OCULAR MANIFESTATIONS IN PAEDIATRIC PATIENTS WITH ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS) AT MUHIMBILI MEDICAL CENTRE, DAR ES SALAAM

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A DISSERTATION SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF MEDICINE (M.MED) IN OPHTHALMOLOGY IN THE UNIVERSITY OF DAR ES SALAAM.

JULY, 1997

ABSTRACT

This study was conducted among 109 children admitted in paediatric wards at Muhimbili Medical Centre. Amongst them, there were 62 HIV seropositive and 47 HIV seronegative. The main objective was to study the prevalence of ocular manifestations of HIV in African children.

The results indicated that the prevalence of ocular manifestations was 38% in HIV seropositive children as compared to 25% in HIV seronegative children. The lesions of the conjunctiva were common in both groups, while corneal and fundus lesions were more prevalent in HIV positive children.

Conjunctival xerosis was a common finding, in both groups of children, indicating poor nutritional status rather than HIV infection. Corneal lesions were more prevalent in HIV seropositive children than in HIV seronegative children. Fundus lesions were markedly high in HIV seropositive children as compared seronegative children. Common lesions were macular edema, haemorrhages and sheathing of the vessels. These findings suggested that the incidence of retinal involvement was high in HIV seropositive children.

In HIV seropositive children the prevalence of abnormal visual acuity was 10% as compared to 6% in HIV seronegative children, indicating that it was not significantly associated with in HIV positivity.

In conclusion, the prevalence of ocular manifestations in African children is high, probably due to the poor nutritional status of the children. In non ocular manifestation, pulmonary tuberculosis was the most frequent diagnosis. Children with systemic diagnosis of tuberculosis, or any other opportunistic infection should be screened for HIV and ocular examination should be performed giving special attention to anterior segment and the fundus.

DECLARATION

I hereby solemnly declare that this dissertation is my original work and has never been submitted for a diploma or degree in any other University.

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ACKNOWLEDGEMENT

I convey my sincere gratitude to Prof. A.T. Mtanda for his tireless supervision, constructive criticism and encouragement for this dissertation.

I would like to express my sincere thanks to Prof. J.L.F. Sangawe and Prof. N.N. Kinabo for constant advise and encouragement. I wish to thank Dr. D.E. Masesa for her constant support and encouragement during the study.

I am very thankful to Prof. R.L. Mbise for allowing me to undertake my study in the paediatric wards, I also thank Dr. N.G. Kawo and Dr. K.P. Manji for their help in reviewing my dissertation.

I also thank Prof. A.B.M. Swai for the assistance and advice he gave me while writing the dissertation.

I would like to thank the mothers and their children who participated in the study. I would like to extend my sincere thanks to doctors of the paediatrics wards for assistance and co-operation which they offered during selection of the patients for the study. The success of the study would not have been possible without the high co-operation from the sisters of the Eye Out Patient Department.

My sincere thanks to statisticians Mrs. Candida Masanja, Mrs. Rose Mpembeni and Mr. C. Makwaya who assisted me, in a very professional manner at all stages of my dissertation.

My acknowledgement will not be complete without extending my thanks to the secretary Consolata who made the write up possible.

Lastly, I wish to extend my sincere and heartfelt gratitude to my wife and son for tolerating my long absence from home during the time when I had to spend many hours at work.

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ABBREVIATIONS

AIDS	:	Acquired Immunodeficiency Syndrome
CDC	:	Centre for Disease Control
HIV	:	Human Immunodeficiency Virus
RNA	:	Ribonucleic acid
DNA	:	Deoxyribonucleic acid
LAS	:	Lymphadenopathy Syndrome
PGL	:	Persistent Generalized Lymphadenopathy
ARC	:	AIDS Related Complex
WHO	:	World Health Organization
CMV	:	Cytomegalovirus
CWS	:	Cotton Wool Spots
HZ	:	Herpes Zoster
HSV	:	Herpes Simplex Virus
TB	:	Tuberculosis
CNS	:	Central Nervous System
KS	:	Kaposi's Sarcoma
NHL	:	Non-Hodgkins Lymphoma
HL	:	Hodgkins Lymphoma
B-ALL	:	B-Acute Lymphocytic Leukaemia

VDRL : Venereal Disease Research Laboratory

TPHA : Treponema Pallidum Haemagglutination Assay

OCULAR MANIFESTATIONS IN PAEDIATRIC PATIENTS WITH ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS)

INTRODUCTION AND REVIEW OF LITERATURE:

The Acquired Immunodeficiency Syndrome (AIDS) is defined by the centres for disease control (CDC) as a disease that is at least moderately indicative of an underlying cellular immune deficiency in a person who has no known cause of underlying cellular deficiency or any other underlying reduced resistance reported to be associated with that disease[1].

The etiology of AIDS is that of transmissable, blood borne agent, one of the retroviruses, the human immuno-deficiency virus. Human immunodeficiency virus (HIV), is the primary etiologic agent of immunodeficiency syndrome AIDS. HIV is a retrovirus, a member of the lentivirinae family. The human AIDS viruses are not homogenous, but most are variants of HIV-1. A second virus, HIV-2 seems to be prevalent only in West Africa and is much less virulent[2]. The virus severely impairs cell-mediated immune response by infecting and killing T-lymphocytes. The HIV virus selectively binds to the membrane of the helper T-cell (T4). The T4 antigen on the surface of these lymphocytes appears to serve as the virus receptor. The cardinal feature of HIV infection is the depletion of T helper inducer lymphocytes. The CD4 molecule is the major receptor for HIV, it has a high affinity for the viral envelop[2].

The consequences of CD4 T cell dysfunction caused by HIV infection are devastating because the CD4 lymphocyte plays a critical role in the human immune response. It is responsible directly or indirectly for induction of a wide array of lymphoid and non-lymphoid cell function. The infectivity of monocytes with HIV suggests that the monocyte servers as a major reservoir for HIV in the body. Unlike the CD4 lymphocyte, the monocyte is relatively refractory to the cytopathic effect of HIV[2]. The AIDS virus has been isolated in saliva, urine, tears, contact lenses and in ocular and neural tissues[3].

