HIV and ophthalmology: An overview

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It is quite remarkable, apparently, that overlooking worldwide the articles about HIV correlated ocular diseases and the ophthalmological field in general, we can notice a decrease of frequency of such references, slowly year after year. What happened then? Lack of interest?

AIDS patients, or simply HIV positive individuals, can be affected by several ocular diseases, the most various, mostly because of opportunistic ones. Historically the first scientific publications about HIV correlated ocular pathologies have been described back in 1982: since then, both the incidence and the severity of most HIV related ocular affections, particularly the most frequent of all, Cytomegalovirus (CMV) retinitis, underwent deep changings from 1997 because of the “Highly Active Antiretroviral Therapy” (HAART). Before the introduction of HAART, 30 up to 40% of patients developed CMV retinitis during their lifetime. Prior to HAART, CMV retinitis resulted in substantial visual morbidity. The risk of CMV infection was correlated to the severity and duration of immunosuppression, so that in patients with a CD4+ cells counts inferior than 100/mm³ for 2 years, the probability was up to 21%. After the introduction of HAART the incidence per year of CMV in AIDS patients dropped as much as seven times, and now it is estimated to be around 3.5%.

EPIDEMIOLOGY

In a broad retrospective american study, published in 1998 by W.G. Hodge et al., the incidence of ocular pathologies is compared between HIV positive and HIV negative patients: it has been demonstrated that the only opportunistic statistically more frequent ocular disease in the HIV positive group was the Cytomegalovirus (CMV) retinitis, whereas the other infections had the same frequency, if not inferior, compared to the HIV negative population. Emphasizing once again, the introduction of HAART determined a drastic reduction of CMV retinitis patients. Therefore, even though maintaining its full seriousness, such disease has diminished its psychological impact. Furthermore, the retinal microangiopathy, a non infective ocular disease, represents a typical outcome in HIV positive patients. It is in fact the most common retinal alteration we can see during the fundus examination in AIDS patients. Such vascular changings are reversible and do not determine visual impairment.

All the other intraocular diseases occurring in HIV positive individuals do not show a different incidence from the general population, but they can have a different clinical course and prognosis. Among them Varicella-Zoster retinitis, and less frequently Toxoplasma Gondii, Pneumocystis Carinii, Candida Albicans, Treponema pallidum and Mycobacterium Tuberculosis retinitis.

Considering the ocular adnexa, two ocular diseases can occur: the one caused by Molluscum Contagiosum and Kaposi sarcoma, both slightly more frequent in HIV positive individuals.

Among ocular pathologies occurring only in AIDS patients, it is important to mention the diseases related to the use of specific drugs such as the “Cidofovir iridocyclitis”. Cidofovir is an antiviral drug specifically used against the Herpes Viridae group (like CMV) and an ocular inflammatory syndrome in eyes with CMV retinitis termed Immuno Recovery Uveitis which can cause substantial vision loss.

Immune Recovery Uveitis (IRU) is characterized by vitritis and posterior segment complications.
thereof, most commonly cystoid macular edema (CME) and/or epiretinal membrane formation. Preretinal neovascularization, papillitis, proliferative vitreoretinopathy, and anterior segment inflammation, sometimes with iris synechiae and cataract, have been reported in a smaller number of cases. Symptoms typically include floaters and/or vision loss, the latter usually of a moderate degree, but occasionally severe. In addition to immune recovery, involvement of a large proportion of the retina with CMV retinitis and prior use of cidofovir have been reported to be risk factors for IRU. Preliminary reports have suggested that CME associated with IRU is responsive to regional corticosteroid therapy in about 50% of cases. Results have been mixed as to whether anti-CMV therapy results in improvement in this setting. Reports of the prevalence of IRU from large HAART-era series are not available, and estimates the incidence of IRU based on a large single-center cohort studies have differed considerably, ranging from 0.11% per person-year to 0.83% per person year.

**HIV MICROANGIOPATHY**

The most frequent retinal alteration in HIV patients. Patients with AIDS may have ill-defined visual symptoms consistent with dysfunction of the retina or optic nerve, or both, despite having normal visual acuity. This has been assessed with the Farnsworth-Munsell 100-Hue color-vision and contrast-sensitivity tests in AIDS patients with normal Snellen distance and near visual acuity, at various stages of their disease. Cotton-wool spots, the most common manifestation of non-infectious HIV retinopathy, may be a cause of visual dysfunction; infarctions may permanently damage the regions of nerve fiber layer, retinal ganglion cells, and the inner nuclear layer. Cotton-wool spots are more common in patients with AIDS than in patients with AIDS-related complex and uncommon in HIV-positive control subjects. Cotton-wool spots correlate with immune dysfunction, as patients with cotton-wool spots have lower T-helper/suppressor cell ratios and are in more advanced clinical stages of HIV infection. Examining optic nerves of patients with AIDS in the laboratory, preliminary evidence of a loss of axons even in eyes without infectious retinitis can be found. At fundus examination the lesions appear as cotton-wool nodules, microaneurisms, retinal small haemorrhages both deep and superficial associated to non-perfused areas.

