

The neuro-ophthalmology of HIV-AIDS review of Neurobehavioral HIV Medicine

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Abstract: Neuro-ophthalmic problems are known to occur both in human immunodeficiency virus (HIV) infection and AIDS. Central nervous system (CNS) opportunistic infections and malignancies such as lymphoma are the major source of these problems but some result from the direct effect of the virus on the CNS. Both the afferent visual pathway and efferent ocular motor system may be affected. Neuro-ophthalmic signs may sometimes be the initial manifestation of AIDS. A variety of neuro-ophthalmic manifestations may be encountered in the same patient. Several large studies on the ophthalmic features of AIDS have included neuro-ophthalmic manifestations in their series. However dedicated comprehensive review articles on this subject are few. Despite the introduction of highly active antiretroviral therapy (HAART), neuro-ophthalmic manifestations still remain a problem in HIV. The aim of this article is to provide an overview of the neuro-ophthalmic sequelae of AIDS.

Keywords: HIV, AIDS, ophthalmology, eye, pupil, cranial nerve, ocular motility, visual loss

Introduction

HIV/AIDS is a global pandemic with cases described in almost every country in the world. AIDS was first recognized as a clinical entity in 1981¹ and the etiologic agent, the human immunodeficiency virus (HIV), a cytopathic retrovirus was first identified in 1983.²

HIV, a neurotrophic virus enters the CNS in the early stages of infection and invades mainly the microglia and macrophages, and rarely the neurons. HIV/AIDS can produce neurological and neuro-ophthalmic abnormalities either as a direct effect of the virus on the nervous tissue or indirectly through opportunistic infections and malignancy resulting from the immunodeficiency. The prevalence of neurological disease in symptomatic HIV infected patients is estimated to be 39%–70%.^{3–5} HAART has largely changed the incidence and prognosis of HIV associated neurological disorders in the developed countries,⁶ but this may not be the case in developing countries.⁷

Ocular manifestations of HIV/AIDS were first reported in 1982.⁸ About 50%–75% of patients infected with HIV will develop ocular manifestations with a cumulative lifetime rate of developing at least one ocular lesion of 52%–100%.^{9,10} The neuro-ophthalmological manifestations result from involvement of the afferent visual pathways, the efferent ocular motor, the pupillary system, and the visual centers in the brain. Not infrequently, neuro-ophthalmic manifestations may be a presenting feature of HIV infection.

Given an extensive body of literature on the subject, we hope to provide a summary of the varied neuro-ophthalmic manifestations resulting from HIV/AIDS.

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Involvement of the eye and ocular adnexa

The lesions of the anterior segment and ocular adnexa include spontaneous staphylococcus aureus eyelid ulcers with blepharitis,¹¹ molluscum contagiosum with eyelid abscess,¹² limbal epibulbar molluscum contagiosum,¹³ Kaposi's sarcoma,^{14–16} conjunctival vascular abnormalities,¹⁷ sub-conjunctival hemorrhages, chronic dacryocystitis, peri-orbital ecchymosis (from HIV related idiopathic thrombocytopenic purpura), episcleritis, dry eyes, keratitis (from herpes simplex virus, cytomegalovirus, and microsporidia), corneal opacity, neurotrophic corneal ulcer, zoster related keratouveitis, anterior uveitis, syphilitic uveitis, drug induced uveitis (rifabutin and cidofovir in the pre- HAART era) and complicated cataract.^{18–22}

HIV can produce retinal microangiopathy that results in cotton wool spots, microaneurysm, intraretinal hemorrhages, white centered hemorrhages, telangiectasia and capillary non perfusion.^{18–23} Other posterior segment findings include choroidal infiltrates (from syphilis, toxoplasma, tuberculosis, pneumocystosis), chorioretinitis, progressive outer retinal necrosis (PORN), acute retinal necrosis (ARN), cytomegalovirus (CMV) retinitis, Bartonella henselae associated multifocal retinitis, frosted branch angitis and retinal detachment following any form of retinitis.^{24–27} Reticulum cell sarcoma (B cell lymphoma of the retina) can present as yellowish white retinochoroidal lesions, peripapillary infiltrates, optic disc swelling and flame shaped hemorrhages.²⁸ Panuveitis, immune recovery uveitis (a form of immune reconstitution syndrome) and endogenous endophthalmitis have also been reported.^{18–23,29} CMV retinitis and HIV microangiopathy are the most common ocular manifestations in AIDS both in the pre HAART and HAART era.³⁰ The presence of retinal microangiopathy has been noted to be associated with increased risk of mortality in AIDS patients.³⁰ The incidence and severity of CMV retinitis has become less after HAART though new cases do exist.^{29,31,32}