HIV uses the viral enzyme, reverse transcriptase, to copy its RNA encoded genome into the host cell DNA. The host cell produces vast amount of new virus which eventually leads to the death of the infected T4 cell. T4 cells are vital to the normal function of the cellular immune system as they are responsible for the generation of cytotoxic cell, activation of macrophages, differentiation of B cells into immunoglobulin secreting plasma cells and the development of active suppressor cells[2].

The range of manifestations of HIV infections may include nothing, non-specific signs and symptoms of illness, autoimmune and neurologic disorders, a host of opportunistic infections, and various types of neoplasia[4]. A condition has been described which includes anorexia, fatigue, fever,malaise, night sweats, weight loss, diarrhoea, oral thrush, and generalized lymphadenopathy. This has been variously referred to as

lymphadenopathy syndrome (LAS), persistent generalized lymphadenopathy (PGL) and AIDS related complex (ARC)[4].

AIDS is most difficult to define in children a population with inherent immunodeficiencies. Most paediatric AIDS cases result from transplacental, perinatal or post natal transmission of human immunodeficiency virus[4]. The duration between primary infection and progression to clinical disease averages about 10 years. Death usually occurs within two years after the onset of clinical symptoms[2].

By 1994 a million cases had been reported to the WHO and the pandemic has now affected all the continents. Estimates give the total population with AIDS in mid 1994 as 4 million and the total number infected with the virus is 16 million; Africa bears the biggest burden of the infection[5]. The WHO has estimated that 30 to 40 million people will be infected with HIV by the end of the century, with 90% of all new infections occurring in developing countries[2].

OCULAR INVOLVEMENT IN AIDS:

Between 40-94% of patients with florid AIDS have ocular involvement[6,7,8]. Furthermore ocular changes have been described in AIDS related complex (ARC) and even in asymptomatic seropositive patients. Diseases of the ocular adnexa are less common than retinal disorders, but they can be equally troublesome[9]. Indeed, ocular

symptoms are sometimes the presenting manifestations of human immunodeficiency virus (HIV) infection[10].

The literature on the ophthalmic manifestation of AIDS in children is still very limited. Study done by Kestelyn[11] in 110 HIV seropositive African children indicates that cotton wool spots, the most frequent ocular sign in adults, is almost absent in children, and that the prevalence of cytomegalovirus (CMV) retinitis is low. The decreased lacrimation is a frequent finding and is probably due to the same pathological process in the lacrimal gland as the salivary gland enlargement which is often seen in children with AIDS[11].

Ophthalmic manifestations in African Children with HIV(11)

Perivasculitis and/or sheathing	52(46%)
Decreased lacrimation	22 (20%)
Microvascular abnormalities	9 (8%)
Chorioretinitis	6 (5%)
Retinal haemorrhages	2 (0.8%)
Cotton wool spots	1 (0.9%)

Average age, 23 months

N=110 m=61 f=49

In other study by Dennehy et al[12], among 40 patients with confirmed AIDS with the age range from 1 month to 5 years 6 months. Eight (20%) patients had abnormal ocular manifestations. Five (12%) patients demonstrated retinal disease and 3(7.5%) had external infection of adnexal structure. It is interesting that all patients with retinal findings were less than 2 years of age and that all had died by the age of 25 months. In contrast, the age of the three patients with external infection ranged from 30 months to 5 years[12].

OCULAR MANIFESTATIONS OF HIV INFECTION:

The changes involved in the eye may lead to severe morbidity and blindness. The ophthalmic complications of AIDS fall into five categories[13,16].

1. Primary retinal microvascular disease
2. Non-opportunistic infections of the eye
3. Opportunistic infections of the eye and adnexa
4. Neoplasms of the eye and adnexa
5. Neuro-ophthalmic abnormalities.

1. **Primary retinal microvascular disease (HIV-related retinopathy):**

The non-infectious retinopathy seen in AIDS patients has sometimes been called "AIDS retinopathy" and consists primarily of cotton wool spots (CWS) and intraretinal haemorrhages. The frequency of CWS has varied from 28-92% but approximately half

of all AIDS patients have been described as having CWS[13]. Retinopathy related to HIV, or microangiopathy is found in 30-60% of infected patients, and may preceed the occurrence of major AIDS related infections[10,13,15,17]. Retinal haemorrhages may be seen in AIDS patients in isolation or in conjunction with CWS. These lesions have been reported in up to 30% of AIDS patients and the incidence may be higher in autopsy series[6]. Retinal microangiopathy is non-progressive and nearly always asymptomatic[16].

Although the pathogenesis of AIDS microangiopathy has not been established, it seems to be related to the degree of immune suppression indicated by the ratio of CD4 (helper) to CD8 (suppressor) T lymphocytes[15]. The hypothesis for AIDS microangiopathy include:-

1. Circulating immune complex disease.[6,13]
2. HIV infection of retinal endothelium[13]
3. Rheologic abnormalities[13]

1.1. **Cotton Wool Spots (CWS):**

Cotton wool spots are the most frequent ocular manifestation, occurring in 27-71% of patients[6,7,13,17]. CWS result from infarction of retinal nerve fibre layer and are seen in a variety of clinical conditions. Most patients with HIV disease, demonstrate CWS at some point during the course of their illness[17]. It appears that CWS in healthy HIV positive patients have relatively little clinical

significance, however present data suggests that CWS in patients with very low CD4+ counts and advanced HIV disease is a negative prognostic sign[34]. Retinal CWS are expansions of a final common pathological pathway of microvascular compromise (ischemic-veno-occlusion) to the prearteriolar capillary network of the retina[13,17].

In AIDS, CWS always appear in conjunction with microvascular defects, which may or may not be seen clinically. These lesions include microaneurysms, telangiectasis, intra-retinal microvascular abnormalities, areas of focal non perfusion and capillary loss[13]. Histologically retinal CWS appear as accumulated axoplasm, mitochondria, nucleoid structure, (pseudonucleus), neurofilaments, and dense bodies composed of lipids[12,13,17]. Calcification of CWS in AIDS patients has been documented by Tenabaum et al.[17]. If CWS are associated with ischemia or edema of the mucula (rare)[13,17], the patient will experience loss of vision. The presence of CWS, in a patient with AIDS does not lead directly to the development of CMV retinitis, but rather signify a compromise in the blood-retinal barrier. This compromise may serve as a portal for the dissemination of CMV[13,17]. Even with experience it can be challenging to differentiate CWS from early CMV retinitis. Perhaps the best way to differentiate the two is through serial observations[17]. The significance of CWS is not clear, except for poor prognosis.

