Fungal burden and raised intracranial pressure are independently associated with visual loss in HIV-associated cryptococcal meningitis

Síle F Molloy[1,2], Brad Ross[1], Cecilia Kanyama[3], Sayoki Mfinanga[4,5], Sokoine Lesikari[4], Robert S Heyderman[6,7,8], Newton Kalata[7,8], Jayne Ellis[7,8,9] , Charles Kouanfack[10], Duncan Chanda[11], Elvis Temfack[12,13,] Shabir Lakhi[14], Anand Moodley[15], Adrienne K. Chan[16,17], Joep J. van Oosterhout[18,19], Yacouba Mapoure[12], Peter Mwaba[20], David G. Lalloo[5], Duolao Wang[5], Olivier Lortholary[21,22], Shabbar Jaffar[5], Mina C Hosseinipour[3,23], Angela Loyse[1,2], Thomas S Harrison[1,2], Tihana Bicanic[1,2]

1. Centre for Global Health, Institute of Infection and Immunity, St George's University of London, London, UK.
2. Clinical Academic Group in Infection, St George's University Hospital, London UK
3. UNC Project, Kamuzu Central Hospital, Lilongwe, Malawi
4. National Institute for Medical Research, Muhimbili Centre, Dar es Salaam, Tanzania.
5. Liverpool School of Tropical Medicine, Liverpool, UK
6. University College London, London, UK
7. Malawi-Liverpool-Wellcome Trust Clinical Research Programme, Blantyre, Malawi,
8. College of Medicine, Queen Elizabeth Hospital, Blantyre, Malawi
9. The Hospital for Tropical Diseases, University College Hospital, London UK
10. Hôpital Central Yaoundé/Site ANRS Cameroun, Yaoundé, Cameroon
11. Institute for Medical Research and Training, University Teaching Hospital, Lusaka, Zambia
12. Douala General Hospital, Douala, Cameroon
13. National Public Health Laboratory, Yaounde, Cameroon.
14. University Teaching Hospital, Lusaka, Zambia
15. Department of Neurology, University of the Free State, Bloemfontein, South Africa
16. Dignitas International, Zomba Central Hospital, Zomba, Malawi,
17. Division of Infectious Diseases, Department of Medicine, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Canada
18. Partners in Hope, Lilongwe Malawi
19. David Geffen School of Medicine, University of California, Los Angeles, USA
20. Department of Internal Medicine and Directorate of Research and Post graduate studies, Lusaka Apex Medical University, Lusaka, Zambia
21. Institut Pasteur, Molecular Mycology Unit, CNRS URA3012, Paris, France
22. Paris Descartes University, Necker Pasteur Center for Infectious Diseases and Tropical Medicine, IHU Imagine, APHP, Paris, France
23. University of North Carolina, Chapel Hill, United States

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Corresponding author: Tihana Bicanic, Institute of Infection and Immunity, St George's University of London, London SW17 0RE, United Kingdom tel +44 20 87252911 tbicanic@sgul.ac.uk

Alternate corresponding author: Sile Molloy (contacts as above) smolloy@sgul.ac.uk

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Abstract

Amongst 472 patients with HIV-associated cryptococcal meningitis, 16% had severe visual loss at presentation, of whom 46% of 4-week survivors remained severely impaired. Baseline CSF opening pressure ≥40 cmH_20 (aOR 2.56, 95% CI 1.36-4.83, p=0.02) and fungal burden >6.0 log_{10}Colonies/ml (aOR 3.01, 95%CI 1.58-5.7, p= 0.003) were independently associated with severe visual loss.

Introduction

HIV-associated cryptococcal meningitis (CM) is the commonest cause of adult meningitis in sub-Saharan Africa, and accounts for ~180,000 deaths/year globally[1]. In addition to headache, CM often presents with altered mental status, raised intracranial pressure (ICP) and hearing and visual loss[2], with survivors often experiencing neurological sequelae[3-5]. In CM, visual loss is usually bilateral, can be sudden or gradual in onset, occurs before or during antifungal treatment, and - especially without intervention - is frequently irreversible[3, 5, 6]. Evaluation of visual acuity in encephalopathic patients is challenging: the few CM cohorts (HIV and non-HIV) that systematically examined visual acuity report a prevalence of 33%-46% for any visual impairment (<6/6 Snellen chart), with profound visual loss (<6/60) occurring in 13% of patients[5-7].