Occlusion of retinal vasculature has been reported in patients with AIDS. Both microvascular and macrovascular disease may co-exist in AIDS.³³ In a retrospective study of 2,484 patients with HIV, 1.3% had retinal vascular occlusion.³⁴ While central retinal vein occlusion was the commonest occlusion in the series, other forms such as branch retinal vein occlusion, hemiretinal vein occlusion, branch retinal artery occlusion, central retinal artery occlusion, combined retinal artery and retinal vein occlusion and Purtscher like retinopathy were also reported.³⁵ These vascular occlusions are believed to result from immune complex

deposition and elevated levels of tumor necrosis factor alpha which produce a pro-thrombotic state.³⁶ Recanalization of an occluded branch retinal artery following treatment with doxycycline for Bartonella henselae retinitis, was reported in a patient with AIDS.²⁶

Neuro-ophthalmic manifestations

The neuro-ophthalmic manifestations of HIV were described in the early years of the HIV pandemic.^{37,38} Neuro-ophthalmic abnormalities have been estimated to occur in 2%–8% of patients with AIDS.^{24,38–40} Other studies have reported neuro-ophthalmic abnormalities in as much as 60% of neurologically symptomatic HIV patients.⁹

Optic neuropathy

Optic neuropathy in patients with HIV/AIDS may result from inflammation, ischemia, infection, compression, infiltration, and increased intracranial pressure. Opportunistic infections account for the largest cause of optic nerve disease and vision loss in AIDS. Optic nerve inflammation in AIDS develops largely from opportunistic infections. However the optic nerve may be a direct site of insult of HIV. All forms of optic neuritis have been reported.

Primary HIV optic neuropathy

HIV optic neuropathy is a diagnosis of exclusion after opportunistic infections and neoplasm have been excluded. Unilateral^{18,41} as well as bilateral presentations have been reported.^{42–46} Clinically, it may present as papillitis, retrobulbar optic neuritis, or neuroretinitis. Visual loss can be variable and severe field loss may be seen.⁴⁴ Optic neuritis accompanied by a relapsing remitting neurological illness (similar to multiple sclerosis) was described in the setting of seropositivity for HIV-1 infection.⁴⁷

The pathogenesis of HIV optic neuropathy remains uncertain. Postmortem morphometric analysis of the optic nerves of HIV infected individuals has shown chronic degeneration and diffuse axonal loss.⁴⁸ Sadun et al have demonstrated HIV DNA within the optic nerves and the retina⁴⁹ of HIV infected patients which was associated with patchy axonal degeneration, oligodendrocyte and myelin degeneration and mononuclear cell infiltration. They postulated that the optic nerve degeneration was mediated by HIV infected macrophages rather than direct HIV infection of the axons. HIV infected macrophages have been shown to release cytokines particularly TNF alpha which can induce neuronal apoptosis and produce optic nerve degeneration,^{50,51} release IL-1B and IL-6 from astrocytes, macrophages and endothelial

cells in the optic nerves, and may also contribute to immune mediated neuronal damage.⁵² It is now felt that HIV optic neuropathy may be immune mediated.

Early initiation of HAART has been shown to improve vision.^{44,53} A relapsing remitting course similar to multiple sclerosis and steroid responsiveness has also been described.⁵⁴ High doses of pentoxifylline have been shown to suppress TNF alpha mediated optic nerve axonal degeneration experimentally.⁵⁵

Infectious optic neuropathy

Optic nerve disease in patients with HIV/AIDS may present as papillitis (disc swelling), retrobulbar optic neuritis (normal optic disc appearance) or optic perineuritis (swollen optic disc with enlarged blind spot and relatively normal visual functions) or neuroretinitis (disc edema with macular exudates with star formation).