1.2. Retinal Perivasculitis:

Retinal perivasculitis may be observed in peripheral fundus of HIV seropositive patients in the absence of infectious retinitis[15]. Yellow white patches accumulate around the vascular walls and may spread towards the posterior pole without reaching it. Veins are more often involved than the arteries and after several weeks to months, the active inflammation is gradually replaced by a residual sheathing of the vessels. It was observed in about 10% of adult patients and it was even more common in seropositive children[18].

Perivasculitis has been reported to occur in 15% of African patients with AIDS and 60% of African children with ARC[13,18]. The perivasculitis should be considered as part of non-infectious AIDS retinopathy together with CWS and haemorrhages[18]. Interestingly Africans have a higher prevalence of perivasculitis, with a much lower incidence of CMV retinitis and ocular Kaposi's sarcoma[13]. Fortunately this form of non-infectious retinopathy does not interfere with vision and does not necessitate treatment.

2. Non-opportunistic infections of the eye associated with HIV:

2.1. Herpes zoster (HZ):

The correlation between severe HZ in young adults and HIV seropositivity is well established[20], and has been used as a marker for HIV infection in Africa[21].

Two distinct differences should be stressed, first, the peak incidence of HIV related HZ ophthalmicus is seen in a young age group, and secondly, the disease tends to run a more severe course in HIV seropositive patients in terms of corneal involvement and post zonal pain[21].

In a study by van-de-Perre[19] done in Kigali, Rwanda, 131 cases of HZ were diagnosed, six of them were children (12-60 months). Ocular complications occurred in 13% of the patients, probably due to the high proportion of cranial nerve involvement. Retinal necrosis after HZ ophthalmicus has been described in 17% of patients with HIV infection in the western population[21].

The illness by HZ virus is characterized by a vesiculobullous rash in the distribution of the ophthalmic branch of the trigeminal nerve, and may be accompanied by blepharitis, conjunctivitis, keratitis and uveitis[19]. HZ virus is also considered to be the agent responsible for a very different clinical pattern of retinitis given the name progressive outer retinal necrosis. This is a much more aggressive retinitis, it is often multifocal and bilateral at presentation and produces little inflammatory response[22].

2.2. Herpes Simplex Virus:

Herpes simplex type I (HSV-I) keratitis has been reported to occur in AIDS patients[23,24]. Its clinical severity, natural history, and resistance to medical

therapy remain poorly understood. In a study by Young et al[24] there were 6 cases of HSV-I keratitis. All were males and ranged in age from 22-50 years. In this study herpetic keratitis appeared to be somewhat atypical. First, there was a definite predilection for marginal, as opposed to central, epithelial keratitis. Peripheral corneal involvement in HSV-I dendritiform keratitis is relatively uncommon in immunologically normal patients. Secondly the keratitis appeared to be more resistant to treatment, the third feature was the frequent recurrence of the herpetic disease.

In experimental models of HSV-I stromal keratitis, investigators have observed a direct correlation between the degree of clinical disease and the presence of sensitized T-lymphocytes[24]. HSV rarely causes a retinopathy in AIDS, the symptoms and signs are basically the same as those of CMV infection.

2.3. Other viral diseases of the eyelids:

Both molluscum contagiosum and verrucae of the eyelids are common cutaneous manifestations of HIV infection in the tropics[25]. These viral diseases are very common in young children in Africa, but were rarely seen in adults before the AIDS era. The presence of multiple verrucae around the eyelids are very suggestive of HIV infection[11].

2.4. Ocular Syphilis:

In the eye, syphilis may cause conjunctivitis, iritis, vitritis, retinitis, papillitis, and optic neuritis, in short it can involve the visual axis at any or all levels[16,26]. Syphilitic disease may progress more rapidly in HIV infected patients and more intense treatment is indicated in these cases[26]. Recent reports of syphilis in HIV infected individuals indicate a severe, accelerated course of syphilis that frequently involves the central nervous system and often does not respond to standard therapy for primary and secondary syphilis. Serological testing for syphilis should be performed on all HIV seropositive patients with ocular inflammation[26].

2.5. Choroidal Tuberculosis:

There is an alarming rise in the prevalence of tuberculosis (TB) since the advent of the HIV (AIDS) epidemic. In Rwanda, examination of 32 HIV positive patients with TB showed that 5 (15.6%), had ocular lesions due to TB, including disseminated choroiditis, phlyctenulosis and solitary choroidal granulomas[27]. However in Malawi, examination of 68 HIV positive TB patients revealed only one with ocular disease which was probably TB related, did not seem to constitute a significant clinical problem in this study[28].

3. Opportunistic Infections:

Infectious agents capable of producing intraocular infection in AIDS patients include Cytomegalovirus (CMV), Cryptococcus neoformans, Pneumocystis carinii, Mycobacterium avium intracellulare, Toxoplasma gondii, Histoplasma capsulatum, and Candida albicans.

3.1. Cytomegalovirus retinitis (CMV-retinitis):

CMV retinitis is the most common opportunistic ocular infection in AIDS[14]. CMV is an ubiquitous virus and is responsible for the commonest opportunistic infection of the retina in AIDS. Its incidence has been reported to be as high as 46%[13].

The single most important predictive factor of CMV retinitis is the $CD4^+$T cell count since CMV retinitis is a manifestation of profound immuno-suppression[21]. CMV retinitis was preceded by the appearance of CWS in all cases[6], it is bilateral in 50% of cases[11]. It starts most often at the posterior pole and has a tendency to follow the major vascular arcades.

For unknown reason the frequency of CMV retinitis in African AIDS patients seem to be much lower than in Europe and the United States and does not exceed 5%[11]. Although up to 56% of children with AIDS may have

disseminated or asymptomatic CMV infection, only six patients with CMV retinitis in children with AIDS have been collected from the literature, in all cases, the disease resulted from vertical transmission[12,29].

The CMV retinitis that occurs in AIDS patients may usually be confirmed by isolation of CMV from blood, urine or by retinal biopsy. Once diagnosed, it necessitates lifelong monitoring and treatment[11,21] because CMV retinitis with AIDS represents a significant vision threatening problem.

