Eye examination for early diagnosis of disseminated tuberculosis in patients with AIDS

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Choroidal tuberculosis is present in 5–20% of patients with disseminated tuberculosis, and point-of-care dilated binocular indirect ophthalmoscopy eye examination can provide immediate diagnosis. In geographical areas of high tuberculosis prevalence and in susceptible patients (CD4 counts less than 200 cells per μL) detection of choroidal granulomas should be accepted as evidence of disseminated tuberculosis. With training and proper support, eye screening can be done by HIV/AIDS clinicians, allowing early tuberculosis treatment. In regions with a high burden of tuberculosis, we recommend that eye screening be a standard part of the initial assessment of susceptible patients, including at a minimum all patients with HIV/AIDS with CD4 less than 100 cells per μL with or without eye symptoms, and with or without suspicion of disseminated tuberculosis.

Introduction

Tuberculosis is the leading cause of death in patients with HIV/AIDS. In 2013 there were 360 000 deaths from tuberculosis in patients infected with HIV,[1] and in many settings up to half of patients with HIV are co-infected with tuberculosis,[2] although there is substantial regional variation. Autopsy data suggest that 32–45% of deaths in some settings might be attributable to tuberculosis,[3] and up to half of patients with AIDS who die from tuberculosis might not be correctly diagnosed until autopsy.[4]

Improving diagnostic capacity for tuberculosis is an important issue. Patients with low CD4 cell counts are the most challenging group to diagnose with tuberculosis quickly because these patients are more likely to have widely disseminated or miliary tuberculosis[5,6] with non-specific symptoms, negative sputum smear microscopy, and a negative chest radiograph.[7] Unfortunately, in middle-income and low-income settings, one in five patients still present with a CD4 cell count less than 100 cells per μL.[8]

Disseminated tuberculosis might present as choroidal tubercles, and in some patients this eye finding can be the earliest sign of disseminated tuberculosis.[9] William Osler[10] and Ernst Fuchs[11] meticulously described the diagnostic value of the choroidal tubercle in their seminal textbooks of medicine and ophthalmology more than a century ago. Yet despite this insightful legacy, eye examination is ignored in WHO diagnostic guidelines,[12] related algorithms,[13] and in analysis of improving tuberculosis diagnostics.[14,15] We revisit this sign for disseminated tuberculosis in a new clinical setting, the global epidemic of HIV/AIDS.

In this Personal View we discuss the diagnostic findings of disseminated tuberculosis visible on eye examination and the historical context of how this tool became neglected. We discuss modern examination techniques and how eye screening can be implemented at the point of care, by non-ophthalmologist HIV/AIDS clinicians. Finally, we discuss the rich clinical value of including systematic point-of-care eye screening in the initial assessment of all patients with AIDS with low CD4 counts, and suggest that the eye examination might be a tool for reduction of all-cause AIDS mortality.

Tuberculosis infection in the eye

Tuberculosis can cause disease in virtually any ocular or adnexal tissue, either directly or by secondary haematogenous spread. The range of symptomatic eye disease caused by tuberculosis has been well described,[8,16–19] including in patients with HIV infection.[20]

Early in the AIDS epidemic, in a large autopsy series from the USA,[21] it was reported that foci of infectious agents that present in the choroid of the eye represented systemic dissemination, and in virtually all cases the infectious organism reported in the choroid was the cause of death. The choroid is the vascular coat of the eye, lying beneath the translucent retina, and provides for the nutrition and oxygenation of the outer retina. The choroidal circulation dissipates the heat generated by the focusing of light at the macula,[22] and this might be the reason it receives the highest blood flow in the body per unit of tissue. A result is that this circulation offloads only a small amount of oxygen, providing the choroid with an oxygen-rich environment analogous to the apex of the lung.