Cytomegalovirus (CMV) can involve the optic nerve during advanced stages of retinal disease^{39,56–59} resulting in severe visual loss. Optic nerve involvement occurs either as a primary optic nerve infection with associated peripapillary retinitis or secondarily by extension of the peripapillary retinitis to the disc margin.⁶⁰ Retrobulbar optic neuritis has also been described.⁶¹ CMV optic neuritis may co-exist with other opportunistic infections and lymphoma, making diagnosis difficult. On histology, CMV inclusions have been seen within all layers of the retina and within the optic nerve.⁶² CMV optic neuritis generally carries a poor prognosis because of irreversible necrosis of the optic disc. In contrast, optic neuritis caused by an extension of the retinitis seems to respond favorably to antiviral therapy.⁶⁰ Treatment includes high doses of intravenous foscarnet and/or gancyclovir⁶³ and also with oral valgancyclovir.⁶⁴ Treatment should be initiated early before the development of optic atrophy.

Toxoplasma optic neuritis can present as papillitis, retrobulbar optic neuritis and neuroretinitis often with retinochoroiditis.⁹ Ocular toxoplasmosis frequently presents with bilateral and multifocal involvement with vitritis. The infection is believed to result from a new infection of dissemination from a non-ocular site.⁶⁵ Toxoplasma has been demonstrated within both the nerve fiber layer and ganglion cell layer.⁶⁶

Herpes simplex virus (HSV) and herpes zoster virus (HZV) may produce acute retinal necrosis (ARN) and progressive outer retinal necrosis (PORN) in patients with AIDS. Optic nerve involvement in the form of disc edema, hyperemia and atrophy may be seen in both ARN and PORN.⁶⁷ Papillitis, retrobulbar optic neuritis^{9,68–74} and neuroretinitis have been

reported in AIDS in association with cutaneous herpes zoster, herpes zoster ophthalmicus and aseptic meningitis.⁷⁵ Optic neuritis has also been reported as the heralding event for the herpetic infection. Intravenous acyclovir is the first line of treatment for optic nerve involvement, but response is variable.⁷⁶ Alternative treatments include foscarnet and gancyclovir in acyclovir resistant cases.

Syphilis occurring concomitantly in patients with HIV infection has an aggressive course with increased incidence and faster progression to neurosyphilis; increased clinical severity and ineffective treatment. Neurosyphilis frequently presents with ocular disease in patients with AIDS and a CSF examination should be performed in all patients with HIV presenting with syphilitic eye disease.⁷⁷ Clinically, optic neuritis may present with papillitis,^{78–83} retrobulbar optic neuritis,^{84–86} neuroretinitis⁸⁷ and optic perineuritis.^{88,89} Optic nerve syphiloma (gummata) seen on ultrasonography has also been reported in a HIV positive patient.⁹⁰ Visual outcomes of optic neuritis with treatment remain variable.

Cryptococcus neoformans infection is another common cause of neurologic and neuro-ophthalmologic disease in AIDS.⁹¹ Optic nerve inflammation can produce papillitis⁹, retrobulbar optic neuritis^{92–94} and optic perineuritis.⁹⁵ Chiasmal involvement with visual field loss has also been reported.⁹⁶ Visual loss in cryptococcal meningitis results either from direct fungal infiltration of the anterior visual pathway and the perioptic meninges with resultant necrosis of optic nerve fibers,^{94,97} or from adhesive or constrictive arachnoiditis leading to vascular compromise or optic nerve compression.⁹⁵ Prompt medical intervention with intravenous amphotericin b and 5-flucytosine before permanent nerve damage develops may preserve vision.

