Ocular disease in patients with TB and HIV presenting with fever in Malawi

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Summary

Aims **- To investigate ocular disease in Malawian patients with tuberculosis (TB) and HIV in presenting with fever, and to determine if indirect ophthalmoscopy is useful in the diagnosis of mycobacteraemia.**

Methods **- A prospective study of all adult patients admitted with fever to Queen Elizabeth Central Hospital, Blantyre. All recruited patients had an ophthalmic examination, HIV tests, chest x-ray, sputum examinations, bacterial and mycobacterial blood cultures and malaria slide.**

Results **- 307 patients were recruited; 109 (36%) had TB, including 53 (17%) with mycobacteraemia; 255 (83%) had HIV and 191 (62%) had AIDS. Of the patients with TB 102 (94%) had HIV. Choroidal granulomas were found in four patients, all of whom had AIDS; three had disseminated TB with mycobacteraemia, and one had persistent fever but no other evidence of TB. Among the patients with AIDS, 32 (17%) had retinal microangiopathy manifest by cotton wool spots; one (0.5%) had signs of active cytomegalovirus (CMV) retinitis. The presence of microangiopathy was not related to TB.**

Conclusions **- In Malawian patients with TB presenting acutely with fever, choroidal granulomas were found in 2.8%, and were concurrent with mycobacteraemia and AIDS. Ophthalmoscopy was not a useful aid in the diagnosis of mycobacteraemia.**

CMV retinitis is rarely seen in African AIDS patients. This may be due to mortality early in the disease course, or differences in race, HIV sub-type or co-morbidity.

Introduction

TB is the most frequent cause for admission of HIV patients in Africa; but data regarding the ocular consequences of co-infection with HIV and TB are limited.[1] In previous studies of AIDS patients in Malawi and Burundi examined for ocular disease, two thirds had TB, but lesions clearly associated with TB, such as choroidal granulomas, were not seen.[2,3]

Bloodstream infection with *M. tuberculosis* (mycobacteraemia) has recently been recognised as a common cause of fever in Africans admitted to hospital.[4,5,6,7] However culture of *M. tuberculosis* from blood requires specialist techniques and prolonged incubation. Any cheap, practical tools which aid in the diagnosis of mycobacteraemia, such as ophthalmoscopy for choroidal granulomas, would be useful in this setting. Choroidal granulomas are seen as small dome-shaped elevations of the retina, which may be pale. They are presumed to spread haematologically, but the ocular manifestations of TB have not previously been examined in relation to mycobacteraemia.

Ocular complications of AIDS are common, occurring in 70 to 80% of patients in Western countries prior to the advent of highly active anti-retroviral therapy (HAART).[8] The available data suggests that the spectrum of ocular disease caused by AIDS is different in Africa, with cytomegalovirus (CMV) retinitis being uncommon, and Herpes Zoster ophthalmicus and conjunctival squamous cell tumours being more prevalent.[1] CMV retinitis has been found to occur in 0 to 8.5% of AIDS patients in Africa.[9] The rates of HIV related microangiopathy, manifest as cotton wool spots (CWS) and small retinal haemorrhages, in AIDS patients are reported as 8 and 25% in West Africa,[10,11] 10% in Burundi3 and 13% in Malawi.[2]

This study was undertaken as part of an investigation of mycobacteraemia in medical patients, with the primary intention of determining whether ocular fundus examination was useful in the diagnosis of mycobacteraemia. We prospectively studied all adults admitted to medical wards with fever in order to also determine the prevalence and type of ocular manifestations of TB, HIV and AIDS seen in this population.

Patients and Methods

The study recruited adults with a fever or history of fever admitted to the medical wards of Queen Elizabeth Central Hospital, Blantyre, Malawi. Patients were eligible if over 13 years old, with an axillary temperature ≥ 37.4°C. They were recruited in 24 hour periods planned over 11 weeks so as to avoid overwhelming clinical staff and laboratory facilities. Recruitment was on a total of 21 days and the actual days of each week were rotated.

The study was explained to all eligible people and consent obtained if they agreed. Those recruited had a clinical examination and laboratory investigations including three sputum samples examined for acid-fast bacilli, chest x-ray, bacterial and mycobacterial blood cultures, two rapid enzyme linked immunosorbent assays (ELISA) HIV tests, full blood count and blood film for malaria parasites. Treatment and further investigations were guided by normal clinical practice. Laboratory investigations were undertaken by The Department of Medicine, Malawi College of Medicine and the Wellcome Trust Research Laboratories, Blantyre.