The choroidal tubercle is the most common form of ocular tuberculosis.[8,18–20,23] Choroidal tubercles were anatomically described in 1855, identified with an ophthalmoscope in 1867, produced experimentally by injecting tuberculous material in 1867, and given detailed ophthalmoscopic description in 1868. *Mycobacterium tuberculosis* was identified in the eye in 1883, only one year after discovery of the organism by Koch.[18]

Clinically, choroidal tubercles (figure) are typically small (a third to half the size of the optic disc), flat or raised greyish-yellow lesions with soft indefinite margins. They might be seen in one or both eyes and are usually located within a few disc diameters from the optic nerve.[23,24] The tubercules can be single or multiple (sometimes exceeding 50), with most eyes harbouring fewer than five lesions. If the infectious focus enlarges to several disc diameters, it can be called a tuberculoma, or a choroidal granuloma; for diagnostic reasons, these lesions can be collectively called choroidal tuberculosis.

Choroidal tuberculosis has a characteristic appearance. Similar lesions can be produced by sarcoidosis,[25] cryptococcus or other infectious organisms,[21] lymphoma,

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Figure: Digital retinal photograph of a typical choroidal tubercle
The optic disc is located at the 6 o'clock position, and the choroidal tubercle is located a disc diameter superior-nasal to the optic disc, lying beneath a retinal vein. The lesion is about a third the diameter of the optic disc.

and metastatic malignancy.[26] Attention should be paid to cryptococcal serology in appropriate cases, because asymptomatic early disseminated cryptococcal disease (ie, cryptococcal antigenaemia in blood) might have a similar prevalence to tuberculosis,[27] and cryptococcal choroiditis can rarely be the initial feature of disseminated cryptococcal infection.[28] If a patient has signs of meningitis and choroidal lesions, a lumbar puncture must be done. However, for a patient with AIDS with a low CD4 count in a setting with high tuberculosis prevalence, a choroidal granuloma has a high positive predictive value for tuberculosis on the basis of Bayesian probability[29] and can be supported by response to treatment.[30]

Clinically, detection of choroidal granulomas in a susceptible population should be accepted as ophthalmoscopic evidence of disseminated tuberculosis, much as ophthalmologically diagnosed cytomegalovirus retinitis was deemed an AIDS-defining illness. Diagnostic lesions might be without symptoms in 70% of cases (table), so eye examination needs to be done in patients with and without eye symptoms, and in patients with and without clinical signs of tuberculosis.

Sharma and colleagues[41] stated that "fundus examination for detecting choroid tubercles must be done in all patients with suspected miliary tuberculosis as their presence is pathognomonic of miliary tuberculosis".

Historical perspective: three eras
From 1890 to the 1950s, decades before the advent of AIDS, careful eye examination was a fundamental part of clinical care. The diagnostic value of the choroidal tubercle was part of the medical canon.[10,17] The limited medical technology and emphasis on physical examination of this period conveys lessons for HIV/AIDS care in resource-limited settings.

In 1948, a review of 737 patients[42] reported detection of choroidal tubercles in 206 (28%) of 737 patients with miliary tuberculosis. A later autopsy study of miliary tuberculosis[43] reported that eye examination exceeded chest radiography in diagnostic sensitivity: diagnostic choroidal tubercles were detected clinically in 25 (52%) of 48 children, whereas chest radiography was positive in only 18 (35%) of 52.[43]

Infants and children were the most conspicuous of those affected[24,43] and miliary tuberculosis was even described as a disease of infancy.[16] As in the case of late-stage HIV disease, such predisposition is probably a result of the relative immunodeficiency of early life.[44] Although findings suggest that the mechanisms underlying such immune suppression in adults infected with HIV and in infants might differ,[45] the patient in each case is less capable of containing or eliminating agents such as tuberculosis than are immunocompetent adults. These early findings made in young children seem to foreshadow the current clinical picture of disseminated tuberculosis in patients with AIDS.

In the 40 years after 1950, the diagnostic value of choroidal tuberculosis was progressively disregarded. In places where clinicians were skilled in eye examination, then mainly the USA and western Europe, disseminated tuberculosis became increasingly uncommon. In Boston, for example, cases of tuberculosis fell by over half in the decade following 1968, with all of the forms of extrapulmonary disease accounting for less than 5% of cases.[46] Miliary tuberculosis became increasingly rare, about 1% of all tuberculosis cases.[47] As new laboratory diagnostic tests became available eye examination gradually received less attention from general physicians and became the domain of specialists.