The shorter life expectancy of AIDS patients in developing countries probably reduces the period of profound immunodeficiency during which the patients are most likely to develop cytomegalovirus retinitis[27]. It appears that the longer the patients survive, the greater the frequency of disease relapse and the greater the cumulative amount of retinal destruction. This results in progressive visual field loss, averaging about 5% of total visual field loss per month, and there is also some gradual reduction in visual acuity[21]. Severe CMV retinitis occurs in the severely immunocompromised patients, and an ocular motility disorder suggests an infectious or neoplastic encephalomeningitis[7]. Untreated lesions may spread to involve the whole retina which may disintegrate to form retinal holes. The holes anterior to the equator may give rise to retinal detachments in up to 15% of patients[13].

3.2. Fungal infections:

Cryptococcus neoformans is the most common life-threatening fungal pathogen and is significantly more common in African patients than in their western counterpart, probably due to the high prevalence of C. neoformans in the environment[30]. The prevalence of cryptococcal disease in different series of patients with AIDS in the United States ranges from 2-9%[30].

In a study of 80 HIV positive patients with cryptococcal infection in Rwanda, papilloedema was observed in 26(32.5%), visual loss in 7(9%), sixth cranial nerve palsy in 7(9%), optic atrophy in 2(2.5%). Actual invasion of the intraocular structure with C. neoformans was an uncommon complication in Rwanda[30]. Candida retinitis is infrequently seen in AIDS patients but may occur in AIDS patients who are intravenous drug users. Early lesions may resemble CWS,[31] fungal endophthalmitis characteristically produces small white yellow retinal infiltrates[31].

3.3. Toxoplasmosis:

Toxoplasmosis accounts for 30 to 50% of all posterior uveitis. It is caused by toxoplasma gondii which is an intestinal parasite found in cats. Toxoplasma from cat's faeces goes to food that man eats. Women who acquire toxoplasmosis during pregnancy may transmit the parasite to the foetus with severe potential complications. Ocular toxoplasmosis, although quite uncommon may be seen in

association with CNS involvement in AIDS. The usual cases of toxoplasmosis in AIDS patients do not demonstrate the typical fundus scar of previous infection[1].

Toxoplasmic retinochoroiditis may be the initial manifestation of AIDS[32]. The patient may present complaining of blurred vision and floaters[21,32]. Vitreous opacities and a white-yellow slightly raised intra-retinal lesions with irregular borders are seen. There is little or no anterior uveitis, and resolution leaves a pigmented often irregular scar. Significant permanent loss of vision may develop if the lesion is located at the macula, papillomacular bundle or optic nerve head[33].

Toxoplasmosis is the most common cause of posterior uveitis in humans[4]. It occurs due to reactivation of a latent congenital infection. In AIDS patients, however, it is generally newly acquired or newly disseminated from non-ocular sites of disease[4]. Less than 1% of patients who acquire toxoplasmosis in adult life develop ocular lesions consequently, the majority of ocular toxoplasmosis cases are thought to be acquired congenitally. However, in the immunocompromised host, toxoplasmosis is an aggressive and often fulminant disease, causing central nervous system, visual and lymph node infection, ocular toxoplasmosis in these circumstances is most unusual[4].

3.4. Pneumocystis carinii choroiditis:

Choroidal P. carinii infection has become more common with the increased use of prophylactic aerosolized pentamidine, although the actual incidence is unknown. The lesions characteristically appear as pale cream or orange, space occupying beneath the retinal vessels. They are unilateral or bilateral, and rarely are symptomatic, or reduce vision[34].

4. Neoplasms of the eye and adnexa:

Kaposi's sarcoma(KS), B-cell lymphoma, and squamous cell carcinoma are the most common malignancies reported in association with HIV infection. In adults infected with HIV, an increased incidence of KS and lymphoma has been noted[35]. In contrast, according to the literature, tumour development in children infected with HIV still seems to be a rare event, and treatment experiences are limited[36].

4.1. Kaposi's Sarcoma (KS):

KS, a malignant mesenchymal tumour of the skin and mucous membrane, is a frequent manifestation of AIDS. AIDS related KS is more aggressive and less responsive to treatment than KS in patients without AIDS[37].The tumours are characterized histologically by spindle shaped cells, vascular clefts, and well formed capillaries[38].

Of all the patients with AIDS, 24% had conjunctival or lid involvement with KS[6,37]. In another study by Shuler et al[37] 20 of the 100 patients with AIDS-related KS had ophthalmic involvement. Out of 20, 13 had only eyelid lesions, 4 had only conjunctival lesions and 3 had both conjunctival and lid involvement. All conjunctival lesions, were located in the lower fornix. Of the patients with eyelid involvement the upper and lower eyelids were involved with equal frequency[37]. A reversal of the helper to suppressor T-cell ratio was noted in all of these cases, which paralleled their inverted peripheral blood ratios. They did not find a similar inversion of the helper to suppressor cell ratio in analyzing a variety of malignant tumours in non-AIDS patients[13].

4.2. Squamous cell carcinoma of the conjunctiva:

There has been a striking increase in the number of patients with conjunctival neoplasms reported from Rwanda, Malawi and Uganda. A case-control study in Rwanda[39] demonstrated that HIV infection is a risk factor for the development of squamous cell dysplasia and neoplasia of the conjunctiva. Data available from Rwanda, Malawi and Uganda indicates that approximately 75-80% of patients with these lesion are HIV positive[39].

Factors that may contribute to the increased incidence of squamous cell carcinoma include exposure to ultraviolet rays and conjunctival papilloma virus[39]. Most tumours arose in the limbus of the eye and the lesions in the HIV patients were aggressive, the duration of symptoms was mostly less than 3 months[39].

4.3. Lymphoma:

In adults, the estimated risk of lymphoma developing in patients with AIDS has ranged from 1-2% per year to as high as 29% in 3 years after the introduction of antiretroviral therapy. There is no data on the incidence of lymphoma in children infected with HIV. Lymphoid malignancy has been reported in 24 patients infected with HIV younger than 16 years of age, 20 with NHL one with HL and three with B-ALL, little is known about these in Africa[40].

