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Evaluation of the incidence of ocular manifestations in HIV-infected pediatric patients: a cross-sectional study

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Abstract

Introduction: Acquired immunodeficiency syndrome (AIDS) is a pandemic affecting about 1.8 million children aged 0-14 years globally (2019). Exposure to human immunodeficiency virus (HIV) occurs in utero, during delivery, and lactation. There is lack of knowledge and information regarding ocular manifestations in HIV-positive children. Aim of the paper was to determine the incidence of ocular manifestations and their correlation with CD4+ count level in HIV-positive children.

Material and methods: A cross-sectional study evaluating ophthalmic manifestations, and correlation of various parameters and severity with ophthalmological findings in HIV-positive children.

Results: For 2 years, 100 HIV-positive children, including 61 boys and 39 girls, were evaluated for ocular manifestations, with most of them aged above 6 years. About 97% of the study's population had CD4+ count above 500 cells/mm^3. The total prevalence of ocular manifestations was 19%, ocular manifestations occurring in the anterior segment was 16%, and 4% had posterior segment ocular manifestations with good visual acuity. Ten (52.6%) patients had molluscum contagiosum, 4 (21%) conjunctival vasculopathy, and 1 (5.2%) each cytomegalovirus retinitis and herpes zoster ophthalmicus.

Conclusions: This comprehensive ocular evaluation, irrespective of the level of visual acuity, showed that there is a possibility for improvement in the guidelines for early detection of HIV, decreasing the transmission of HIV from mother-to-child, early initiation of highly active antiretroviral therapy (HAART) in mothers and children as well as children's adherence to HAART, eye care, screening, and follow-up of HIV-positive children.

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Key words: HIV, CD4+ count, mother-to-child transmission.

Introduction

Acquired immunodeficiency syndrome (AIDS) is a pandemic affecting about 36.9 million globally, out of whom nearly 1.8 million are children aged 0-14 years, as of 2019. According to UNICEF 2022 report, the estimated new child infection rate among children aged 0-14 years in 2020 was 150,000 [1]. The world fell far short of fewer than 20,000 new infections in that age group by the end of 2020. In India, according to National AIDS Control Organization (a division of the Ministry of Health and Family Welfare, Government of India), the total number of people living with human immunodeficiency virus (HIV) is estimated at 1.38 million [2]. In India, 145,000 children younger than 15 years of age are infected with HIV/AIDS, and about 22,000 new infections occur every year. Children account for 7% of all new HIV

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infections, while two fifth (40.5%) of the total HIV infections occur among females. The global highly active antiretroviral therapy (HAART) access among pregnant women coverage has stagnated at around 85% over the past five years, which is far below 95% target for 2020. Moreover, the 54% access to ART in children lags far behind that of adults (74%) and pregnant women (85%). As a result, children continue to be at disproportionately heightened risk of dying from AIDS, as demonstrated by estimated 100,000 deaths among children in 2020. In western countries, mother-to-child HIV transmission has almost been eliminated, but this is not the case in India. According to a study by Nath [3] among pediatric HIV patients in India, mother-to-child HIV transmission occurs in 90% of children. A large number of pregnant females do not seek HIV testing due to social stigma. The annual pregnancy rate in India is 27 million, of which only half attend health services and even less than half of those get tested for HIV. In this pediatric HIV population, there is small percentage of children adhering to HAART. As per Aaparna Mukerjee's research, factors responsible for non-adherence to HAART include lack of disclosure of HIV diagnosis by women and children, deficiency in awareness about prevention of mother-to-child HIV transmission, no adherence to HAART treatment by women and children, and delayed infant diagnosis. Furthermore, delayed infant diagnosis, lack of pediatric drug formulations, and absence of skilled personnel in Indian setting have contributed to poor control of pediatric HIV cases. An estimated 50% of infants infected with HIV at the time of birth will die before the age of two years, while in 2019, about 95,000 children died of AIDS-related illnesses (WHO).

Common anterior segment manifestations in pediatric patients include allergic conjunctivitis, herpes zoster ophthalmicus, dry eye, hordeolum, molluscum contagiosum, and blepharitis. Common posterior segment manifestations are retinal vasculitis, cytomegalovirus (CMV) retinitis, posterior uveitis, toxoplasmosis choroiditis, and tubercular choroiditis. Exposure to HIV infection occurs in utero; post-HAART period treatment of HIV children starts in their early life improving their immunity. There is paucity of knowledge regarding ocular manifestations in HIV-infected children, whether there are any differences in ocular manifestations from those occurring in HIV-positive adults. Therefore, this study was a comprehensive evaluation of ocular manifestations and their correlations with CD4+ count in HIV-positive pediatric population.