Proposed mechanisms of visual loss include direct optic nerve infiltration by cryptococci (demonstrated on autopsy as well as tissue biopsy), inflammatory arachnoiditis, or optic nerve compression through raised ICP or a more localised optic nerve compartment syndrome[5], with both fungal burden and raised ICP implicated in its pathophysiology[3, 8]. Prior, small retrospective cohorts (<100 patients) suggested that high fungal burden (cerebrospinal fluid (CSF) cryptococcal antigen titre>1024) or raised ICP (CSF opening pressure(OP) >30cm H_20) are associated with visual loss in CM, but have been too small to undertake multivariable analyses[3, 6]. Here we report on the prevalence, risk factors and reversibility of visual loss in a large prospective CM patient multi-country cohort in sub-Saharan Africa[9].

Methods

Anonymised data from the ACTA (Advancing Cryptococcal Meningitis Treatment in Africa, ISCRTN 45035509) trial formed the dataset for this pre-planned sub-study[9]. Between 2013 and 2016, 678 adults with HIV CM were randomised to oral fluconazole plus flucytosine or amphotericin B-based therapy for one or two weeks. Patients had protocol-specified lumbar punctures (LPs) on day 1, 7 and 14 with OP measurements and therapeutic CSF drainage according to guidelines[10].

Visual acuity (VA) was measured at baseline ($\leq$3 days from enrolment) and at 4 weeks using the standardised logMAR chart in surviving patients whose conscious level permitted assessment. The score, ranging from 0 (able to read all letters on the smallest line) to 1.375 (unable to read any letters), was recorded for each eye. Those unable to read any letters were assessed for finger counting, hand movement and light perception. Those without light perception were considered blind. Patients were classified into 6 categories: 1. Near-normal vision (score<0.5), 2. Moderate visual loss (score ≥0.5 but <1.0), 3. Finger counting (score ≥1.0 and able to count fingers), 4. Hand motion perception, 5. Light perception, or 6. No light perception. When VA varied between the left and right eye (9.3%, 44/472), data for the worst eye was analysed. Patients did not routinely undergo CT brain or fundoscopy to assess for papilloedema or other ocular pathology.

Data were analyzed using Stata v15 (StataCorp, USA), using Kruskal-Wallis tests for continuous variables, chi-squared tests for categorical variables and quantile regression to test for trend across the 6 visual acuity categories. Based on proposed pathophysiological mechanisms, univariable and multivariable logistic regression was used to investigate the association between baseline visual loss and CSF white cell count (WCC), OP and fungal burden, adjusted *a priori* for age. Sex, CD4 count and ART status (naïve or exposed) were not associated with visual loss and no other measured variables were hypothesised to confound the relationship. For analysis of the association between VA, CSF OP and fungal burden, VA was dichotomised into near-normal/moderate vision (categories 1 and 2) and severe visual loss (categories 3-6), similar to definitions in [4].

To assess impact of antifungal therapy and therapeutic LPs on reversibility of visual impairment, rate of clearance of infection, number of LPs performed, total CSF volume removed and change in OP over 2 weeks' treatment was compared between those with repeat measurements at 4 weeks in whom acuity deteriorated and those who improved; and in those that remained severe vs improved from severe.

Patient consent statement

Written informed consent was obtained from all participants in ACTA. Ethical approval was granted by the London School of Hygiene and Tropical Medicine Research Ethics Committee and by national research ethics committees and regulatory bodies in Malawi, Zambia, Cameroon and Tanzania.

Results

Baseline data

Of 678 ACTA participants, VA was measured in 472 (69.6%) at baseline. 75 patients (15.9%) had severe visual loss with 20 (4%) classed as blind. One fifth (15/75) of those with severe visual loss also reported hearing loss.

Overall, 206 (47.1%) patients had raised baseline ICP (OP≥25cm H_20) and median fungal burden was 4.9 log_{10}colonies/ml (IQR: 3.7-5.8) (Supplementary Table 1). *C neoformans* was the predominant species causing CM in this African cohort (337/382 sequenced isolates). Due to difficulties in measuring VA in unconscious patients, the VA cohort had less abnormal mental status (GCS<15) (12.5% vs 50.5%, p<0.001) and lower median OP (19 vs 25cmH_20, p<0.001), but no significant differences in median fungal burden (4.9 vs 5.1 log_{10}colonies/ml, p=0.74), compared to the entire trial cohort.