5. Neuro-ophthalmic Manifestations:

HIV infection may be associated with a large variety of neuro-ophthalmological manifestations including optic nerve disease (edema, atrophy or inflammation) visual field defects, cortical blindness, pupillary defects and ocular motor nerve palsies. Most of the disorders are due to infectious lesions of the CNS[11].

Cryptococcal meningitis is particularly common in Africa, probably due to the high prevalence of Cryptococcus neoformans in domestic environment[3]. In a study by Jabs et al[13] in a series of 200 patients, neuro-ophthalmic lesions were found in 8% of AIDS patients. These lesions included a third nerve palsy (0.5%), fifth nerve palsy (0.5%), sixth nerve palsy (2%), seventh nerve palsy (0.5%), a skew deviation (0.5%) and opsidoms (0.5%), optic neuropathy with visual loss and optic atrophy, secondary to cryptococcal meningitis or syphilis (2.5%) and papilledema, secondary to cryptococcal meningitis (1.5%). The most common etiology for the neuro-ophthalmic lesions in these 16 patients was cryptococcal meningitis, accounting for 56% of the neuro-ophthalmic cases.

The HIV virus has a propensity for neural tissues and causes an encephalopathy characterized by a progressive dementia. Gaze palsies such as internuclear ophthalmoplegia and nystagmus are seen[41]. Extra ocular motility disorders with consequent diplopia, may be an early manifestation of intra-cranial pathology in persons with AIDS[7,16].

OBJECTIVES

Broad Objective:

To describe the ocular manifestations of HIV in African children in Dar es Salaam.

Specific Objectives:

1. To determine the most common ocular manifestations of HIV positive children as compared to HIV negative children.
2. To determine the relationship between visual acuity and ocular manifestations of HIV positive children.

MATERIALS AND METHODS:

A comparative study of ocular manifestations of HIV positive children and HIV negative children was conducted from July 1996 to December 1996. This was a case control study, the ratio between the two groups was 1:1. Sixty two patients were collected in HIV positive group and 47 in HIV negative group, bringing the sample size to 109 patients. The sample size was calculated by the formula given below:

$$n=\frac{[U;P_1(1-P_1)+P_2(1-P_2)]+V[2P(1-P)]^2}{(P_1-P_2)^2}$$

where $P = \frac{P_1+P_2}{2}$ and U = if power=80% then U = 1.28

V = if significant level =5%, V = 1.96

$P_1 = 0.2$ $P_2=0.02$

Case Selection:

The study population included all patients aged 18 months to 14 years.

For the purpose of study the patients were divided into three age groups as follows:

i. less than 24 months

ii. age 25 - 60 months, and

iii. more than 60 months

The patients were collected from inpatient and outpatient departments with at least two of the following criteria: chronic cough, weight loss > 10%, persistent diarrhoea for two weeks, oropharyngeal candidiasis, severe scabies, recurrent fungal infections of the skin and fever > 1 months.

All subjects included in the study had their HIV status determined, if it was not already known. The HIV testing was done as recommended by the NACP. For each child a questionnaire was completed. The following information was recorded: Serial number, registration number, name, age, sex, address, father's name, date of examination, weight, clinical criteria for selection, diagnosis, HIV status and examination of eyes.

Patients were recruited from:

1. Paediatrics, inpatient and outpatient departments of Muhimbili Medical Centre.
2. Medical, inpatient and outpatient departments of Muhimbili Medical Centre.

The patients attending paediatric or medical outpatient or inpatient departments of Muhimbili Medical Centre were examined at the Eye Clinic of Muhimbili Medical Centre.

Ocular Examination:

The visual acuity was assessed with the help of snellen's or E chart. For younger

children moving objects, moving light source or colourful objects, provided a rough estimate of the vision.

Ocular examination included a detailed inspection of the ocular adnexa and anterior segment for the presence or absence of eye discharge, conjunctival injection or growth, corneal disorders, size and reaction of the pupil and abnormalities of the lens. Detailed examination of the posterior segment was also carried out. Slit lamp examination was performed (on the patients who could manage to sit with or without support) for more detailed examination of cornea, anterior segment, the anterior uvea, the lens and vitreous.

Corneal ulcers were examined under cobalt blue light after staining with fluorescein. Direct and indirect ophthalmoscopy was carried out after full pupillary dilation using phenylephrine hydrochloride 5% and tropicamide 0.5%. The central and peripheral retina was examined for retinopathy, infective retinochoroiditis, papilloedema and optic atrophy. Evaluation of ocular motility was done in a search for neuro-ophthalmological manifestations of HIV such as cranial nerve palsies.

Laboratory Investigations:

1. The children with suspected ocular syphilis lesions were tested for syphilis by VDRL. Positive VDRL results were confirmed by TPHA.

2. In cases of tumours and growths involving the eyelids and conjunctiva, excision of the lesions were undertaken by the author himself under general anaesthesia. The specimen were submitted for histopathology examination at the central pathology laboratory by a pathologist.

3. In cases of corneal ulcers, corneal scrapings were taken and subjected to examination by gram and potassium hydroxide staining.

4. In case of discharge from the eye, swabs were collected from the conjunctival sac for culture and sensitivity. The samples were put in Stuart's transport medium and cultured on blood agar, chocolate agar and Sabouraud's dextrose agar. All the above cultures were performed by a laboratory technician and read by a microbiologist.