Optic neuritis has also been reported with mycobacterium tuberculosis,⁹ histoplasmosis,^{98,99} hepatitis B¹⁰⁰ and Bartonella henselae (neuroretinitis and aseptic meningitis).¹⁰¹ Sudden blindness from chiasmal infarction caused by progressive rhino-orbital cerebral mucormycosis that produced occlusive vasculitis was reported in a patient with both diabetes and AIDS.¹⁰²

Papilledema

The incidence of papilledema in AIDS is highly variable with a range of 1.5%–27%.^{9,39,103} Papilledema may develop from raised intracranial pressure from CNS infections or neoplastic processes. Papilledema in AIDS patients has been reported in cryptococcal meningitis,^{104–109} cerebral toxoplasmosis, herpes zoster, neurosyphilis,¹¹⁰ cytomegalovirus,¹¹¹ lymphoma,¹¹² tuberculous meningitis and tuberculoma.

Rarely, papilledema from direct CNS involvement by HIV has also been described.^{9,113} Optic nerve sheath fenestration procedure has been used to preserve vision in cases of papilledema resulting from cryptococcal meningitis.^{114,115}

Other causes of optic neuropathy

Lymphomatous infiltration of the optic nerve has been reported in patients with HIV/AIDS.¹¹³ Dense lymphomatous infiltration of optic nerves with necrotizing vasculitis of the peripapillary retinal vessels was found in a patient with AIDS who suffered bilateral sequential central retinal vein occlusion.¹¹⁶ Lymphomatous infiltration of the anterior visual pathways was reported in patients with AIDS by other authors.^{117,118}

Brack et al describe a patient with anterior ischemic optic neuropathy confirmed on fluorescein angiogram as the presenting symptom of AIDS.¹¹⁹

A case of bilateral sequential optic neuropathy attributable to LHON (genetic analysis was positive for 14484 mutation) was seen in an AIDS patient on antiretroviral therapy. It was proposed that LHON was precipitated by mitochondrial toxicity induced by the antiretroviral therapy.¹²⁰

While optic atrophy may develop following any form of optic neuropathy in HIV/AIDS, atrophy may develop in the absence of known prior history of optic nerve disease.^{9,22}

Other abnormalities of the afferent pathways

Visual field defects in AIDS are produced by lesions involving the afferent pathways. The anterior visual pathway lesions as described above usually produce nerve fiber bundle defects. Lesions of the retrochiasmal pathways produce homonymous hemianopia and have resulted from toxoplasmosis, cryptococcosis, cerebral astrocytoma,¹²¹ neurosyphilis,¹²² tuberculosis, progressive multifocal leukoencephalopathy,^{123–129} and lymphoma. Visual field defects have been reported in patients with normal visual acuity^{130,131} and without infectious retinopathy^{131,132} and are believed to result from damage to the inner retina. Cortical blindness and visuo-spatial abnormalities could result from involvement of the primary or association visual cortices.

Abnormal contrast sensitivity and abnormal color vision^{133–137} has been reported in patients with HIV infection despite good immune status and visual acuity. While severe impairments producing tritan defect reflects neuroretinal dysfunction, presence of deutan and proton defects indicate probable optic nerve involvement.^{135,136}

Abnormalities on the visual evoked potential (VEP) may be seen in 3%–49% patients with HIV, despite normal visual acuity indicating subclinical dysfunction of the afferent pathways.^{9,138–142} While VEP latency may be normal in asymptomatic seropositive subjects, prolonged latency can be seen in neurologically symptomatic subjects with AIDS¹⁴³ suggesting that neurologically symptomatic patients may have more damage to the visual pathway.

HIV neuro-retinal disorder

Monochromatic photography has demonstrated nerve fiber layer infarcts in HIV patients with and without retinopathy¹⁴⁴ believed to reflect primary lesions of the retinal ganglion cells or nerve fibers. Optical coherence tomography (OCT) and frequency doubling perimetry have shown that visual dysfunction can occur in eyes of HIV patients without infectious retinopathy from damage to the inner retina (HIV-neuroretinal disorder).¹⁴⁵ Studies using the third-generation OCT have demonstrated significant retinal nerve fiber layer (RNFL) thinning in HIV patients with low CD4 counts and without infectious retinitis compared with a subgroup of patients with CD4 count above 100 and HIV-negative control subjects.^{146,147} This may prove useful in detecting early subclinical HIV associated visual loss. The loss of the nerve fiber layer leads to sub-clinical deficits. Abnormalities of color vision and contrast sensitivity have been shown to correlate with thinning of peripapillary RNFL particularly the temporal quadrant. Preferential damage to small-caliber axons in the maculopapillary bundle possibly associated with mitochondrial dysfunction has been hypothesized. This provides a potential disease mechanism for HIV-associated “neuroretinal disorder.”¹⁴⁸