Patients had an ocular examination during the first 24 hours of their admission by an ophthalmologist (NB) who was not aware of their diagnosis. This consisted of a bedside examination of eye movements, and torch examination of the external eye, anterior segment and pupillary reactions. After pupil dilation with tropicamide 1% and phenyl ephrine 2.5% eyedrops, the fundus was examined by standard direct ophthalmoscopy, and indirect ophthalmoscopy which requires a specialist technique and equipment to obtain a wide view of the fundus.

The study was approved by the Malawi College of Medicine Research Committee. Differences between proportions were examined for significance by a chi-squared test.

Results

There were 634 people admitted on study days, of whom 347 were eligible for the study, and 334 were recruited. Ocular examinations were not done on 27 patients due to death, discharge or unavailability of patients. 307 (92%) had an ocular examination, and the remaining analysis is on these patients.

The mean age was 32 years (range 14 – 64), and 55% were women. The number of patients with TB was 109 (36%), including 53 (17%) with positive mycobacterial blood cultures. 255 (83%) patients were HIV positive, and 191 (62%) had AIDS. AIDS was defined by the expanded WHO case definition for AIDS surveillance,[12] or Stage 3 or 4 of HIV Disease according to the WHO Staging System.[13] By these definitions TB is an AIDS defining illness in the presence of HIV. Of patients with TB, 102 (94%) had HIV, and therefore AIDS. Patients with TB were 53% of all AIDS cases.

External and Anterior Eye findings

The results of external and anterior eye examination on 307 patients are given in table 1.

Table 1. External eye and anterior segment findings.

External and anterior segment findings	Number. of patients
Corneal scar	6
Conjunctival tumour	3*
Posterior synechiae	3*

* all patients had AIDS

Two of the conjunctival tumours were excised and examined histologically. They were reported as carcinoma in situ, and "squamous cell hyperplasia, with mild to moderate dysplasia".

Signs of previous anterior uveitis (posterior synechiae) were seen in three patients with AIDS. One had mycobacteraemia, but no others had TB.

There were no patients with skin stigmata of previous Herpes Zoster ophthalmicus.

Neuro-ophthalmological findings

Optic disc findings are given in table 2.

Table 2. Optic Disc Findings

Disc Finding	Number of patients n (%)	Diagnosis	Number of patients All	HIV+	AIDS
Normal	282 (92)				
Bilateral disc swelling/ Papilloedema	11 (3.6)	Cryptococcal meningitis & TB	1	1	1
		TB meningitis	1	1	1
		Bacterial meningitis	2	1	1
		Sepsis or pneumonia	4	3	2
		Malaria	1	1	1
		Pyrexia of unknown origin	2	2	2
Hyperaemic discs	7 (2.3)				
		Malaria	4	3	0
		Pneumonia/ Sepsis	3	3	2
Unilateral Disc swelling	2 (0.7)	Pulmonary TB	2	2	2
Disc Haemorrhages	2 (0.7)	Sepsis	1	1	1
		TB adenitis & mycobacteraemia	1	0	0
Other	3				
		Disc drusen	2		
		Myelinated fibres	1		

Two (0.7%) patients with AIDS were diagnosed with cryptococcal meningitis by India ink stain of cerebrospinal fluid. One had a normal ocular examination; one had papilloedema and a sixth cranial nerve palsy.

Chorioretinal findings

Four people, all with AIDS, had clinically suspected choroidal TB granulomas (table 3).

Table 3. Patients with choroidal granulomas. CXR indicates chest X-ray

Patient	Sex	*M. tuberculosis* in sputum	Other findings	Mycobacterial blood cultures	AIDS status	Number of granulomas
1	F	Positive	Pericardial effusion	Positive	AIDS	1
2	M	Positive	TB changes on CXR*	Positive	AIDS	4
3	F	Negative	Miliary TB on CXR	Positive	AIDS	5
4	M	Negative	Persistent fever	Negative	AIDS	2

*infiltration in all 6 zones

Three (2.8% of those with TB) had TB including mycobacteraemia. The fourth person was given a therapeutic trial of TB treatment, because of persistent unexplained fever not responding to broad-spectrum antibiotics. He had no other findings specific to TB, or other causes of choroidal granuloma.

Chorioretinal findings are given in table 4.

Table 4. Chorioretinal findings in all patients, patients with AIDS and patients with TB. CWS indicates cotton wool spot; haem indicates haemorrhage.

Retinal Finding	Number of patients (%) *All*	*AIDS*	*TB*
Normal	243 (79)	140 (73)	84 (77)
CWS alone	29 (9)	23 (13)	17 (16)
CWS and retinal haem	9 (3)	8 (4)	2 (2)
Choroidal granuloma	4* (1)	4* (2)	3 (3)
Active retinitis	1 (0.3)	1 (0.5)	0 (0)
1 – 4 retinal haemorrhages	5 (1)	2 (0)	0 (0)
>25 retinal haemorrhages	2 (0.7)	2 (1)	0 (0)
Scars & incidental findings	16 (5)	11 (6)	3 (3)
Total	307	191	109

(* one also had CWS)

Cotton wool spots (CWS), with or without small retinal haemorrhages, in the presence of HIV were regarded as microangiopathy. 35 (14%) patients with HIV, and 32 (17%) with AIDS, had microangiopathy.