The aim of the present study was to determine the incidence of ocular manifestations in HIV-positive pediatric patients, and to correlate CD4+ count level with the incidence of ocular manifestations.

Material and methods

A cross-sectional study evaluating ophthalmic manifestations in HIV-diagnosed children at an urban ophthalmological center was conducted. HIV testing and CD4+ count estimation were done by a pediatrician using standard methods and according to national guidelines. Thorough physician evaluation and detailed ophthalmological examination were performed. Visual acuity estimation using Snellen chart in older children and dilated refraction were carried out in all children; however, in children aged below 4 years, estimation of vision was not possible. Detailed anterior segment examination was done using slit lamp and fundus examinations with indirect ophthalmoscope. The examining consultant determined the presence of specific condition based on clinical findings visualized. Patients' demographic characteristics and HIV status (CD4+ count, HAART treatment) were documented.

Statistical methods

Collected data were analyzed using SPSS statistics software version 23.0 (IBM). To describe data's' descriptive statistics frequency analysis, percentage analysis was applied for categorical variables, and mean and SD were used for continuous variables. For significance in categorical data, χ^2 test was employed. In the above tools, the probability value of 0.05 was considered statistically significant.

Results

In Table 1, demographic characteristics of the study's cohort are presented. For 2 years, 100 HIV-positive patients were evaluated, out of whom, 61 were boys and 39 girls. Forty-one (41%) patients were aged between 0-5 years. The way of HIV transmission in all the patients was mother-to-child. About 97% of the children had CD4+ count above 500 cells/mm^3. Table 2 shows the prevalence of ocular manifestations based on gender and age distribution among the 100 patients. Nineteen (19%) patients were found to have ocular manifestations. The prevalence of ocular manifestations was higher in males (n = 15, 15%) than in females (n = 4, 4%), with a p-value of 0.116 (Table 2). Ocular manifestations were more common in the age group of 0-5 years (13%), with a p-value of 0.021. Of the 100 patients, 19 (19%) were found to have ocular manifestations, with 14 (14%) patients having an anterior segment and ocular adnexal lesions, and 5 (5%) posterior segment pathologies.

The prevalence of vision based on gender, age, duration of HIV infection, and CD4+ count is demonstrated in Table 3. Visual acuity in the age group of 0-5 years was not possible to assess due to patients' age and inability to read Snellen chart. Cycloplegics refraction was done in all children, with refraction reading normal in 95% of children and 5 children having myopia. One 13-year-old patient who manifested with bilateral CMV retinitis and treated with intra-vitreal ganciclovir, had vision less than one meter using finger counting. There was no correlation between CD4+ count and visual acuity in HIV-positive children. P-value was not significant for correlation between visual acuity, age, gender, and CD4+ count.

Table 1. Demographic characteristics of the patients

Factor	*n* (%)
Gender	
Male	61 (61)
Female	39 (39)
Age (years)	
0-5	41 (41)
> 6	59 (59)
CD4+ count (cells/mm^3)	
≤ 200	0 (0)
201-500	3 (3)
501-1,000	36 (36)
> 1,000	61 (61)

Table 2. Prevalence (*n*) of ocular manifestations based on gender and age distribution

Factor	Ocular manifestation	No ocular manifestation	*p*-value
Gender			
Male	15	46	0.116
Female	4	34	
Age (years)			
0-5	13	28	0.021
> 6	6	52	

Ocular manifestation	Anterior segment manifestation	Posterior segment manifestation
19	14	5

Table 3. Prevalence of vision based on gender, age, HIV duration, and CD+ count (*n*)

Vision	Normal 6/6-6/60	Abnormal less than 6/60 PL	Non recordable	*p*-value
Gender				
Male	37	1	23	1
Female	26	0	13	
Age (years)				
0-5	6	0	35	1
> 6 years	55	1	3	
CD4+ count (cells/mm^3)				
< 200	0	0	0	1
> 200	63	1	36	

Table 4. Distributions of ocular lesions based on CD+ count (*n*)

CD4+ count (cells/mm^3)	Ocular manifestation	Infectious etiology	Posterior segment ocular manifestation
< 200	0	0	0
200-500	2	2	0
500-1,000	8	8	2
> 1,000	9	7	3

Table 4 shows distributions of ocular lesions based on CD4+ count and mean CD4+ count of the patients with ocular involvements. As shown in Table 4, each of the items (i.e., ocular manifestation, infectious etiology, posterior segment, and ocular manifestation) were in higher proportion in CD4+ count > 1,000. In the study, about 19 of children had ocular manifestations, out of whom, 17 (90%) had infectious diseases. Posterior segment lesion were in less incidence (15.78%) as compared with anterior segment and adnexal lesions, constituting 89.5%. The lowest CD4+ count was 29, and the highest CD4+ count was 700 cells/mm^3.