Abnormalities of ocular motility

Ocular dysmotility in HIV/AIDS can result from nuclear, supranuclear, or infranuclear lesions resulting in cranial nerve palsy, gaze palsies, internuclear ophthalmoplegia and nystagmus⁴⁰ often in association with other neurological deficits such as hemiplegia, hemianesthesia, ataxia, and tremors. Rarely, they form the presenting features of HIV/AIDS.¹⁴⁹

Supranuclear defects

Disorders of conjugate gaze dynamics are common in AIDS. Saccadic and smooth pursuit dysfunction has been noted in patients with AIDS and can be an early sign of CNS HIV infection.^{150–152} Most patients are unaware of their ocular motility defects. Imaging may not reveal any structural abnormality. Using simple bedside techniques for testing saccades,

prolonged saccadic latency, or slowed saccadic movement has been reported in AIDS and may indicate disease involving basal ganglia.¹⁵¹ Infrared oculography has demonstrated abnormal saccades and smooth pursuit in patients with HIV and AIDS.^{153,154} Saccadic problems in HIV positive patients include hypometric saccades, anticipatory saccades, wrong way saccades, abnormal antisaccades, fixation instability with saccadic intrusions and square wave jerks, slowed saccadic duration both for abducting and adducting saccades, and reduced saccadic velocity.^{153–156} Smooth pursuit dysfunction includes saccadic pursuit and decreased smooth pursuit gain.

Abnormal saccades and smooth pursuit may be an early indicator of AIDS dementia complex (ADC)^{153,155,157} characterized by progressive cognitive loss with behavioral problems and slowing of rapid motor movements. These ocular motility problems may be encountered even in patients without signs of ADC.¹⁵² Early detection may lead to prompt treatment with a better prognosis. Severity of the ocular motility dysfunction has been correlated with the severity of AIDS dementia.

The neuroanatomic substrate causing slowed saccades in HIV infection is unknown. However it has been postulated that the defect may lie in the burst neurons of the parafontine reticular formation rather than a defect in the neural input from the frontal eye field. Also it has been proposed that involvement of basal ganglia in ADC may give abnormal voluntary saccades and diffuse cortical atrophy in ADC may affect the generation of smooth pursuit movement.

Other supranuclear abnormalities of eye movements include convergence insufficiency,¹⁵⁰ reverse ocular dipping (slow upward deviation of the eyes followed by a rapid return to midposition),¹⁵⁸ and nystagmus (from brainstem and cerebellar lesions).¹⁵⁹

Opsoclonus-myoclonus-ataxia (OMA) syndrome is a rare neurological disorder characterized by multidirectional chaotic saccadic eye movements, accompanied by myoclonus and rarely cerebellar ataxia. HIV-associated OMA has been described as a consequence of a deranged immune system when the CD4/CD8 ratio is reduced,¹⁶⁰ at the time of probable seroconversion in HIV^{161,162} and immune reconstitution^{162,163} following initiation of anti-retroviral therapy. Spontaneous recovery may occur.¹⁶² Improvement with use of lorazepam,¹⁶¹ immunoglobulins¹⁶⁴ and prednisone has been noted.

