*: no inflammation or scarring	N/A	Surgical repair of left exotropia, complicated with pulled in two syndrome

case series, indicating concomitant connective and adipose tissue involvement.

4.3. Pathophysiology

Due to their high metabolic activity, extraocular muscles are particularly susceptible to impairment in mitochondrial dysfunction disorders. Ocular muscle involvement seems to results from cumulative mitochondrial toxicity of ART. NRTIs are the major group associated with skeletal muscle mitochondrial dysfunction, mainly zidovudine [2]. They competitively bind to both HIV reverse transcriptase and mitochondrial (mt) DNA polymerase subunit gamma, which is responsible for mtDNA replication [15]. This leads to mtDNA depletion, impaired oxidative phosphorylation, elevated superoxide levels, and the formation of structurally abnormal mitochondria [16]. PIs, on the other hand, contribute to mitochondrial dysfunction through effects on lipid and glucose metabolism and by increasing oxidative stress [17]. Evidence shows that ART drugs can cause multiple mtDNA mutations in HIV-1-infected children on long-term therapy, some of which are linked to mitochondrial diseases [18,19]. While newer ART drugs appear to carry a lower risk of mitochondrial toxicity, further research is needed to confirm this [20,21]. In our patients, as in previously reported cases, multiple ART combinations (including NRTIs, NNRTIs and PIs) were administered over many years, supporting the conclusion that the toxic effects are likely cumulative and synergistic across different drug classes rather than attributable to a single drug. Additionally, HIV infection itself, combined with aging and potential genetic predisposition, may contribute further to mitochondrial dysfunction [5,10,21].

4.4. Differential diagnosis

The primary differential diagnoses for adult-onset ptosis, with and without ophthalmoparesis, include neurogenic, neuromuscular junction, myogenic, aponeurotic and mechanical causes. Among neurogenic etiologies, Horner syndrome and oculomotor (III) nerve palsy are the main considerations. However, these conditions are unlikely given the progressive nature, bilateral presentation, and lack of pupil involvement in our cases. Furthermore, the presence of ophthalmoparesis that does not respect cranial nerve territory excludes III nerve palsy.

In neuromuscular junction disorders, *myasthenia gravis* is the most common acquired cause of adult-onset ptosis. However, features such as long-standing progression without fatigability, negative results for AChR, MuSK, and LRP4 autoantibodies, normal *orbicularis oculi* jitter, and lack of response to pyridostigmine or steroids argue against this diagnosis. Lambert-Eaton syndrome is another adult-onset neuromuscular junction disorder, but ocular involvement is rare, particularly in the absence of limb muscle weakness, dysautonomia, or absent reflexes.

Myogenic causes include chronic progressive external ophthalmoplegia (CPEO) and related mitochondrial myopathies, such as Kearns-Sayre syndrome, oculopharyngeal muscular dystrophy, and myotonic dystrophy. CPEO in its isolated form is characterized by progressive ptosis and ophthalmoparesis and is typically caused by deletions in mtDNA (most commonly) or nuclear DNA, which may be inherited or arise *de novo*. Our patients, like those previously reported, presented with a CPEO-like syndrome. Negative blood genetic testing for CPEO in all patients suggests a non-genetic cause, although mtDNA mutations can be acquired through drug exposure [18,19]. Other CPEO-related conditions, such as Kearns-Sayre syndrome, typically present earlier in life and are associated with features like retinopathy, ataxia, and cardiac conduction abnormalities, all of which were absent in our cases. In oculopharyngeal muscular dystrophy, dysphagia is nearly universal (occurring in 96–100 % of cases), and limb muscle weakness is seen in 71–86 % of cases, both of which were absent in our patients [22]. Oculopharyngeal distal myopathy, a related but rarer and genetically heterogeneous condition, usually presents in early adulthood (20 s to 30 s) with ptosis, often accompanied by facial and distal muscle

weakness. Muscle biopsy in this condition commonly reveals rimmed vacuoles, variability in muscle fiber size, and connective tissue hyperplasia, none of which were observed in our patients [23]. Myotonic dystrophy can present with features such as myotonia, limb weakness, early-onset cataracts, and systemic involvement (e.g., cognitive, gastrointestinal, pulmonary), none of which were present. Ptosis in myotonic dystrophy typically appears in more advanced cases, is more common in congenital and childhood-onset forms, and is often accompanied by facial features like *temporalis* muscle atrophy and facial muscle weakness [24].

Aponeurotic ptosis is an acquired form of ptosis that commonly affects older adults. It occurs by dehiscence, disinsertion or stretching of the levator aponeurosis. This can be related to aging, trauma, prolonged contact lens wear, or previous eye surgery. Unlike our patients, individuals with aponeurotic ptosis usually maintain normal levator muscle function.

Among mechanical causes, dermatochalasis is the primary consideration in older patients. This condition involves excess, loose skin on the upper or lower eyelids due to age-related changes, which may mimic ptosis in appearance but generally presents with a normal MRD1 and preserved levator function, which were abnormal in our cases. Other mechanical causes, such as orbital space-occupying lesions, thyroid orbitopathy, and sarcoidosis, which can lead to pseudoptosis and occasionally ophthalmoparesis, were also ruled out.