Association between severe baseline visual loss, opening pressure and fungal burden

Across 6 categories from near-normal to blind, decreasing visual acuity was associated with both increased OP and higher fungal burden at baseline (p=0.02 and p<0.008, respectively) (Fig 1a and b). High OP and fungal burden were also associated, with 55 (25.6%) patients with fungal burden above the median (≥4.9 log_{10} colonies/ml) also experiencing high OP (>40cm H_20)- compared to 33 (15.4%) with lower fungal burden (p=0.009).

In multivariable analyses, age; baseline CSF pressure <25 cm vs ≥40cmH_20: aOR 2.56 (95% CI 1.36-4.83, p=0.02) and fungal burden (<5 vs >6.0log_{10}Colonies/ml: aOR 3.01 (95% CI 1.58-5.7, p= 0.003) were independently associated with severe visual loss (Table 1). There was no association between baseline CNS inflammation (CSF WCC>10x10^9/L) and visual loss on either univariable or multivariable analyses.

Changes in visual acuity over time

Paired visual acuity data were available for 336/472 (71.2%) patients at baseline and week 4. Of these 171 (50.9%) had normal vision, 128 (38.1%) had moderate vision and 37 (11.0%) had severe visual loss at baseline. Death before follow-up was the main reason for missing data at 4 weeks (98/136, 72.1%).

VA remained unchanged over time for 210 (62.5%) patients. No significant differences were observed in rate of clearance of infection, number of LPs performed, total volume of CSF removed and change in OP over the first 2 weeks of treatment between the group remaining the same, those in whom VA deteriorated (n=51, 15.2%) and those that improved (n=75, 22.3%) ($p>0.1$, all comparisons Supplementary Table 2).

Of 37 (11%) patients with severe visual loss at baseline, 12 (32.4%) improved to near-normal, 8 (21.6%) improved to moderate and 17 (46.0%) remained severe. Again, there were no significant differences in the above parameters between patients remaining severely impaired and those improving (Supplementary Table 3), though numbers for comparison were low.

Discussion

This prospective study within a large African trial is the first to demonstrate an independent association of both fungal burden and raised ICP, in addition to age, with visual loss at presentation with HIV-CM. At presentation, 16% of patients had severe visual loss and 4% were blind: in those with repeat measurements at 4 weeks, following fungicidal treatment regimens and aggressive management of raised ICP, 54% of patients with severe baseline visual loss improved to near-normal or moderate vision, while 46% remained severely impaired.

In a case series comprising both HIV-infected and uninfected patients (n=49), the authors proposed dichotomous mechanisms of visual loss, optic neuritis due to fungal infiltration accounting for early rapid visual loss, and optic nerve compression due to raised ICP accounting for a slower onset. Interventions aimed at reducing ICP were the only ones associated with any success[3]. In a study of immunocompetent adults with *C gattii* meningitis, where ICP was not consistently measured or managed, 37% of 57 survivors remained blind, compared to 5% in our cohort[6]. The uniformity of our cohort, in terms of use of fungicidal regimens and pressure management, may not have permitted us to show a significant impact of rate of clearance or changes in pressure-related parameters on reversibility of visual loss.

The most comprehensive mechanistic study of visual loss in HIV-CM[5] observed frequent optic nerve conduction and visual field defects compatible with raised ICP, and no evidence of optic neuritis on MRI, presenting evidence for an optic nerve compartment syndrome, caused by cryptococcal plugging of channels between the intracranial and the peri-optic subarachnoid space, as an additional cause of optic nerve dysfunction in CM[8]. In practise, these mechanisms may well overlap[8]: our prior work[2] and findings from this study suggest a relationship between fungal burden and raised pressure at the highest extremes of each. These two factors likely converge in an individual patient, possibly more susceptible due to neuroanatomical variation, rendering them either temporarily or- in the absence of intervention- permanently visually impaired.

Limitations of our cohort include the lack of visual assessment at baseline or reversibility at 4 weeks in the sickest of patients who subsequently die, possibly underestimating the prevalence of visual loss. We did not capture self-reported visual impairment predating CM onset which may have impacted on baseline VA, nor were we able to exclude other conditions that can impair vision in this advanced HIV cohort (e.g. CMV retinitis). Nonetheless, our findings underscore the importance of interventions targeted at *both* fungal burden and raised ICP in mitigating visual loss, and underline the need for continued efforts towards earlier diagnosis and treatment of CM, given that, almost half of those with severe impairment failed to improve despite fungicidal regimens and aggressive management of raised CSF pressure.

