

## WORLD VIEW

## Ocular disease in patients with tuberculosis and HIV presenting with fever in Africa

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**Aims:** To investigate ocular disease in patients with tuberculosis (TB) and HIV in Africa 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 a large central hospital in Malawi, Africa. All recruited patients had an ophthalmic examination, HIV tests, chest x ray, sputum examinations, bacterial and mycobacterial blood cultures, and malaria slide to observe the presence of parasites.**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 (2.8% of those with TB) had disseminated TB with mycobacteraemia, and one had persistent fever but no other evidence of TB. Among the patients with AIDS, 32 (17%) had 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. Cytomegalovirus (CMV) retinitis is rarely seen in African AIDS patients. This may be the result of mortality early in the disease course, or differences in race, HIV subtype, or comorbidity.

In the past 15 years sub-Saharan Africa has seen an enormous increase in tuberculosis (TB) cases, largely as a result of associated HIV infection. HIV increases the development of active TB to around 30% of subjects infected with tubercle bacilli.<sup>1</sup> Furthermore, 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.<sup>2</sup> Two thirds of AIDS patients in Malawi and Burundi examined for ocular disease had TB, but lesions clearly associated with TB were not seen.<sup>3,4</sup>

Bloodstream infection with *Mycobacterium tuberculosis* (mycobacteraemia) has recently been recognised as a common cause of fever in Africans admitted to hospital.<sup>5–8</sup> 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 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 70–80% of patients in Western countries before the advent of highly active antiretroviral therapy (HAART).<sup>9</sup> However, the greatest burden of HIV is in sub-Saharan Africa where at least 30 million people are infected, with poor health care and no access to antiviral drugs.<sup>10</sup>

The available data suggest that the spectrum of ocular disease caused by AIDS is different in Africa, with CMV retinitis being less common, and herpes zoster ophthalmicus and conjunctival squamous cell tumours being more prevalent.<sup>2</sup> CMV retinitis has been found to occur in 0–8.5% of AIDS patients in Africa.<sup>11</sup> 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,<sup>12,13</sup> 10% in Burundi,<sup>4</sup> and 13% in Malawi.<sup>3</sup> The prevalent HIV type

in Malawi is almost exclusively HIV-1, in common with other countries in east and southern Africa.

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. This is a large central hospital serving the city of Blantyre and surrounding districts. Patients were eligible if over 13 years old, with either an axillary temperature  $\geq 37.4^{\circ}\text{C}$  or a history of high fever in the preceding 4 days. 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 in their own language, 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 (Uni-Gold, Trinity Biotech, Bray, Ireland, and Abbot Determine, Dainabot Company, Tokyo, Japan), full blood count, and blood film for malaria parasites. The HIV tests did not differentiate HIV-1 and HIV-2 antibodies, and two were used in order to minimise false positive or negative results. 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.

**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.

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. Posterior synechiae were noted but microscopic signs of previous or active uveitis would not have been detected. The fundus was examined by direct and indirect ophthalmoscopy after pupil dilatation with tropicamide 1% and phenylephrine 2.5%.

The study was approved by the Malawi College of Medicine research committee and the tenets of the Declaration of Helsinki were observed.

Differences between proportions were examined for significance by a  $\chi^2$  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 owing 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. A total of 255 (83%) patients were HIV positive and 191 (62%) had AIDS. AIDS was defined by the expanded World Health Organization (WHO) case definition for AIDS surveillance,<sup>14</sup> or stage 3 or 4 of HIV disease according to the WHO staging system.<sup>15</sup> 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 eye and anterior segment findings

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

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. Eleven (4%) patients were judged to have papilloedema; of these eight had AIDS (4% of those with AIDS), and two (2%) had TB, including one with TB meningitis. Two patients with pulmonary TB had unilateral disc swelling, both had AIDS, and neither had evidence of disseminated TB.

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

## Chorioretinal findings

Four people, all with AIDS, had clinically suspected choroidal TB granulomas (Table 3). Three 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. Cotton wool spots (CWS), with or without small retinal haemorrhages, in the presence of HIV were regarded as microangiopathy. Thirty five (14%) of all patients with HIV, and 32 (17%) of those with AIDS, had microangiopathy. Three (5%) patients with HIV, but without AIDS defining features, had microangiopathy (Table 5).