4.5. Complementary exams

4.5.1. Blood workup

Blood workup including thyroid function, autoimmunity, and anti-AchR, anti-MuSK, and anti-LRP4 antibodies were negative in all our patients. In one of our patients there was a slight elevation of CK baseline levels associated with occasional myalgias. While the elevated CK levels may be attributed to the patient's African background [25], the presence of myalgias may suggest the possibility of more diffuse, subclinical muscle involvement, despite the absence of confirmatory findings on clinical examination, EMG or muscle biopsy. In the literature, anti-AchR antibodies were tested in ten patients [3,7,9,11] and thyroid function was assessed in two patients [3,7], with unremarkable results. Pfeffer *et al.* reported slightly elevated serum lactate levels [5], while normal levels were noted by Dinges *et al.* [3].

4.5.2. Imaging

In our cases, MRI did not show any changes in the extraocular muscles. However, one patient exhibited proptosis with slight expansion of intraorbital fat, which may correlate with the *spectrum* of metabolic abnormalities observed in these patients and differential fat distribution. In contrast, Pineles *et al.* reported that orbital MRI revealed patchy hyperintensity in the extraocular muscles, with normal volume and no signs of inflammation, a finding also observed in patients with genetic CPEO [9].

4.5.3. Neurophysiology

In our cases, all patients underwent single-fiber EMG and limb EMG with motor unit quantitative analysis, all of which were normal, consistent with findings previously reported in the literature [3,9,11].

4.5.4. Histopathology

Three studies have documented histopathological findings in the levator muscle consistent with mitochondrial myopathy, including atrophy, ragged-red fibers, and cytochrome c oxidase (COX) deficiency [5,6,8]. However, in the reports by Dinges *et al.*, Chapman *et al.*, and Jones *et al.*, no microscopic or electronic abnormalities were identified [3,10]. Consistent with the study by Pfeffer *et al.* [5], the two patients in our study who underwent limb muscle biopsies showed non-specific findings without abnormalities in mitochondrial respiratory chain enzyme analysis. Therefore, muscle biopsy results may be normal or exhibit non-specific changes for this age group.

4.5.5. Genetic testing

Genetic blood testing for CPEO was negative in our patients; however, no genetic testing was conducted on the muscle biopsy samples, so a definitive genetic cause for CPEO could not be ruled out. Two studies identified mtDNA deletions in *levator palpebrae superioris* muscle samples [5,10]. This suggests two possibilities: firstly, in genetically predisposed individuals, factors such as HIV infection, ART, and aging may unmask an underlying mitochondriopathy; secondly, it corroborates that long-term exposure to ART may induce *de novo* mtDNA mutations through mitochondrial toxicity [18,19].

4.6. Management and treatment outcomes

Regarding management, Pfeffer *et al.* reported improvement with the temporary suspension of the ART in one case [5]. Switching ART scheme was also tried in other studies but yielded little to no benefit [5,7]. The most consistently effective long-term treatment for ptosis appears to be ptosis repair, with favourable outcomes reported in the literature, particularly in terms of quality of life improvement [3,4,6–8,10]. Ptosis repair should be considered when it leads to visual obstruction or causes neck pain from continuous neck retroflexion to compensate for the ptosis. Various surgical techniques were reported, including the skin-orbicularis-levator-orbicularis-skin suture technique [4], external levator aponeurosis reinsertion [10], and bilateral levator resection [6,8], all of which yielded satisfactory results. Moscato *et al.* noted that levator advancement via anterior incision produced an insufficient intraoperative correction, requiring a subsequent anterior levator resection [8]. Regarding external ophthalmoparesis, only Jones *et al.* reported a surgical repair for *strabismus* that was complicated by an extraocular muscle rupture ('pulled-in-two' syndrome), attributed to the friability of the lateral rectus muscle [11].

5. Conclusion

In conclusion, extraocular muscles involvement is a complex complication of chronic HIV infection and long-term ART, likely due to cumulative mitochondrial dysfunction. Ptosis seems to be the main manifestation. Diagnosis is challenging and requires the exclusion of mimicking conditions. Surgical intervention for ptosis represents a viable option for significantly improving the quality of life of these patients. Given the increasing number of individuals living with chronic HIV infection, heightened awareness of this potential complication is essential.

CRediT authorship contribution statement

Miguel Oliveira Santos: Writing – review & editing, Methodology, Investigation, Formal analysis. **Fábio Cota de Medeiros:** Writing – review & editing, Methodology, Investigation, Formal analysis. **Rafael Roque:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation. **Pedro Coelho:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation. **Ana Cláudia Fonseca:** Writing – review & editing, Methodology, Investigation, Data curation. **Bárbara Martins:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Beatriz Nunes Vicente:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Cláudia Santos Silva:** Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Mamede de Carvalho:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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