Two patients had CWS but did not have HIV, including one with TB abdominal adenitis and mycobacteraemia, and one with heart failure secondary to rheumatic heart disease (single CWS).

One (0.5%) patient with AIDS had widespread bilateral retinitis with opacified retina, confluent haemorrhages, CWS and vascular sheathing consistent with a CMV retinitis.

Two patients had a large number of discrete retinal haemorrhages, numbering approximately 30 in each eye, over 50% of which were white-centred blot haemorrhages. Both had AIDS and were severely anaemic with haemoglobin values of 3.0 and 3.8 g/dL (median haemoglobin of all patients was 9.6 g/dL, interquartile range 7.4 – 11.6 g/dL). In each case no malaria parasites were found on a single slide examination which makes clinical malaria in immune adults extremely unlikely. Two patients had retinal signs associated with severe malaria in children.[14]

Discussion

This prospective study of ocular disease in Malawian patients presenting with fever includes comprehensive data on TB, mycobacteraemia and HIV. We found presumed choroidal granulomas in 2.8% of febrile Malawians with proven TB. All three TB patients with choroidal granulomas had disseminated TB with M.tuberculosis bloodstream infection (mycobacteraemia). This is the first time that choroidal granulomas have been linked to mycobacteraemia, and the finding is consistent with the

presumed haematological spread of bacilli found in choroidal tubercles.[15,16]

Modern data on the prevalence of choroidal granulomas in TB are extremely limited. Historical data suggests they may be seen in as many as 60% of patients with miliary TB, but are rare in pulmonary TB.[17,18,19] Our figure suggests the prevalence of choroidal granulomas in acute medical admissions with TB in Africa is somewhere in-between. This figure reflects the relatively high prevalence of disseminated TB associated with HIV and immunosuppression. In this study patients with TB mainly had pulmonary TB, but there were eight patients with chest x-ray changes of miliary TB and a high proportion (49%) with disseminated TB in the form of bloodstream infection. It should be noted that one patient with suspected choroidal granuloma had no evidence for TB apart from persistent fever.

We found microangiopathy in 17% of patients with AIDS, which is similar to, although slightly higher than, other studies in central and eastern Africa[2,3] Microangiopathy was also present in 5% of adult medical admissions with HIV, but without AIDS defining illnesses.

Although HIV microangiopathy is the commonest cause of CWS, it is important to recognise that not all patients in African medical wards with CWS and small blot retinal haemorrhages have HIV.

The number of patients with signs of previous anterior uveitis is too small to make any firm conclusions. However all patients with posterior synechiae had AIDS, which may account for the relatively high prevalence of anterior uveitis in general hospital admissions. HIV infection has been associated with uveitis in 170 patients in Zimbabwe.[20]

We found CMV retinitis to be very uncommon, in keeping with other surveys of patients with AIDS in Africa. CMV antibodies are widespread in this population, appearing in 89% of antenatal women (E.Molyneux, personal communication). The reason for the rarity of CMV retinitis in Africa is generally considered to be due to mortality of people with AIDS early in the disease progression, before or shortly after, the onset of profound immunosuppression.[2,3,9] Accelerated disease progression in Africa may mean that life expectancy is short, and hence CMV retinitis is rarely seen.

A second possibility is that differences in race, HIV sub-type and comorbidity may influence the occurrence of CMV retinitis in Africa. A study of 313 Africans with AIDS living in London found that although the prevalence of CMV disease at presentation in Africans was equal to Europeans (4%), the Africans' mean CD4 count was lower than controls (25/mm^3 versus 45/mm^3), and the number subsequently developing CMV disease was significantly lower, despite treatment at the same centres[21]. It remains a possibility that other factors apart from life expectancy influence the development of CMV retinitis. However unless life expectancy dramatically improves for patients with AIDS in Africa it would be difficult to demonstrate the play of other factors. At present CMV retinitis is a rarity in Malawian hospital admissions.

This study has demonstrated that choroidal granulomas occur concurrently with bloodstream infection with *M. tuberculosis*, and that the rate of choroidal granulomas is 2.8% in African TB patients presenting acutely with fever. Examining fundi for choroidal granulomas is not a useful aid in the diagnosis of mycobacteraemia, but their presence can confirm a diagnosis of disseminated TB.

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