Cranial nerve palsies

Toxoplasma has a predilection for involving the brainstem and thalamus and can produce nuclear third,^{165,166} fourth,

and sixth cranial nerve palsies. Other opportunistic infections such as CMV, herpes simplex and herpes zoster can cause brainstem encephalitis resulting in brainstem neuro-ophthalmic signs such as internuclear ophthalmoplegia,^{167–69} vertical gaze palsy,^{170,171} horizontal gaze palsy,^{172,173} bilateral fourth nerve palsy,¹⁷⁴ sixth nerve palsy,¹⁷⁵ seventh nerve palsy,^{169,170,173} and nystagmus. Dorsal midbrain syndrome characterized by impaired upgaze, lid retraction (Collier's sign), convergence retraction nystagmus, light near dissociation and ataxia has also been described in AIDS.^{176–180}

Isolated and multiple cranial neuropathies have been reported in HIV/AIDS. These result from brainstem encephalitis, neoplastic meningitis (lymphoma), mass lesions and vasculitis. Nine percent of HIV related neurological disease is heralded by cranial neuropathy.¹⁸⁰ In a study of 589 patients with neurological manifestations, 3% had ocular cranial nerve palsy¹⁸¹ with third and sixth nerve palsies being the most common. Toxoplasmosis and cryptococcosis have been reported as the two most common causes. Multiple cranial neuropathies can occur at the time of HIV seroconversion,¹⁸² and have been reported with cryptococcal meningitis,¹⁸³ toxoplasmosis, CNS lymphoma,^{184,185} and multifocal CMV encephalitis.¹⁸⁶

Unilateral or bilateral third nerve palsy in AIDS has been reported secondary to toxoplasmosis,¹⁸⁷ cryptococcosis,⁹ tuberculosis, herpes zoster, CMV polyradiculopathy (involving the oculomotor nerve exit zone),¹⁷⁵ leptomeningeal lymphoma,^{184,188} and Burkitt's lymphoma.¹⁸⁹ Episodic third nerve palsy has been reported in cryptococcal meningitis occurring in AIDS and was attributed to elevated intracranial pressure.¹⁹⁰

Trochlear nerve palsy is rare in AIDS and has been reported with CNS toxoplasmosis, varicella zoster cryptococcal meningitis, primary HIV infection, and lymphoma. Ischemic trochlear nerve palsy was described in an HIV infected individual on anti-retroviral therapy.¹⁹¹ Bilateral trochlear nerve palsy has been reported in HSV1 brainstem encephalitis¹⁷⁴ and in cryptococcal meningitis¹⁹² from post inflammatory shrinking of the arachnoid that stretched the fourth nerve at its emergence from the dorsal midbrain. Bilateral trochlear nerve palsy was also seen in primary CNS lymphoma invading the dorsal mesencephalon and producing hydrocephalus.¹⁹³

The abducens nerve is the most commonly affected cranial nerve in HIV/AIDS. It has been reported in toxoplasmosis,¹⁹⁴ cryptococcal meningitis,¹⁹⁵ tuberculosis, histoplasmosis, herpes encephalitis, primary HIV infection, and meningeal lymphomatosis.¹⁸⁴ Neurosyphilis can rarely affect the abducens nerve.¹⁹⁶ Abducens nerve palsy in AIDS has also

Table 1 Summary of the neuro-ophthalmic manifestations of afferent visual pathway disease in patients with HIV/AIDS