There was no association between the presence of microangiopathy and TB ( $\chi^2$   $p=0.72$ ). The proportion of AIDS patients who had microangiopathy was larger in the group with mycobacteraemia than in those without mycobacteraemia, but this was not statistically significant ( $\chi^2$   $p=0.18$ ).

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).

**Table 2** Optic disc findings

Disc finding	Number of patients		Number of patients		
	No (%)	Diagnosis	All	HIV+	AIDS
Normal	282 (92)				
Bilateral disc swelling/papilloedema	11 (3.6)				
		Cryptococcal meningitis and 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 and mycobacteraemia	1	0	0
Other	3				
		Disc drusen	2		
		Myelinated fibres	1		

**Table 3** Patients with choroidal granulomas

Patient	Sex	<i>M tuberculosis</i> 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

CXR = chest x ray.

\*Infiltration in all 6 zones.

**Table 4** Chorioretinal findings in all patients, patients with AIDS, and patients with TB

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 haemorrhage	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 and incidental findings	16 (5)	11 (6)	3 (3)
Total	307	191	109

CWS = cotton wool spot.

\*One also had CWS.

**Table 5** Proportion of patients with microangiopathy in different groups

AIDS, HIV, and TB status	Proportion with microangiopathy (%)	$\chi^2$ , p value
AIDS	32/191 (17%)	0.72
All HIV	35/255 (14%)	
HIV without AIDS	3/64 (5%)	
AIDS and TB	18/102 (18%)	
AIDS and no TB	14/89 (16%)	
AIDS and mycobacteraemia	12/53 (23%)	0.18
AIDS and no mycobacteraemia	20/138 (14%)	

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.

#### Incidental retinal findings

Sixteen (5%) patients had incidental retinal findings including macular and peripheral chorioretinal scars, epiretinal membrane, and macular hole. One patient had peripheral retinal bone spicule pigmentation with attenuated vessels characteristic of retinitis pigmentosa. Two patients had retinal signs associated with severe malaria.<sup>16</sup>

#### 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 proved TB. All three TB patients with choroidal granulomas had disseminated TB with *M tuberculosis* bloodstream infection (mycobacteraemia). In all there were 53 patients (49% of TB cases) with mycobacteraemia recognised using specialised blood culture techniques with prolonged incubation. 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.<sup>17 18</sup>

Modern data on the prevalence of choroidal granulomas in TB are extremely limited, particularly since the development of AIDS or even the introduction of the indirect ophthalmoscope. Choroidal tubercles were reported in 28% of 737 patients with miliary TB reviewed in the literature by Illingworth and Wright in 1948, although they found 60% in 42 miliary TB patients.<sup>19</sup> Series of patients in TB sanitariums report choroidal granulomas only rarely.<sup>20 21</sup>

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.<sup>3 4</sup> Microangiopathy was also present in 5% of adult medical admissions with HIV, but without AIDS defining illnesses. Morgan *et al* found no microangiopathy in 105 people with HIV living in the community in Uganda,<sup>22</sup> but patients in our study are likely to be further in the disease progression than the HIV population at large.

The presence of microangiopathy was not related to TB. AIDS patients with mycobacteraemia tended to have more

retinal microangiopathy, but this was not statistically significant. A higher prevalence of microangiopathy in patients with mycobacteraemia may reflect their overall worse state of health.

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 posterior synechiae is too small to draw any firm conclusions. However, only one patient with this sign of previous anterior uveitis had TB, and this was detected by mycobacteraemia alone. 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.<sup>23</sup>

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.<sup>3,4,11</sup> The prevalence of CMV retinitis in pre-HAART American AIDS patients was 20%, 2 years after their CD4 count fell below  $100 \times 10^6/l$ .<sup>24</sup> CD4 counts have been found to be below  $100 \times 10^6/l$  in as many as 25% of hospitalised AIDS patients in Africa,<sup>4</sup> but accelerated disease progression may mean that their life expectancy is short, and hence CMV retinitis is rarely seen.

A second possibility is that differences in race, HIV subtype, and comorbidity may influence the occurrence of CMV retinitis in Africa. This hypothesis is strengthened by a study of 313 Africans with AIDS living in London.<sup>25</sup> Although the prevalence of CMV disease at presentation in Africans was equal to controls (4%), the Africans' mean CD4 count was lower than controls ( $25 \times 10^6/l$  versus  $45 \times 10^6/l$ ), and the number subsequently developing CMV disease was significantly lower, despite treatment at the same centres. 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 effect of other factors.

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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