In the 1960s, choroidal tubercles were reported in four (57%) of seven patients in one study[48] and five (13%) of 40 patients in another.[49] But by 1980, an autopsy series of 100 cases of late generalised tuberculosis reported that seven (50%) of the 14 eyes available for study had granulomas in the choroid[50] that could have easily been noted ante mortem—although none of these patients had been diagnosed with tuberculosis based on their eye findings. A subsequent review[46] of 71 patients with extrapulmonary tuberculosis provided no information about examination of the eye and a series[51] of 857 patients with confirmed tuberculosis meningitis does not describe properly looking for, or report finding, a single example of a choroidal tubercle.

By 1990, with miliary tuberculosis increasingly rare in high-income countries, few infectious disease specialists had ever seen choroidal tuberculosis. This included most ophthalmologists who were expert in the ocular features

	Location	Study features	Tuberculosis status	HIV status	Choroidal tuberculosis	Eye symptoms
Lewallen, 1994[31]	Malawi	Consecutive patients admitted to a general hospital	69% with tuberculosis (68/99)	All with AIDS CD4 counts unknown	1% (1/99)	Single patient had no eye symptoms
Bouza, 1997[23]	Spain	Randomly selected patients with extrapulmonary tuberculosis	All patients with positive culture and extrapulmonary tuberculosis	11/17 of choroidal TB patients HIV positive over half of patients HIV positive	17% (17/100)	65% (11/17) with no eye symptoms
Cochereau, 1999[32]	Burundi	Consecutive patients admitted to a general hospital	61% with tuberculosis	All with AIDS CD4 >100 cells per µL in 75% (86/115) of patients tested	0	..
Mert, 2001[33]	Turkey	Retrospective record review of 38 patients 23 patients had eye exam	All with miliary tuberculosis	No patients with diagnosed HIV But no patients screened for HIV	17% (4/23)	No information
Beare, 2002[34]	Malawi	Prospective study of 307 adults admitted to general hospital with fever; 109 with tuberculosis; 102 with tuberculosis and AIDS	All 102 patients with tuberculosis Blood culture positive for tuberculosis in 53 patients	All 102 patients with AIDS CD4 counts unknown	3·9% (4/102) of patients with AIDS and tuberculosis 5·7% (3/53) of patients with AIDS and tuberculosis blood culture	No information
Mehta, 2004[35]	India	Ten patients in the intensive care unit with mycobacteraemic sepsis	Blood culture positive for tuberculosis	All patients HIV negative	50% (5/10)	No information
Mehta, 2005[36]	India	Prospective cross-sectional study of 46 patients from an outpatient HIV clinic	17 patients with active tuberculosis	All HIV positive CD4 counts: 58, 45, 131, NA	24% (4/17)	50% (2/4) with no eye symptoms
Mehta, 2006[37]	India	Prospective study of 52 patients with neurotuberculosis	All with tuberculosis CNS disease	Four patients HIV positive	35% (18/52)	No information
Babu, 2006[20]	India	Tertiary care eye hospital Patients with eye symptoms	About half with tuberculosis	All HIV positive, with eye symptoms or CD4 <200 cells per µL	1·7% (13/766)	All with eye symptoms
Saranchuk, 2013[38]	Southern Africa	Consecutive series Screening for cytomegalovirus retinitis	About half with tuberculosis	All HIV positive with CD4 <100 cells per µL	5·2% (10/192)	No information
Heiden, 2013[39]	Uganda, South Africa, Thailand, Laos, Myanmar, China, Russia	Consecutive series Screening for cytomegalovirus retinitis	About half with tuberculosis	All HIV positive with CD4 <100 cells per µL	5·8% (66/1137)	87·9% (58/66) with no eye symptoms
Mehta, 2013[40]	India	Cross-sectional study of 47 patients co-infected with HIV and multidrug-resistant tuberculosis	All with multidrug-resistant tuberculosis	All HIV positive	10·6% (5/47)	No information

Table: Reports of choroidal tuberculosis in patients with and without HIV infection since 1990

of HIV/AIDS, because the HIV epidemic first unfolded in high-income countries where the prevalence of tuberculosis is low. There is no mention of tuberculosis in the early landmark reports on ocular features of HIV/AIDS because it was not encountered clinically,[52,53] and reviews gave tuberculosis negligible attention.[54] The collective clinical memory of the diagnostic value of the choroidal tubercle was lost over a gap of more than two generations.