	Manifestations	Treatment
Primary HIV optic neuropathy	Papillitis, retrobulbar optic neuritis, neuroretinitis	HAART
Infectious optic neuropathy		
CMV	papillitis with peripapillary retinitis, retro-bulbar neuritis	Intravenous foscarnet/gancyclovir or oral valacyclovir
Toxoplasmosis	Papillitis, retro-bulbar optic neuritis and neuroretinitis often with retinochoroiditis	Systemic therapy – sulphadiazine, pyrimethamine, clindamycin, trimethoprim-sulphamethoxazole, minocycline; Intravitreal clindamycin
Herpes zoster	Optic neuritis (papillitis, retrobulbar optic neuritis and neuroretinitis); herpes zoster ophthalmicus (HZO); acute retinal necrosis (ARN), progressive outer retinal necrosis (PORN)	Intravenous acyclovir, alternatively IV foscarnet and gancyclovir
Herpes simplex	Papillitis and optic atrophy in association with ARN, PORN	Intravenous acyclovir, alternatively IV foscarnet and gancyclovir
Syphilis	Papillitis, retrobulbar optic neuritis, neuroretinitis, optic perineuritis, optic nerve syphiloma	Procaine penicillin G and probenacid
Cryptococcus neoformans	Papillitis, retrobulbar optic neuritis, optic perineuritis and chiasmitis	Intravenous amphotericin b and 5-flucytosine, oral fluconazole, oral itraconazole
Others: Mycobacterium tuberculosis, Hepatitis B, Histoplasmosis, Bartonella	Papillitis, retrobulbar neuritis, neuroretinitis	Treat underlying cause
Other optic neuropathy	Loss of vision with optic nerve swelling or pallor	No specific treatment except treatment of underlying cause such as lymphoma if found
Anterior ischemic optic neuropathy		
Infiltrative optic neuropathy		
Optic atrophy		
Retrochiasmal pathway lesions (meningitis, encephalitis)	Papilledema	Treat underlying disorder
Toxoplasmosis, CMV, Cryptococcosis, Neurosyphilis, Tuberculosis, Progressive multifocal leukoencephalopathy, Lymphoma	Visual field defects (homonymous) Cortical blindness	
HIV-Neuro-retinal disorder	Retinal nerve fiber layer defects Retinal nerve fiber thinning	HAART
Other disturbances of visual function	Abnormal contrast sensitivity Abnormal color vision Abnormal VEP	No specific therapy; HAART

Abbreviations: ARN, Acute retinal necrosis; CMV, Cytomegalovirus; HIV/AIDS, Human Immunodeficiency Virus/acquired immune deficiency syndrome; HZO, Herpes Zoster Ophthalmicus; PORN, Progressive outer retinal necrosis; VEP, Visual Evoked Potential.

been reported with petrous apex involvement (Gradenigo's syndrome)^{197,198} and with lymphomatous involvement of the cavernous sinus.¹⁹⁹

Peripheral seventh nerve palsy can occur at any stage of HIV infection^{9,200} including the very early stages before sero-conversion. Unilateral and bilateral peripheral facial palsies have been reported to be the presenting features of HIV.²⁰¹ Neurologic prognosis for recovery in these cases is good. Etiologic cause of the peripheral seventh nerve palsy in AIDS patients include HIV encephalopathy,²⁰² Herpes zoster infection,^{200,203} cryptococcal meningitis, neurosyphilis,²⁰⁴ and meningeal lymphomatosis.^{184,205} Not infrequently, neurosyphilis can produce palsies of the seventh and eighth cranial nerves.^{196,206}

Multiple cranial neuropathies can also result from involvement of the cavernous sinus and orbital apex from

lymphomatous infiltration and secondary infections in HIV/AIDS. Bilateral enlargement of cavernous sinuses from lymphomatous infiltration was described in an HIV positive patient who presented with bilateral fifth and sixth nerve palsies.²⁰⁷ Complete ophthalmoplegia with ptosis was reported in an HIV positive patient from Burkitt's lymphoma infiltrating the cavernous sinus.²⁰⁸ A 3½-year old boy with complete ophthalmoplegia in one eye and sixth nerve palsy in the other was found to have non-Hodgkin's lymphoma in the nasopharynx extending into the ethmoid sinus and medial orbits.¹⁹⁹ Other causes of cranial neuropathy from involvement of the cavernous sinus and orbital apex include herpes zoster ophthalmicus,²⁰⁹ eosinophilic granuloma of the cavernous sinus, superior orbital fissure and orbital apex,²¹⁰ and sino-orbital aspergillosis.²¹¹

Table 2 Summary of the neuro-ophthalmic manifestations of efferent visual pathway disease in patients with HIV/AIDS