Table 5 presents the distributions of individual ocular manifestations and their correlation with CD4+ count. Ocular manifestation was more common in the group with CD4+ count more than 1,000 cells/mm^3. Molluscum contagiosum lids lesion was present in 10 children, constituting the most common ocular manifestation found in the current study. Six of ten children with molluscum contagiosum lesions had a CD4+ count more than 1,000 cells/mm^3. CMV retinitis was present in 1 child with CD4+ count above 1,000 cells/mm^3. Conjunctival vasculopathy, herpes zoster ophthalmicus, and toxo-retinochoroiditis were present in HIV children with CD4+ count more than 500 cells/mm^3.

Table 5. Distribution of individual ocular manifestations and their correlations with CD+ count (cells/mm^3) and *p*-value (*p*-value < 0.005 considered significant)

Diagnosis	< 200	201-500	501-1,000	> 1,000	*p*-value
Conjunctival vasculopathy	0	0	3	1	1
Molluscum contagiosum	0	2	2	6	1
Herpes zoster ophthalmicus	0	0	0	1	1
Uveitis	0	0	0	1	1
CMV retinitis	0	0	0	1	1
Toxo-retinochoroiditis	0	0	1	0	1
Tubercular choroiditis	0	0	0	1	1
Primary optic atrophy	0	0	0	1	1

Discussion

In this cross-sectional study, 100 HIV-positive children were evaluated for ocular manifestations, and all were on HAART, with their CD4+ count estimations available. Ophthalmological evaluation was done regardless of their ocular symptoms.

Age

In the study, 59% patients were in the age group of > 6 years, with mean age of 8 years, which is comparable with the mean age of ocular examination among HIV-positive children in studies by Mohod *et al.* [4] (8-year-old) and Venkatesh *et al.* [5] (9-years-old).

Gender

Boys constituted 61%, and girls 39%, which is line with a study by Mohod *et al.* [4] (64.2% of boys) and Venkatesh *et al.* Venkatesh [5] (73.2% of boys). Demographic patterns in the present study appear to be similar to the Indian national HIV statistics, and hence this study population can be considered as representative.

Duration of HIV

According to Nath [3] study on pediatric HIV patients in India, mother-to-child transmission of HIV occurs in nearly 90% of children. In the current paper, mother-to-child transmission was the most common way of HIV transmission in HIV-positive children; therefore, this study can be considered as representative.

Visual impairment

In the study, all cases had a good visual acuity, except for one patient who manifested with bilateral CMV retinitis at the age of 13 years, who was treated with intra-vitreal ganciclovir.

Total prevalence

The incidence of ocular complications in HIV-infected children varies from 7-75%. The prevalence of ocular manifestations in pediatric patients with HIV in the current study was 19%, as compared with Indian pediatric patients reported by Biswas *et al.* [6] (50%), Venkatesh *et al.* [5] (21%), and in African study by Denney *et al.* [7] (19.8%). The prevalence of ocular manifestations in the present study was comparable with both national and international studies, except for Biswas *et al.* [6].

Types of lesions: anterior and posterior

In the study, the total prevalence of ocular manifestations was 19%, of which 14% had anterior segment involvement and 5% had posterior segment ocular manifestations. Duration of HAART of more than 10 years is a protective factor against development of ophthalmological disease. The aim of antiretroviral treatment is to restore immunity by inhibiting viral replication that reduce the occurrence of ophthalmological disease. In the present research, out of the 19 patients who had any ocular manifestations, 10 (52.6%) had molluscum contagiosum, 4 (21%) conjunctival vasculopathy, and 1 (5.2%) each had CMV retinitis, herpes zoster ophthalmicus, uveitis, toxo-retinochoroiditis, tubercular choroiditis, and primary optic atrophy.