Since 1990, more than 50 million people have become infected with HIV in geographical regions of high tuberculosis prevalence, and ophthalmic diagnostic capacity has improved in several regions with a high burden of tuberculosis, such as India. Published work is uneven and inconsistent, particularly with regard to Africa,[31,32,34,38,39] for reasons that remain unclear. Studies are difficult to compare because of differences in design, patient population, and reporting of HIV status. A variable that is even more difficult to address is differences in skill, technique and motivation of the clinicians performing the eye examination.

Two studies[34,35] specifically address choroidal tuberculosis in patients later discovered to have bacteraemia because of *Mycobacterium tuberculosis*: lesions were identified in three (5·7%) of 53 consecutive patients admitted to a hospital in Malawi because of fever[34] and in five (50%) of ten patients who were in an intensive care unit in a hospital in India.[35] Mycobacteraemia was first reported in patients with AIDS in 1986,[55] and is associated with low CD4 counts, disseminated infection, severe disease, and high mortality,[56] including a report from Tanzania of 50% mortality in 36 days.[57]

Many modern investigators have endorsed the diagnostic value of eye examination for diagnosis of disseminated tuberculosis.[23,41,42,58–60] Summarised in the table are reports of choroidal tuberculosis since 1990, in patients both with and without HIV infection.[33,36,37,40] Taking current and historical data as a whole, it seems that at least in areas of high tuberculosis prevalence in Asia, choroidal tuberculosis (usually without symptoms) might be detected in 5–20% of patients with disseminated tuberculosis.

Implementation

HIV/AIDS clinicians are best positioned for performing eye screening for tuberculosis because diagnosis of

opportunistic infections is an integral part of their work. Ophthalmologists are not often available to do routine eye examinations for patients with HIV/AIDS in resource-limited settings,[61] and in middle-income and low-income countries they have other defined priorities that fit their availability and skills.[62] A realistic role for ophthalmologists is to provide training, support for operational research, and quality control, but not routine eye examination at the point of care.

Eye examination by appropriately trained (non-ophthalmologist) clinicians at the point of care is feasible. A pilot study[38] by a trained clinician in southern Africa reported diagnostic signs of choroidal tuberculosis in ten (5·2%) of 192 consecutive patients with AIDS with CD4 counts less than 100 cells per μL. Since 2007, indirect ophthalmoscopy has been taught to HIV/AIDS clinicians in Myanmar, China, and Russia.[63] In Myanmar, most patients newly diagnosed with HIV infection and having a CD4 count under 100 cells have routine retinal examination with indirect ophthal-moscopy by HIV clinicians at the point of care[63,64] and, although the initial motivation was for improved diagnosis of cytomegalovirus retinitis,[64] attention is increasingly being given to diagnosis of disseminated tuberculosis. Non-ophthalmologists can accurately diagnose cytomegalovirus retinitis with an indirect ophthalmoscope, which suggests that they would be able to reliably diagnose choroidal tuberculosis if given appropriate training.[65]

In all relevant clinical settings we encourage eye examination with the best tools available. For clinicians without training in indirect ophthalmoscopy but already skilled in use of the direct ophthalmoscope (or variations thereof—eg, the PanOptic Ophthalmoscope, Welch

Allyn, Skaneateles Falls, NY, USA), we note that there has never been a comparative study, and that most choroidal tubercles are within several disc diameters of the optic nerve. However, eye examination for choroidal tuberculosis with the direct ophthalmoscope, with only a narrow 7-degree field of view is laborious, and it is easy to pass by and miss choroidal tubercles that are small and have indefinite margins.

