

## HIV/Syphilis Coinfection in Patients with Uveitis

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### ABSTRACT

Ocular syphilis has reemerged as an important cause of uveitis, associated epidemiologically with human immunodeficiency virus infection. To determine the HIV / syphilis coinfection in Cuban patients with uveitis in the period of one year. The study was conducted in patients with intraocular inflammation examined in the uveitis service of Cuban Institute of Ophthalmology "Ramón Pando Ferrer", a one-year period. For detection of antibodies against HIV, a diagnostic algorithm was applied, including screening tests by means of the third and fourth generation enzyme linked immunosorbent assay, and western blot confirmatory tests for HIV-1 and HIV-2. For serological diagnosis of syphilis, the samples confirmed as positive for HIV were subjected to non-treponemal and treponemal tests. A total of 95 serum samples of patients with uveitis were evaluated, three of which were positive for both syphilis and HIV-1. In all three cases, uveitis presented bilateral form. Uveitis in two patients presented as posterior uveitis and the other one as panuveitis. CD4 + values ranged from 250 to 409 cells /mL. These findings hold that uveitis can often lead to the diagnosis of HIV infection and syphilis. They also corroborate that intraocular inflammation in patients co-infected with HIV / syphilis can occur severely, so it is necessary to diagnose infections early and apply appropriate treatment to prevent irreversible complications.

**Keywords:** HIV/syphilis coinfection, human immunodeficiency virus, syphilis, uveitis, ocular syphilis

### INTRODUCTION

Uveitis is inflammation of the internal ocular structures and the most common form of inflammatory eye disease. It has a considerable impact on visual health, being responsible for 2.8-10% of blindness in much of the world. Its etiology can include alterations of the immune system or infectious diseases.<sup>[1]</sup>

*Treponema pallidum* is the etiologic agent of syphilis, one of the infections related to inflammation of the uveal tract. Syphilitic uveitis has recently regained attention due to the reemergence of syphilis worldwide. In the clinical course of this infection, four stages are

described: primary, secondary, latent and tertiary syphilis. Ocular syphilis is very rare, it is equivalent to 1-2% of uveitis and can occur at any stage except the primary one, but it is more frequent during the secondary or latency stages. However, syphilitic uveitis can manifest itself clinically in various ways, often leading to delay in diagnosis and treatment, resulting in a serious ocular complication and irreversible loss of vision.<sup>[2]</sup>

Syphilis is currently epidemiologically associated with human immunodeficiency virus (HIV) infection. Both are considered sexually transmitted infections (STIs) with significant

morbidity and mortality in the younger sectors of the population. According to the World Health Organization (WHO), 36.9 million people lived with HIV in 2017 and estimates that annually there are about 357 million new cases of STIs in the world, of that total, 5.6 million are due to syphilis.<sup>[3,4]</sup>

HIV infection can modify the response to treatment of *T. pallidum* infection and clinical development, favoring atypical clinical pictures. In coinfecting individuals, an increase in ophthalmic and neurological conditions may be common early.<sup>[5]</sup>

Due to the fact of not finding enough reports of studies in Cuba on HIV / syphilis coinfection in patients with intraocular inflammation, and the importance of early diagnosis of these cases, it was proposed to determine coinfection by these sexually transmitted pathogens in Cuban patients with uveitis within a year.

### MATERIALS AND METHODS

A descriptive and cross-sectional study was carried out in patients with intraocular inflammation examined in the uveitis service of the "Ramón Pando Ferrer" Cuban Institute of Ophthalmology, in a period of one year.

For the detection of antibodies against HIV, the diagnostic algorithm established in Cuba was applied, which includes screening tests by means of the third and fourth generation enzyme-linked immunosorbent assay (ELISA), and confirmatory by western blot for HIV-1 and HIV-2.<sup>[6]</sup>

Non-treponemal and treponemal tests were performed on the samples confirmed as positive for HIV, which detect nonspecific and specific antibodies, respectively, taking into account the methodology used in Cuba to establish the diagnosis of syphilis.<sup>[6]</sup>

An epidemiological survey was applied to the patients included in the study and demographic, clinical and epidemiological data were obtained. The variables analyzed were: age, sex, sexual orientation, location and laterality of intraocular inflammation, and CD4 cell levels.

### RESULTS AND DISCUSSION

A total of 95 serum samples from patients with uveitis were evaluated, seven (6.6%) were confirmed positive for HIV-1 and three (3.2%) of them showed reactivity also for syphilis. No patient was HIV-2 seropositive.

The average age of patients with uveitis and coinfecting with HIV / syphilis was 55 years in a range between 49 and 65 years of age. The three

patients are male, two (66.7%) of them are men who have sex with other men (MSM).

When analyzing the characteristics of the ocular lesions, it was evidenced that in one of the patients the inflammation presented as posterior uveitis (33.3%) and in the rest as panuveitis for 66.7%. Regarding the laterality of the uveitis, it was bilateral in the three patients. CD4 + values ranged from 250 to 409 cells/mL (average 320 cells/mL).