RESULTS

1. Description of study population:

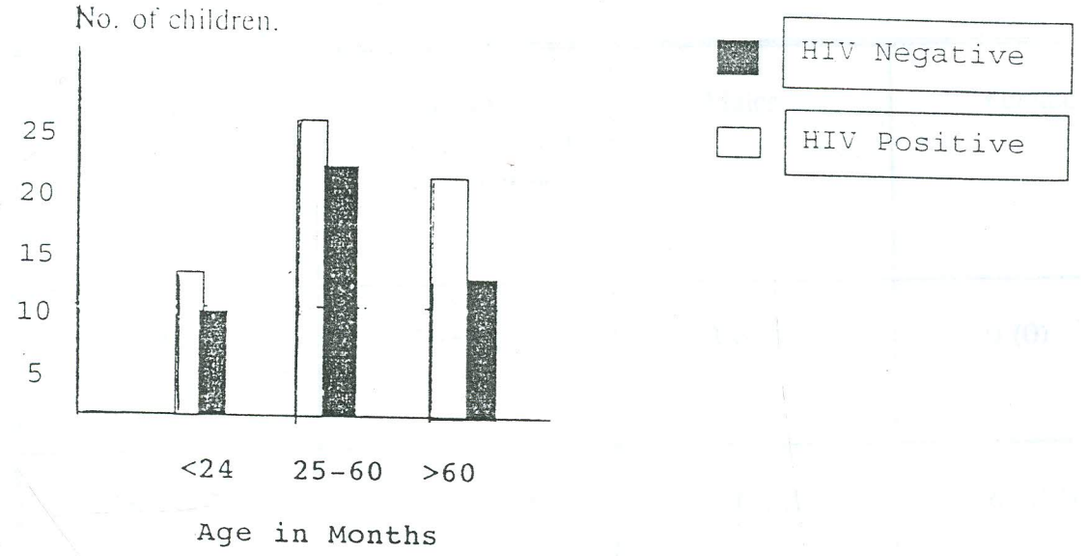
The study population included 109 patients, 56 males and 53 females. The age range was 18 months to 14 years, with a mean age of 44.5 months.

Sixty two children were HIV positive, whereas 47 were HIV negative. The age and sex distribution as well as HIV status are illustrated in table 1 and graphically in graph 1.

Table 1: Age and sex distribution of the children in HIV positive and HIV negative groups

Age in month	HIV positive n = 62			HIV negative n = 47			Total
	No (%)	M (%)	F (%)	No (%)	M (%)	F (%)	
<24	14(22.5)	11(18)	3 (5)	11(23)	4(8.5)	7(15)	25(23)
25-60	26(42)	13(21)	13(21)	23(49)	14(30)	9(19)	49(45)
>60	22(35.5)	7(11)	15(24)	13(27.65)	7(15)	6(13)	35(32)
Total	62(100)	31(50)	31(50)	47(100)	25(53)	22(47)	109(100)

Graph I: Age distribution in HIV positive and HIV negative children



1.1. Data in table 1 and graph 1 shows that:

i. There were 25 children below age 24 months, 49 children aged 25-60 months and 35 children aged more than 60 months.

ii. In HIV positive group there are 31 male and 31 female children and in the HIV negative group there were 25 male and 22 female children.

iii. In both HIV groups there were more children in the age range 25-60 months (Graph 1) that is 26/62 in the HIV positive group and 23/47 in the HIV negative group.

iv. 65% of HIV positive children were aged less than 60 months.

v. HIV positively was seen in 14/25 children in age group < 24 month, in 26/49 children in the age range 25-60 months and in 22/35 children aged more than 60 months.

Table 2: **Age and sex distribution of HIV positive children with ocular lesions**

Age (in months)	No. of children with ocular lesions	Males	Females
< 24	3 (5%)	3 (5%)	0 (0)
25 - 60	13 (21%)	7 (11%)	6 (10%)
>60	8 (13%)	3 (5%)	5 (8%)
Total	24 (38%)	13 (21%)	11 (18%)

2. **Prevalence of ocular lesions in HIV positive children:**

Clinical assessment of 62 HIV positive children showed that 24 had ocular lesions, 13 were males and 11 females. Their distribution in the various age groups is shown in table 2.

Table 3: **Anatomical distribution of ocular lesions in both HIV positive and HIV negative children**

Ocular site of lesions	HIV positive n = 62	HIV negative n = 47
Conjunctiva	15 (24%)	9 (19%)
Cornea	6 (10%)	1 (2%)
Anterior Chamber (AC)	0 (0)	0 (0)
Iris and pupil	0 (0)	0 (0)
Lens	0 (0)	1 (2%)
Fundus	11 (18%)	2 (4%)

2.1. **Anatomical distribution of ocular lesions in HIV positive children:**

As shown in table 3, ocular lesions were predominatly found in the conjunctiva, cornea and the fundus of the eye. No abnormality was found in the anterior chamber, iris, pupil and lens.

Table 4: **Clinical types of lesions in HIV positive and HIV negative children**

Clinical types of lesions	FREQUENCY	
	HIV positive	HIV negative
Conjunctiva		
- Xerosis	14 (22.5%)	9 (19%)
- Bitot's spots	1(1.5%)	4 (8.5%)
- Phlyctenules	1(1.5%)	0 (0)
Cornea		
- Opacities	3 (5%)	1 (2%)
- Phlyctenule	2 (3%)	0 (0)
- Keratomalacia	1 (1.5%)	0 (0)
Lens - Cataracts	0 (0)	1 (2%)
Fundus		
- Haemorrhages	2 (3%)	0 (0)
- Macular edema	8 (13%)	2 (4%)
- Sheathing	2 (3%)	0 (0)
- Opricatrophy	0 (0)	1 (2%)
- Neovascularization	1 (1.5%)	0(0)
- Other lesions	0 (0)	3 (6%)

2.2. **Clinical types of ocular lesions in HIV positive children:**

The clinical types of lesions found in each anatomical area are shown in table 4.

In the conjunctiva the main lesion was xerosis seen in 14 cases followed by few cases of phlyctenules, opacities, keratomalacia and Bitot's spots (table 4).

In the fundus there were 8 cases with macular edema, 2 cases each of retinal haemorrhage and sheathing of vessels. Only one case had neovascularization of the retina below the discs. (Table 4).

Table 5: Age and sex distribution of HIV negative children with ocular lesion

Age (in months)	No of children with ocular lesion	Males	Females
< 24	2 (4%)	0 (0)	2 (4%)
25 - 60	7 (15%)	4 (8.5%)	3 (6%)
>60	3 (6%)	3 (6.3%)	0 (0)
Total	12 (25%)	7 (15%)	5 (10%)

3. Prevalence of ocular lesions in HIV negative children:

A similar evaluation was carried out amongst 47 children who were HIV negative, 12 childen (7 male and 5 female) had ocular lesions. Their distribution in the various age groups in shown in table 5.

It is shown in table 5 that, 10 of the 12 children are above 24 months, this is similar to the situation in HIV positive children, where 21 out of 24 children were above age 24 months (table 2).

3.1. Anatomical distribution of ocular lesions in HIV negative children:

As shown in table 3, ocular lesions were found in the conjunctiva, cornea, lens and fundus in a small number of cases.