In the 1950s the binocular indirect ophthalmoscope largely supplanted the direct ophthalmoscope as the standard tool for study of the retina. With even basic proficiency, superiority of the indirect ophthalmoscope is obvious. The binocular indirect allows a wide-field birds-eye view (58–75 degrees with the Volk 30 Diopter lens), a three-dimensional image, and detection of small lesions.

Irrespective of the instrument, the pupil of the eye must be well dilated before examination of the eye. In a cooperative patient with dilated pupils, a trained clinician can perform retinal examination by indirect ophthalmoscopy at the point of care (ie, at the bedside or in any inpatient or outpatient clinical setting) in less than 2 min.

The costs of equipment for implementation are low: an indirect ophthalmoscope (eg, ScanOptic model 2200) costs about US$1892, with a 28 dioptre lens (eg, Volk, model V28LC) costing about $265, and both can be used an indefinite number of times for periods as long as a decade. A bottle of eye drops to dilate the eyes of 25 patients for examination cost 4 cents per patient (eg, Aurolab, Auromide Plus 5 mL, $1·10/bottle), and training can be provided in a 4-day workshop.[65] Once equipment, dilating drops, and skills are in place the incremental cost of including eye examination as part of the standard physical examination is negligible. Eye examination easily fulfils criteria for an appropriate screening test for both choroidal tuberculosis and cytomegalovirus retinitis, disorders that are common, treatable, and easy to diagnose, and for which the result of delayed diagnosis is severe.[66]

Telemedicine, an additional approach for identifying diagnostic eye findings, has been investigated.[67] Although the choroidal tubercle is most common and easily identified, there is variability in the appearance of tuberculosis in the eye.[19,68] With retinal photography and telemedicine support, a reference library, and panel of expert consultants, the diagnostic accuracy for detection of retinal lesions could continually be improved. An analysis[69] of clinical decision making showed that the visual specialties have the lowest rates of diagnostic error.

Physical eye examination in patients with AIDS

The first moments with a patient establish both the effectiveness and cost of subsequent care.[70] History and physical examination offer the possibility of immediately clinching a diagnosis at the earliest possible stage of disease, yet investigations into the precision and accuracy of physical examination have lagged behind laboratory tests. Among other reasons, one observation is that most

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Panel 1: Two cases of disseminated tuberculosis diagnosed with eye examination

1) A 36-year-old woman presented Jan 15, 2015 with 2 months of non-specific symptoms (decreased appetite, weight loss, intermittent fever, and intermittent cough) and a CD4 count of 39 cells per μL. On initial examination the patient was afebrile with clear lungs, but based on identification of a choroidal tubercle the patient was diagnosed with disseminated tuberculosis and started on treatment. The decision was made to attempt sputum induction, and 4 days later a specimen was obtained. The scant specimen was smear negative, but positive by Xpert MTB/RIF assay. On examination March 12, 2015, the patient was afebrile, had gained weight, the cough had cleared, and the choroidal tubercle was healed.

2) A 34-year-old woman with CD4 count of 6 cells per μL was started on antiretroviral therapy (ART) in late December, 2012, after standard tuberculosis screening, including sputum microscopy and abdominal ultrasonography, had been negative. In the following month on ART there had been no weight gain or clinical improvement. There were no eye symptoms and vision was normal when indirect ophthalmoscopy was done after a month of failed ART (indirect ophthalmoscopy was just then introduced into the programme). The right eye showed two typical choroidal tubercles and the left eye showed active cytomegalovirus retinitis. The patient was started on tuberculosis treatment, and was given intraocular ganciclovir injection for cytomegalovirus retinitis (no systemic cytomegalovirus treatment was available). The patient did not survive.

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clinical investigators are not particularly clinical and spend little time at the bedside.[70] We have included two case summaries to provide a bedside perspective (panel 1).

The identification of choroidal tuberculosis enables the clinician to make two crucial decisions. First, the clinician can immediately initiate tuberculosis therapy, before radiographic or bacteriological studies are even ordered. Second, if drug-resistant tuberculosis is a concern, the clinician immediately knows that it is necessary to aggressively proceed with appropriate measures to obtain a bacteriological specimen to test for drug resistance. Case 1 provides an example of both points.