The cotton-wool nodules can be single or multifocal, unilateral or bilateral ad are sited mostly along the vascular arcades at the posterior pole or in the peripapillary area. All these findings are the expression of microinfarctions of the nerve fiber layers, whereas the microaneurisms and the deep retinal haemorrhages, mostly found in the retinal periphery, are expression of circulatory failure. Patients with AIDS have significant visual impairments in color vision and contrast sensitivity according to the tests mentioned. To explain the nature of such lesions, a direct damage of the endothelial cells in retinal vessels caused
by HIV virus has been described and/or a major haematic hyperviscosity descending from circulating immunocomplexes (deport vasculopathy). Microangiopathy seems to be more frequent in patients with less than CD4+ cells counts of 100/mm³. These vascular changings seem to be self-limitant and reversible as a whole and do not need any medical or surgical treatment.

**CYTOMEGALOVIRUS RETINITIS**

Cytomegalovirus (CMV) retinitis, the most common intraocular infection in patients with Human Immunodeficiency Virus disease, was estimated to affect 30% of person with AIDS before the availability of HAART. Prior to HAART, CMV resulted in substantial visual morbidity. In the era of HAART, the incidence of CMV retinitis has declined by approximately 75% to 90%, and the progression of CMV retinitis for patients who use HAART has substantially improved, with a lower risk of retinitis progression, retinal detachment (RD), vision loss, and mortality. Although anti-CMV agents halted the progression of retinitis, maintenance therapy with anti-CMV agents was required because of chronic immunodeficiency, and progression of retinitis is common despite treatment prior to HAART era.

Infact, prior to HAART, the median time to visual acuity of 20/50 or worse among eyes with CMV retinitis was approximately 8 months, and the median time to visual acuity of 20/20 vision was 13 months.

Treatment with HAART suppresses Human Immunodeficiency Virus replication in the blood, which may allow for immune recovery and the restoration of specific anti-CMV immunity. Immune recovery has resulted in a declining number of opportunistic infections, including as approximate 75% reduction in the number of new cases of CMV retinitis.

Nowadays, new cases of retinitis or recurrences are only reported in patients with a recent AIDS diagnosis or in those who cannot undergo HAART treatment with CD4+ cells count less than 100/mm³.

**Ophthalmoscopy**

Typically the fundus is characterized by retinal white-yellowish exudates, haemorrhages, edema and occlusive vasculitis without vitritis. The infection produces retinal necrosis and a complete atrophy. In clinical practice, diagnosis is certain after fundoscopy, CD4+ cell counts and the existence of other localizations such as exophagus or enteric ulcers, pneumonia, encephalitis or systemic signs of CMV infection. We can also analyze the aqueous of the anterior chamber to confirm the presence of CMV viral DNA through the Polymerase Chain Reaction (PCR). Differential diagnosis must be done with other viral retinitis such as Herpes Simplex, Varicella-Zoster, Toxoplasmosis and parcellar venous occlusions.

**Treatment**

The first drug to be used were ganciclovir (5mg/Kg and foscarnet (90mg/Kg) twice a day intravenously for 14/21 days. The maintenance therapy with same dosage once a day for longer period. At the same time, when possible, a HAART treatment has to be performed, determining a rapid immunorecovery. In some localized severe retinitis, critical for the visual prognosis as in the macula or in the optic nerve, an intravitreal injection of ganciclovir can be performed with the aim of stopping more rapidly the progression of the lesion.

The ganciclovir implant (Vitrasert-Bausch and Lomb), is an effective treatment for CMV retinitis in severely immunosuppressed patients with AIDS. It releases ganciclovir slowly into the vitreous humour until the implant is depleted of drug after approximately 8 months. The ganciclovir implant was developed before the era of HAART, when media patient survival was approximately 12 months and long-term complications of the implant were not major concerns. With introduction of HAART, life expectancy for patients with AIDS has increased substantially, and treatment strategies for the management of CMV retinitis have been reassessed. Because patients may not require specific anti-CMV therapy after immune reconstitution with HAART, the ganciclovir implant usually is not used as initial therapy in HAART-naïve patients who present with AIDS related CMV retinitis.

Cidofovir showed to be a powerful drug against CMV-retinitis; thanks its long emilife, administration every 15 days intravenous permits to achieve a stable viral suppression.