	Manifestations	Treatment
Supranuclear defects	Saccadic abnormalities Smooth pursuit abnormalities Convergence insufficiency Opsoclonus myoclonus ataxia syndrome Dorsal midbrain syndrome, Internuclear ophthalmoplegia, Gaze palsy-Horizontal and vertical, Cranial neuropathy, Nystagmus	HAART Convergence exercise Lorazepam, immunoglobulins, prednisone Treat underlying cause
Nuclear and infranuclear defects		
Oculomotor nerve palsy	Toxoplasmosis, cryptococcosis, tuberculosis, herpes zoster, CMV, polyradiculopathy, Leptomenigeal lymphoma, Burkitt's lymphoma	Treat underlying cause Strabismus surgery if needed
Trochlear nerve palsy	Toxoplasmosis, varicella zoster, Cryptococcal meningitis, Primary HIV infection, HSV I brainstem encephalitis, lymphoma, ischemia	Treat underlying cause Strabismus surgery if needed
Abducens nerve palsy	Toxoplasmosis, cryptococcal meningitis, Tuberculosis, Histoplasmosis, Herpes encephalitis, Neurosyphilis, Primary HIV infection, Meningeal lymphomatosis	Treat underlying cause Strabismus surgery if needed
Facial nerve palsy	HIV, herpes zoster infection, Cryptococcal meningitis, Neurosyphilis, Meningeal lymphomatosis	Treat underlying cause Protect corneal exposure
Multiple cranial neuropathies	Brainstem encephalitis Cryptococcal meningitis Toxoplasmosis Multifocal CMV encephalitis Neoplastic meningitis Cavernous sinus and orbital apex lesions	Treat underlying cause
Muscle disease	CPEO like syndromes from HAART	Ptosis – surgical repair Withdraw offending agents or use alternate HAART drugs
Pupillary abnormalities	Abnormal pupil cycle time Holmes Adie's pupil Horner's syndrome Light near dissociation (syphilis)	No specific treatment

Abbreviations: CMV, Cytomegalovirus; CPEO, chronic progressive external ophthalmoplegia; HAART, highly active antiretroviral therapy; HIV, Human Immunodeficiency Virus; HSV, Herpes simplex virus.

Chronic progressive external ophthalmoplegia (CPEO)

CPEO- like syndromes consisting of ptosis and ophthalmoplegia occasionally occur in patients with long-standing HIV infection especially with long-term treatment with HAART.^{212–214} It has been postulated that these syndromes may develop from accumulated mitochondrial toxicity induced by the anti-retroviral drugs and superimposed upon a preexisting subclinical genetic mitochondrial disorder.²¹³ Lipodystrophy is an adverse effect of HAART that usually precedes the development of ophthalmoplegia in these cases. Improvement has been documented by withdrawing the offending agents or by using alternative regimens.

Pupillary abnormalities

Pupillary abnormalities seen in HIV/AIDS include light-near dissociation secondary to syphilis and other opportunistic infections,⁴⁰ bilateral Holmes-Adies pupil (believed to be secondary to loss of ganglion cells in the parasympathetic ciliary ganglia from autonomic HIV neuropathy)²¹⁵ and Horner's

syndrome.^{40,216} Abnormalities of the pupil-cycle time in HIV infected subjects and controls demonstrated dysfunction in the pupil reflex arc²¹⁷ which indicates subclinical ocular autonomic dysfunction starting in the early stages of HIV infection.

Screening

There are no specific screening guidelines for neuro-ophthalmic manifestations in HIV-AIDS, although protocols for other ocular manifestations such as CMV retinitis exist. Ocular screening (particularly aimed at CMV retinitis) at onset of AIDS and 3–6 monthly thereafter has been proposed.^{218–220}

With reports of subclinical visual dysfunction such as retinal nerve fiber layer loss in HIV neuro-retinal disorder, we recommend a comprehensive ocular examination at baseline and annually thereafter for patients without AIDS. All patients with AIDS, especially neurological AIDS should be screened at 3–6 monthly intervals. Screening should include assessment of visual function (acuity, color, contrast and fields), ocular motility, anterior and posterior segment examination, and examination of ocular adnexa, pupils and retinal nerve fiber layer thickness.

Conclusion

Neuro-ophthalmic manifestations of AIDS are protean and complex and could involve any part of the afferent and efferent system. The bulk of the problems arise from opportunistic infections and malignancies. However, HIV itself may be the underlying cause in some cases. Adequate ocular screening protocols for neuro-ophthalmologic manifestations currently do not exist. The authors propose a comprehensive ocular screening examination at baseline and periodically thereafter.

Disclosure

The authors report no conflict of interest in this work.

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