The study determined that 3.2% of patients with uveitis were co-infected with HIV / syphilis. Currently both STIs, due to their high incidence, constitute a serious public health problem. Recently, the Center for Disease Control (CDC) reported a significant increase in cases of primary and secondary syphilis co-infected with HIV<sup>[7]</sup>. Likewise, in studies evaluating HIV/STI coinfection carried out in Cuba between 2015 and 2016, they showed that syphilis was the most frequent STI associated with HIV infection<sup>[8,9]</sup>. In addition, in a study of the behavior of ophthalmological diseases in patients with HIV-AIDS at the Cuban Institute of Ophthalmology "Ramón Pando Ferrer", stated that ocular syphilis was the most frequent ophthalmological disease<sup>[10]</sup>. In contrast, in the tertiary uveitis service at Tianjin Medical University Eye Hospital, between 2011 and 2016, of 27 patients with syphilitic uveitis, only one was HIV positive.<sup>[11]</sup>

Concomitant HIV infection and syphilis were diagnosed in the three co-infected patients in the study based on evaluation of uveitis. Similarly, in a series of cases in the United States and Europe, it was shown that 52% of patients received the diagnosis of HIV infection in conjunction with the diagnosis of syphilis<sup>[12]</sup>. These results and those described by other authors<sup>[13, 14, 15]</sup> suggest that ocular syphilis may be the first manifestation of HIV infection and that frequently the ophthalmological evaluation can lead to the diagnosis of infection by this retrovirus.

There are several hypotheses regarding the increase in the dual infection of HIV and syphilis. Both infections have similar transmission mechanisms and risk factors, and there is also evidence that suggests a synergism between the two pathogens. Syphilis facilitates the transmission of HIV by breaking the protective mucosal barrier with the formation of the syphilitic chancre that functions as a gateway for HIV and recruits susceptible immune system cells to the site of infection,

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allowing easy access of the virus to the blood circulation of the host and promotes viral replication. For its part, HIV can modify the natural course of syphilis in these patients by modulating the immune response to *T. pallidum*, favoring the development of more aggressive manifestations, rapid progression to the tertiary stage, shortening the latency period, for what is common in these patients is primo-secondaryism that leads to ocular and central nervous system involvement.<sup>[16,17]</sup>

The mean age of the patients at work (55 years) differs from the mean age of the patients studied by Zhang<sup>[11]</sup> and Widdrington<sup>[17]</sup>, which was 45.5 and 49.7 years of age, respectively.

The increase in high-risk sexual behavior results in an increase in the rate of STIs, including syphilis, among people living with HIV / AIDS. During the last decade, the proportion of syphilis infection has increased particularly in MSM<sup>[11,15,17,18]</sup>. The results of the research are consistent with the previous approach and with the results of a national study on venereal syphilis in MSM carried out at the Hospital Center of the Institute of Tropical Medicine "Pedro Kouri", in which, of 81 individuals with syphilis, 75 were HIV positive. Considering that this center is the reference clinic for the care of this type of patients in Cuba, it justifies that the percentage of HIV-positive people is higher in relation to those who do not present this condition.<sup>[20]</sup>

Although syphilis can affect the eye in different ways, uveitis is the most common ocular presentation. The diagnosis of ocular syphilis is based on ophthalmological findings; however, it is often challenging due to the lack of pathognomonic symptoms<sup>[14]</sup>. Despite the above, in the study there was no diversity in the ocular findings of syphilis since in the three coinfecting patients the posterior segment of the uvea was affected, in the form of panuveitis in 66.7% and the rest of uveitis later, a result that coincides with that of other authors<sup>[14,17,19]</sup>. Similarly, Mathew<sup>[21]</sup> and Hughes<sup>[22]</sup> reported a higher proportion of panuveitis and posterior uveitis in HIV-infected patients than in seronegative patients.

Such findings suggest that HIV infection can modulate the severity of ocular syphilis. Posterior uveitis or panuveitis caused by syphilis can cause severe signs of vision loss or blindness and a high risk of penetration of *T. pallidum* into the central nervous system<sup>[14,15,18,19]</sup>.

Ophthalmological diseases commonly occur in patients with CD4 counts below 200 cells<sup>[23]</sup>. Along the same lines, there are authors who support the association between posterior uveitis and panuveitis with low CD4 cell counts<sup>[11]</sup>. In the study, uveitis in coinfecting patients was not related to CD4+ cell values that ranged between 250 and 409 (average 320 cells/mL), which is consistent with the work of Rose-Nussbaumer<sup>[24]</sup> whose values ranged between 207-1777 cells/mL (median 421 cells/mL) and with Ambou<sup>[10]</sup>, where 44.4% of patients with manifestations of ocular syphilis had values greater than 200 cells/mL.

## CONCLUSIONS

The findings obtained in our work support that uveitis can frequently lead to the diagnosis of HIV infection and syphilis. They also corroborate that intraocular inflammation in patients coinfecting with HIV / syphilis can present in a serious way, which is why it is necessary to diagnose infections early and apply the appropriate treatment to prevent irreversible complications such as loss of vision and the involvement of the central nervous system.

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**Citation:** Juliet María Enriquez Puertas et.al, “HIV/Syphilis Coinfection in Patients with Uveitis”, *International Journal of Research Studies in Medical and Health Sciences.* 2020; 5(9): 10-13.

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