Nevertheless, after a few days or months after treatment, iridocyclitis with synechiae and bulbar hypotonies have been described. These uveal reactions can be easily controlled with topic corticosteroids or by stopping the treatment. Ganciclovir and foscarnet, the 2 first drugs currently approved for treating CMV retinitis, have significant disadvantages. Both require intravenous administration with the problems and inconveniences of long-term intravenous access. Neither drug is virucidal so that relapse invariably occurs after prolonged administration. Both have significant toxicity which has limited their usefulness. Ganciclovir causes dose-dependent myelosuppres-
sion, requiring dose reduction or interruption of treatment in approximately one third of treated patients. The side effects of foscarnet are more pronounced including nausea, vomiting, headache, nephrotoxicity, and electrolyte imbalance. Nevertheless, both drugs are effective in long-term control of CMV retinitis. There is also evidence that both drugs prolong survival, presumably by suppressing systemic CMV infection.

For these reasons, there has been interest in developing local forms of treatment for CMV retinitis. Intravitreal injection of ganciclovir was first reported in 1987. Long term treatment of CMV retinitis is possible with this approach. With the development of myeloproliferative growth factors (G-CSF) and the availability of foscarnet, the need of intravitreal therapy has been reduced significantly. Nevertheless, there are situation where intravitreal ganciclovir or foscarnet may be used to supplement or replace intravenous treatment. The need for repeated injections, the risk of systemic CMV infection, and the potential complication of endophthalmitis have limited the usefulness of intravitreal injections.

The search for a better form of local CMV treatment continues. The development of ganciclovir implants by Sanborn et al. in 1992 was a significant advance. The surgically implanted device may control CMV retinitis for up to 8 months. Studies currently are under way using oral ganciclovir combined with the ganciclovir implant. By suppressing systemic CMV infection, this form of local therapy becomes even more attractive. Intravitreal injection of liposome-encapsulated ganciclovir is another approach that may prolong treatment effect and reduce the frequency of injections. Cidofovir is an acyclic nucleoside phosphonate ana-
logue with broad spectrum anti-DNA virus activity. It is a potent inhibitor of CMV in vitro with 10 times the activity of ganciclovir and 200 times the activity of foscarinet. Unlike foscarinet and ganciclovir, cidofovir has a prolonged anti-viral effect, making less frequent dosing possible. Toxicity studies have shown that intravitreal doses up to 100 micrograms are tolerated in animals. Cidofovir may be effective in patients with ganciclovir resistant CMV because it does not require virus-specific phosphorylation for its activity. One of the first studies about cidofovir in intravitreal use (Kirsch and co-workers) shows that it is effective in long-term treatment of CMV retinitis. It is important to

**Fig. 1.** A (top left): Posterior pole of the right eye at initial examination showing 500-μm area of deep retinitis and choroiditis superior to fovea and a 1-disc diameter lesion along the superior temporal arcade vessel. B (top right), C (middle left): Posterior pole of the left eye at initial examination showing ill-defined deep retinitis at the inferior nasal margin of optic disc, and 100 micron lesion superior and temporal to fovea.

**Fig. 2.** A (middle right), B (bottom left), C (bottom right): One week after initial examination note progression of the lesions in both eyes. The retinal vessels still remain uninvolved.
emphasize that this clinical trial was conducted in an unrandomized, unmasked and uncontrolled fashion. Patients were selected with active CMV retinitis who had either had a relapse or who were intolerant of intravenous therapy. Patients who were non compliant or refused intravenous therapy also were included. The standard for comparison of any form of treatment of CMV retinitis is the time of progression. This usually is defined as the expansion of an existing lesion by 750 micrometers or the appearance of a new lesion at least 750 micrometers in size. In this study, the median time to progression after a single injection was 55 days. This compares favourably with the results for systemic treatment with ganciclovir and foscarnet (56 and 59 days respectively). After a second injection, the median time to retinitis progression was 63 days, suggesting no resistance to the antiviral effect.

Local side effects include mild iritis and a significant decrease of intraocular pressure (IOP). The iritis was controlled with topical steroids. The decline of IOP was unrelated to inflammation. The authors believe the IOP-lowering effect may be mediated by inhibition of the ciliary epithelium. Similar effects on the renal tubule were seen during systemic administration of cidofovir. Probencid was used in this trial specifically to counteract the effect on the ciliary epithelium.

VARICELLA-ZOSTER VIRUS

It is well known that zoster virus occurs more frequently in immunocompromised subjects. On the contrary no incidence difference has been observed between HIV patients and the general population. Clinically, retinitis can occur in two forms, Acute Retinal Necrosis or Progressive...
Outer Retinal Necrosis secondary to varicella-zoster virus; it is likely that there are two different clinical appearance of the same disease, so that in patients with CD4+ cells counts more than 50 cell/mm³ develops an Acute necrosis retinitis, whereas with CD4+ cells counts inferior than 50 cell/mm³ appears as Progressive outer retinal necrosis (POR n). Funduscopic examination reveals multifocal lesions which can be numerous in the peripheral retina from 100 to 200 micrometers of diameter.