In Biswas *et al.*'s [6] study, the most common ocular lesions were anterior uveitis and CMV retinitis (33% each), followed by retinal detachment (16.6%) and vitreous hemorrhage (16.6%). Mohod *et al.* [4] reported retinal perivasculitis as the most common ocular finding (17.1%), followed by allergic conjunctivitis (12.9%). In Venkatesh *et al.*'s [5] study, the most common ocular manifestation was retinal vasculitis (58.9%; 23/39), followed by molluscum contagiosum (10.2%), corneal opacity (7.6%), and neuro-ophthalmic optic atrophy (7.6%). In the current study, molluscum contagiosum was the most common ocular manifestation, followed by conjunctivae vasculopathy (4%). There was no cases of retinal perivasculitis seen in the study. Mohod

et al. [4] found CMV retinitis in five children and two with bilateral involvement. CMV retinitis was reported by Biswas *et al.* [6] with 4 cases, Venkatesh *et al.* [5] with 3 patients, and Kestelyn *et al.* [8] showed 3 cases. In the present study, there was 1 case of CMV retinitis with bilateral involvement, treated with intra-vitreal injection of ganciclovir and HAART.

In HIV-positive adults, the most common ocular manifestations are HIV retinopathy and CMV retinitis. HIV retinopathy manifestation includes cotton-wool spots, intra-retinal hemorrhage, micro-aneurysm, and exudates. Cotton-wool spots are the most common ocular lesions occurring in 25-50% of AIDS patients, and are confined to the posterior pole near the optic disc. Moreover, cotton-wool spots are thought to be the end result of a chain of events, such as elevated levels of circulating immune complexes, deposition of immune complexes, and resultant micro-vascular lesions ischemia, with final stasis of axoplasmic flow. Retinal hemorrhages are seen in up to 30% of AIDS-infected individuals in the form of flame-shaped lesions in the posterior pole, dot-blot hemorrhages, punctate intra-retinal hemorrhages peripherally, and Roth's spots. CMV retinitis is the most common ocular opportunistic infection affecting approximately 20-40% of HIV-infected patients, and the leading cause of 90% blindness associated with AIDS worldwide. CMV and HIV are found to trans-activate each other, leading to greater degree of immune suppression in HIV patients. This is a possible explanation for why CMV retinitis is more commonly seen in HIV-positive patients, as opposed to non-HIV immune-suppressed individuals. Additional risk factors include CD8+ T lymphocytes counts, higher HIV blood level, lack of antiretroviral therapy, and male gender. It has been observed that HIV patients on HAART with lower than 10 fold decrease in HIV viral loads during the treatment period, are at elevated risk for opportunistic infections, such as reactivation of CMV retinitis. HIV-related retinopathy is an ocular risk factor for CMV retinitis development. It is unclear why cotton-wool spots are not seen in AIDS children; however, Munro *et al.* [9] stated that HIV retinopathy is associated with lower CD4 +count cell and higher plasma HIV RNA levels, but is a non-infectious micro-angiopathy.

In the current study, since all the children had CD4+ count more than 500 cells/mm^3 (except for 2 children with CD4+ count less than 500 cells/mm^3) and were on HAART from early childhood, the HIV virus load was reduced, which correlates very well with ocular manifestations in HIV-positive children in the study. With none of the pediatric patients presenting with typical isolated cotton-wool spots or HIV retinopathy and one having CMV retinitis, CMV, tuberculosis, toxoplasmosis, and cryptococcosis are less likely to develop in these children, because they have not yet been infected with these organisms unlike adults, in whom reactivation of potent infection occurs when the immune system deteriorates. CMV retinitis in children is usually more aggressive, bilateral, having a predilection for the macula, and may not interfere even with frequent advanced vision loss, therefore ophthalmic screening is necessary for early detection and initiation of treatment. Molluscum contagiosum constituted the majority of infectious and contagious diseases, as most of the children stayed in common dormitories, which is a limitation of the current study.

Correlation with CD4+

In our study, 97% of HIV-positive children had CD4+ count more than 500 cells/mm^3, because they were on HAART for more than one year, except for the patient who developed bilateral CMV retinitis.

Conclusions

In this study, the incidence of ocular manifestations in HIV-positive children, especially HIV retinopathy and posterior segment, was less. The CD4+ count levels are higher in post-HAART. HIV-positive children are more prone to contagious infectious diseases, such as molluscum contagiosum and CMV retinitis. Therefore, the focus should be on comprehensive ocular evaluation, irrespective of the level of visual acuity. There is a scope for improvement in the guidelines for early HIV detection, decreasing the transmission of HIV infection from mother-to-child, early initiation of HAART in mothers and children, and children's adherence to HAART as well as eye care, screening, and follow-up of HIV-positive children.

Disclosures

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2. Assistance with the article: None.
3. Financial support and sponsorship: None.
4. Conflicts of interest: None.

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