3.2. Clinical types of ocular lesions in HIV negative children:

In the anterior segment, conjunctival xerosis predominated having 9 cases, Bitot's spots were seen in 4 children, corneal opacities in one case and one child presented with bilateral cataracts. In the fundus two children had macular edema, one with optic atrophy, again there were no abnormalities of the anterior chamber, iris or pupils (table 4)

Table 6: Visual acuity abnormalities in HIV positive children:

S No.	Age	Sex	Ocular lesions	Visual Acuity
1.	19M	M	RE:Perforated LE: Normal	RE: NLP LE: Follows objects at 3m
2.	2Y	M	Bilateral macular edema	BE follow objects at 2m.
3.	3Y	F	Bilateral conjunctival xerosis & macular edema	BE follow objects at 2m
4.	3Y	F	Bilateral conjunctival xerosis, macular edema and sheathing of vessels near the inferior poles of discs	BE follow objects at 2m
5.	7Y	M	RE: Macular edema LE: Normal	RE: 6/18 LE: 6/6
6.	5½Y	M	Bilateral macular edema with sheathing of vessels near inferior poles of discs.	RE: 6/60 LE: 6/60

4. **Prevalence of visual acuity abnormality in HIV positive children:**

In HIV positive children there were only 6(10%) children who had abnormal visual acuity remaing 56 had normal visual acuity (Table 6). Normal visual acuity considered was as follows:

i. < 24 months: follows objects at 3 metres

ii. 25-60 months: follows objects at 4 metres

iii. > 60 months: 6/6 by snellen's and E chart

Table 7: Visual acuity findings in HIV negative children:

S No	Age	Sex	Ocular Findings	Visual Acuity
1.	19M	F	LE: Esotropia RE: Normal	LE:LP (amblyopia) RE: Normal
2.	2¼Y	M	Bilateral congenital cataracts	BE can follow light
3.	5Y	M	Bilateral optic atrophy with macular edema	BE: NLP

5. **Prevalence of visual acuity abnormality in HIV negative children:**

In HIV negative children there were 3 (6%) children with abnormal visual acuity, as shown in table 7.

6. As there was no case of corneal ulcer, conjunctival and eyelid tumours and conjunctival discharge in our series, therefore no laboratory specimen was collected regarding these manifestations.

DISCUSSION

It is now established that AIDS is a disease that affects mainly the sexually active members of the community. The 15-44 age group constitutes 87.7% of all reported AIDS cases, while in general population they make up only 39.9% of the total[42]. The incidence of HIV infection amongst children 0-4 years is 3.7% and children constitute 19.9% of the population in Tanzania. A greater proportion of these get the disease through perinatal route[42], similar findings have been documented in Uganda and Zaire[43,44]. With the recorded HIV seroprevalence among pregnant women, and assuming 30% transmission from pregnant women to their offspring, appromaximately 5% (range from 0.6% - 7.5%) of the newborn may be infected[42].

We studied 109 patients, 62(56%) were HIV positive. This figure of 56% appears high and probably reflects the fact that this was biased sample of symptomatic hospitalized children. Sixty five percent (65%) of the HIV positive children were aged less than 5 years, HIV positivity increased slightly with increasing age (table 1).

1. **Ocular manifestations of HIV:**

   Whereas between 40-94% of adults with florid AIDS have ocular involvement, the incidence of ocular manifestations in children with HIV infection was lower.

   Dennehy[12] reported 20% of paediatric patients with AIDS presented with ocular manifestations in USA whereas Kestelyn[18] studying children with HIV in

Rwanda found incidence of 33%. This figure of Kestelyn, closely approaches our finding of 38% incidence of ocular manifestations in HIV positive children.

2. Lesions of anterior segment:

2.1. Conjunctival lesions:

Our observation in table 4 shows a slightly higher rate of vitamin A deficiency in HIV positive children. Similar findings were documented by Semba[14] in Rwanda indicating that in HIV positive children and adults vitamin A deficiency is common. These high figure from developing nations may indicate an inverse relationship between HIV ocular manifestations and nutritional status. Statiscially, the relation between two groups is not significant ($P > 0.05$) (table 3).

As our study groups were hospitalized, malnourished children and suffering from chronic infections, so it is likely that these lesions reflect more, the poor vitamin A status resulting from malnutrition in both HIV positive and HIV negative children rather than HIV infection as such. This factor is supported by the studies done by Gopalan[45] and Pirie A[46] in India showing that treatment of malnourished child with high protein diet even without vitamin A supplementation, brought about a significant increase in the levels of vitamin A, thus showing a clear relationship between vitamin A deficiency and nutritional status.

In HIV positive group, there was one child with conjunctival phlyctenule, this is in agreement with the study done by Kestelyn[47], in which there was one case of phlyctenular conjunctivitis. The possible cause of conjunctival phlyctenule may be the hypersensitivity to tuberculin protein, because the patient had a diagnosis of tuberculous adenitis.

2.2. Corneal lesions:

In the literature from U.S.A. bacterial conjunctivitis and keratitis have been reported in patients with AIDS[16]. In another study from USA by Young[24] HSV keratitis was found to be common in immunodeficient individuals and there was a definite predilection for the margins, the keratitis was resistant to treatment. Another study by Marsh[41] in UK indicated that secondary becterial infection of the corneal lesions is always a risk, and bacteria that are often regarded as commensals may behave quite virulently in an immunodeificient environment. The facts discussed above seem to suggest that the unilateral opacities found were most probably due to bacterial or viral keratitis since there was no history of trauma. All opacities were towards the periphery and we know that in immunodeficient individuals viral keratitis (HSV-I) has predilection for the corneal margins[24]. There is also a possibility of keratomalacia which caused corneal opacity because many children had vitamin A deficiency.

The explanation for the bilateral opacities in the lower part of cornea was due to decreased lacrimation. This hypothesis is supported by the study done by Kestelyn[11] in Rwanda, which shows that decreased lacrimation is indicative of lacrimal gland pathology and is a frequent finding in about 20% of African children. The other possibility, of corneal opacities may be due to exposure keratitis because all the children were sick and weak.

There were two children with phlyctenules one had bilateral. The possible explanation again was the hypersensitivity to tuberculin protein because one patient had diagnosis of pulmonary tuberculosis and other had tuberculous arthiritis. One child had perforated RE due to keratomalacia.