Retinal vascular involvement does not occur early in the course of this disease. The syndrome progresses rapidly, with lesions enlarging and becoming confluent, despite therapy with intravenous acyclovir, ganciclovir or both. Retina appears pale, oedematous, necrotic with few haemorrhages. Typical is a clear vitreous cavity. The lesions originate from the periphery and they rapidly merge toward the posterior pole affecting not always the macula, the visual prognosis is generally poor, the visual acuity mostly drops to counting fingers secondary to retinal and optic atrophy, furthermore to light perception in the most severe cases.

TOXOPLASMA GONDII

Toxoplasmosis choroiditis occurs with the same incidence both in HIV-patients and in the general population, no matter how is the CD4+ cells counts. Nevertheless, unlike ocular toxoplasmosis in immunocompetent individuals, the retinal lesions in patients with AIDS are extensive and can cause visual impairment if left untreated. The infection can be generalized, involving the brain, eyes, lungs, heart, digestive tract, lymphnodes, liver, spleen and bone marrow. Cerebral toxoplasmosis is the most common infection in AIDS and requires urgent treatment because it can be rapidly fatal. The prevalence of toxoplasmosis varies according to dietary habits, and therefore, from country to country.

Active toxoplasmosis choroiditis lesions consists of yellow-white, oedematous areas of necrotizing retinitis. The lesions have fluffy borders, few scattered intraretinal haemorrhages and occasional vascular sheathing. Usually this is accompanied by overlying vitreal inflammation reaction, with extensive haze. Inactive lesions consist of atrophic chroids and retina with epithelial pigment clumping and occasional vitreal strands; they occur on both sides of the vascular arcades at the posterior pole.

The treatment consists of combination of pyrimethamine with either sulfadiazine or clindamycin administered orally. Folinic acid has to be added in every case. Like other opportunistic lesions in AIDS, toxoplasmosis recurs when therapy is discontinued; treatment therefore consists of two phases: an induction regimen to obtain complete healing of the retino-choroidal toxoplasmasmic lesions, followed by a maintenance regimen. The daily dosage in the induction phase usually is 50mg of pyrimethamine, 4 to 6g. of sulfadiazine ad 2,4g. of clindamycin. Maintenance therapy consists of 25 or 50mg pyrimethamine per day, combined with sulfadiazine or clindamycin given at half dosage, or less, according to patient's
tolerance. Maintenance therapy is to be continued as long as possible. Corticosteroids are generally not used.

MOLLUSCUM CONTAGIOSUM

Molluscum contagiosum eyelid lesions are also associated with AIDS. These findings are usually seen in individuals who previously have been diagnosed with AIDS and the skin lesions are often considered to be a marker of late-stage disease. Nevertheless, ophthalmologists often are the first medical personnel to check HIV antibodies for suspected CMV retinitis, Kaposi Sarcoma of the conjunctiva and molluscum contagiosum of the eyelids. Atypical abundant confluent molluscum contagiosum lesions on the eyelids also warrant HIV antibody testing along the comprehensive ophthalmic examination including dilated ophthalmoscopy which must be always be performed.

In a study of 1996 of David G. Gritz et al. to determine whether there are quantitative or qualitative differences in the ocular flora of patients with AIDS compared with Human Immunodeficiency Virus–negative patients, no differences were observed in the types or numbers of organisms isolated from the conjunctiva or lids. Ocular flora was not influenced by use of systemic antibiotics, level of immunosuppression as measured by CD4 lymphocyte counts, keratoconjunctivitis sicca or other ocular-surface disease.

CONCLUSIONS

The changes in the AIDS epidemic are having a substantial effect in the field of ophthalmology. The most evident is a declining incidence of CMV retinitis (from 1992 to 1997 a decrease of 55%, from 1997 to 2005 another 41% dropdown). The most likely explanation is the consequence of improved immune function in patients on HAART.

To understand how new treatment for AIDS have affected the ocular manifestations of AIDS, it is important to understand these manifestations before the availability of new treatments. As the life span of patients with AIDS increases and the incidence of CMV retinitis decreases, other causes of vision loss will assume increasing importance.

Mueller and associates, suggest that HIV-infected patients, even those with good visual acuity, will have subtle abnormalities on a variety of visual tests. The pathogenesis of this problem is still unknown, although a cumulative insult from HIV retinopathy or a direct HIV toxicity on visual structures have both been suggested.

In conclusion, this era is one of transition of the treatment of patients with HIV infection and, in particular, of patients with AIDS. These changes have already affected and will continue to affect the field of ophthalmology for the next several years. Multiple issues have been raised, many of which do not yet have answers, and studies will be needed to help resolve them. (Douglas et al. AIDS and Ophthalmology).
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