The patient in case 2 did not survive, but might have survived if disseminated tuberculosis had been treated a month earlier. Perhaps the patient died from disseminated cytomegalovirus infection, or the inter-action of both unchecked infections with HIV. We have no doubt that integrating eye screening by indirect ophthalmoscopy into routine care for all patients first presenting with advanced HIV will reduce all-cause mortality. However, the isolated contribution to reducing tuberculosis mortality might be unknowable (panel 2).

The optimum CD4 count threshold for screening eye examination is unclear. Extrapulmonary tuberculosis is most common in patients with CD4 less than 200 cells per µL, and disseminated or miliary tuberculosis more common in patients with CD4 less than 100 cells per µL.[5–7] Cytomegalovirus retinitis, as in case 2, might be diagnosed in 5–20% of the patients with CD4 less than 100 cells per µL.[53–54] Cytomegalovirus retinitis is strongly linked to mortality, commonly underdiagnosed, and rarely treated with needed systemic drugs.[71] A study from Myanmar reported that a third of patients diagnosed with cytomegalovirus retinitis on eye screening and given only local intraocular ganciclovir failed to survive 3 months.[72]

Cotton wool spots, present in 15–50% of patients with low CD4 counts,[52–54] are strongly associated with high HIV viral load.[73] They resolve quickly with ART, and might be clinically helpful for monitoring response to ART in settings without access to viral load testing, identifying patients who are non-adherent. In 1–3% of patients, eye examination might show ocular syphilis, necrotising herpetic retinopathy, or toxoplasmosis.[52–54]

As articulated by Leff,[74] "all stakeholders should encourage and reward diligent bedside care".

Conclusion

Early detection of disseminated tuberculosis is paramount in patients with low CD4 counts, because they are at high risk of mortality. Choroidal tubercles represent an oft-overlooked diagnostic sign. As summarised in panel 2, it is feasible for HIV/AIDS clinicians to perform eye examination by indirect ophthalmoscopy at the point of care, and we suggest that retinal examination should be part of the basic initial

> **Panel 2: Steps to establish eye examination in the diagnostic strategy for diagnosis of disseminated tuberculosis in patients with HIV/AIDS**
>
> - Update of WHO guidelines for diagnosis of extrapulmonary tuberculosis and smear negative tuberculosis to incorporate eye examination by indirect ophthalmoscopy.
> - Institution of pilot programmes for eye screening in selected HIV/AIDS treatment projects, with provision of training, dilating drops, equipment, and supervision.
> - Development of a training website devoted to eye skills for HIV/AIDS clinicians. The website will host training material; mechanisms for self-instruction, testing, and competency validation of didactic material; links to instructional videos; key references from the medical literature; links and references for obtaining and maintaining necessary equipment and drugs; and a bulletin board or chat room so that geographically distant clinicians can share lessons learned and seek solution to difficulties.
> - Formalisation of eye workshop training module with development of curriculum for training the trainers.
> - Development of a simple, reliable, affordable digital retinal camera that will allow telemedicine for mentoring newly trained clinicians, quality control, and operational research.
> - Development of a photographic reference library with examples of variations in the appearance of choroidal tuberculosis.
> - Operational research to establish the cost-benefit of eye examination compared with other diagnostic measures, and this analysis would include adjunct benefits of eye exam, such as detection of cytomegalovirus retinitis and HIV retinopathy.
> - Operational research in how to most effectively integrate eye examination with other diagnostic measures.
> - A prospective randomly controlled trial of HIV/AIDS patients who first present with advanced disease, comparing all-cause mortality in a cohort that has immediate point-of-care eye screening for opportunistic infections with a cohort that does not have eye screening.

clinical assessment for at least all patients with CD4 less than 100 cells per µL, and for all patients infected with HIV, irrespective of CD4 count, if there are eye symptoms or clinical suspicion of disseminated tuberculosis. HIV/AIDS clinicians need training in indirect ophthalmoscopy and eye diagnostic skills, and we call for WHO leadership to provide appropriate guidelines for use of eye examination, and support countries' efforts to scale up this service. Finally, we encourage operational research to promote the implementation of eye examination into clinical practice.

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