It seems therefore, that corneal lesions are not only more prevalent in HIV positive children, but their pathogenesis is in agreement with what is known about the effect of opportunistic infections of the ocular surface indicating their relationship with HIV infection in children. If we compare corneal lesions in both groups statistically the relationship is not significant ($P > 0.05$) probably because the children suffering from corneal lesions were less or the sample size was small to compare. Conjunctival and corneal phlyctenule are only seen in HIV positive children indicating their importance for HIV infection.

3. **Prevalence of fundus abnormality:**

The prevalence of fundus lesions was markedly high in HIV positive children. The incidence was 18% as compared to 4% in HIV negative children. This relationship was statistically significant ($P < 0.05$) (table 3). Similar findings have been reported by Dennehy[12] from USA and Lewallan[28] from Malawi. The incidence of fundus abnormalities in adults is much higher than in children[10,14,15].

Non infectious retinopathy and retinitis is less common in African patients especially African children as compared to patients, from other countries[11,28]. Most of the authors agree that these children die of other severe infections, such as tuberculosis, and do not survive long enough for non-infectious retinopathy to be a major problem.

Bilateral macular edema was the most frequent finding in our series, affecting 8 of the HIV positive children, one had unilateral macular edema. Two of the children seen above, had sheathing of vessels near the inferior poles of the discs. There were two children with haemorrhages one child had bilateral neovascularization below the discs (table 5).

In the literature we have been able to find a case of peripheral vascular sheathing in a study done in Malawi[28]. In another two studies done in Rwanda by Kestelyn[11,18], there were reports of 33% and 46% of peripheral vascular sheathing respectively. Perivascular sheathing was especially very high in African children, perivascular sheathing without an infectious retinitis has been reported but is unusual in AIDS patients in the United States. While the reasons for the difference between Caucasian and African patients in the frequency of perivascular sheathing remains unclear, but it remains a fact that HIV retinopathy in Africans, including our cases, manifest with vascular sheathing and edema of the macula.

The incidence of perivascular sheathing in our series is only 3%, it is contradictory to the figures given by Kestelyn[11,18]. We do not know the exact reasons for the difference but the incidence of perivascular sheathing ranges from 0-15%[13] in different series. We assume that this perivascular sheathing is not an infectious lesion, but probably part of non-infectious AIDS retinopathy[13,21].

In a study done in Rwanda by Kestelyn[27] on 32 HIV positive patients with TB, 5(15.6%) patients revealed ocular lesion due to TB, including disseminated choroiditis, phlyctenulosis, and solitary choroidal granuloma. There are cases presenting with edema of the disc and retina[16] that have been found to have

underlying choroiditis. There was also accompanying TB meningitis, it follows therefore that edema of the retina portends the presence of underlying choroidal disease usually infectious. TB would then be the primary suspect[11,14,28]. In the literature reviewed above, the most probable cause of macular edema could be choroidal tuberculosis because 6 patients had the diagnosis of Pulmonary TB and 2 had TB meningitis, it is quite in a agreement with the outlined pathogenesis of the lesion.

There were two children with haemorrhages, one had a solitary haemorrhage on the nasal side of the disc in the LE, the other had multiple blot haemorrhages below the discs; both children had systemic diagnosis of PTB. Thus it appears that beside edema and sheathing of vessels TB manifests with haemorrhages into the retina. Studies indicate that HIV retinopathy which includes cotton wool spots and haemorrhages are low in children[18], where as the incidence is high in adults[6]. We consider that these retinal haemorrhages are part of HIV retinopathy and we don't know the reason for the low incidence in children[6,14,15,28]. One patients had bilateral neovascularization just below the disc margins, the patients had systemic diagnosis of PTB. Neovascularization may be due to inflammatory condition such as perivasculitis[48].

In HIV negative group of children there was one child with marasmus and bilateral macular edema, we suspect choroiditis as the etiology. The second patient had bilateral optic atrophy and macular edema due to meningitis (table 5). Optic atrophy was probably due to contiguous inflammation secondary to meningitis. Since it is known that neuritis may accompany acute meningitis in children and adults[49].

In HIV negative group of children there was not a single case of retinal haemorrhage, sheathing of retinal vessels and no significant cases of macular edema indicating that fundus findings are specific for HIV postivity.

4. **Other lesions in HIV positive children:**

In the present series there was not a single case of cotton wool spots and CMV retinitis. This it contradictory to studies done elsewhere in children and adults[6,7,10,12,13,17]. The possible reason for the low incidence of cotton wool spots and CMV retinitis is rather high mortality seen in paediatric AIDS[5,12]. The African children die of other severe infections such as TB, as the incidence of TB is very high (74%) in our series. None of our patients manifested Kaposi's carcinoma, cranial nerve palsies and opportunistic infections.

5. **Prevalence of visual acuity abnormality:**

It was a difficulty task to assess the visual acuity in children, however we had a good idea of the gross impairment of vision. In HIV positive children there were 6(10%) children whose visual acuity was abnormal, out of six children only one had NLP-RE due to keratomalacia. The other children had decreased vision due to macular edema in most of the cases (table 6). In HIV retinopathy there is no serious threat to vision unless it is associated with some opportunistic infection which was not found in our series.

CONCLUSIONS AND RECOMMENDATIONS:

This study has shown that the prevalence of ocular manifestations in African children with HIV infecton is high. The commonest manifestations were found in the anterior segment and the fundus. The most frequent finding in the anterior segment was conjunctival xerosis, which was equally prevalent in both HIV positive and HIV negative children. The corneal and retinal findings were more prevalent in HIV positive children indicating its relationship to HIV positivity.

The major systemic diagnosis in both groups was tuberculosis, i.e. in HIV positive it was 74% and HIV negative group it was 37%, indicating its association with HIV infection. In the light of the study done it is recommended that:-

1. All the malnourished children, whether HIV positive or HIV negative, should be given vitamin A supplements with high protein diet.
2. Childen with the diagnosis of tuberculosis should be screened for HIV status.
3. Children with systemic diagnosis of tuberculosis, or with any other opportunistic infections should be thoroughly examined by ophthalmologist, to identify the specific ocular lesions of HIV infection and for possible treatment.

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