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Conflict of Interests

TB has received Speaking fees from Gilead Sciences and Pfizer and research funding from Gilead Sciences unrelated to the submitted work. TSH reports non-financial support from Immuno-Mycologics during the conduct of the study; grants and personal fees from Gilead Sciences, personal fees from Viamet, and personal fees from Pfizer outside the submitted work. OL reports grants and personal fees from Gilead Sciences, personal fees from Merck, personal fees from Astellas, personal fees from Pfizer, and personal fees from Novartis outside the submitted work. All other authors report no conflicts.

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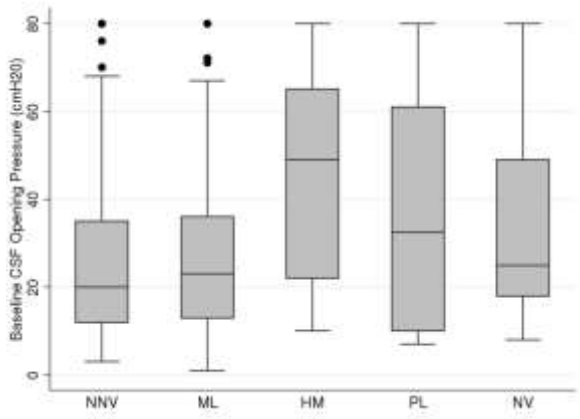
Figure 1: **a.** Box plot (median, IQR, range) of baseline Cerebrospinal fluid (CSF) opening pressure by visual acuity group at presentation. **b**. Box plot of baseline fungal burden by visual acuity group at presentation. NN-Near normal; ML- moderate loss; CF- Counting fingers; LP- Light perception; NV- No vision (Blind)

a



b

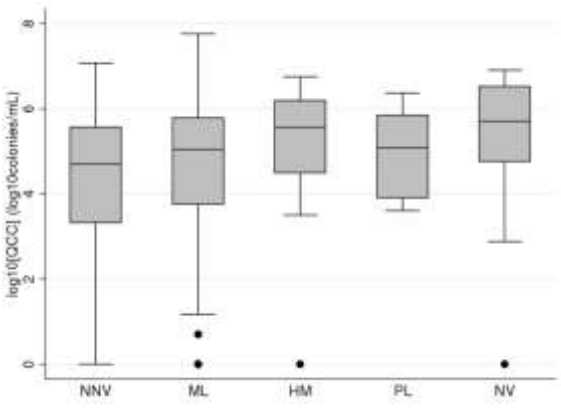


Table 1. Univariable and multivariable analysis for the association between age, baseline CSF opening pressure, baseline CSF fungal burden and CSF white cell count and severe visual loss at presentation.

Variable (baseline)	Visual Acuity at CM presentation (no. (%))		Unadjusted OR (95% CI)		p-value	Adjusted OR (95% CI)		p-value*
	Normal or Moderate Loss	Severe Loss						
Age								
<50 year	356 (89.7)	41 (10.3)	1			1		
≥50 years	61 (81.3)	14 (18.7)	1.99	(1.03-3.87)	0.04	2.47	(1.22 - 5.05)	0.04
CSF opening pressure (cmH_20)								
<25	200 (86.6.0)	31 (13.4)	1			1		
25-39	98 (85.2)	17 (14.8)	1.12	(0.59-2.12)		1.28	(0.66-2.47)	
≥40	66 (72.5)	25 (27.5)	2.44	(1.35-4.43)	0.003	2.56	(1.36-4.83)	0.02
Fungal Burden (log_{10}colonies/ml)								
<5.0	206 (88.4)	27 (11.6)	1			1		
5.0-5.9	113 (84.3)	21 (15.7)	1.42	(0.77- 2.62)		1.31	(0.69 - 2.47)	
>6.0	62 (70.5)	26 (29.5)	3.20	(1.74 -5.88)	0.001	3.01	(1.58 - 5.70)	0.003
White cell count (x 10^9/L)								
<10	249 (82.2)	54 (17.8)	1			1		
≥10	126 (86.3)	20 (13.7)	0.73	(0.42 - 1.28)	0.27	0.70	(0.39 – 1.25)	0.22

*Adjusted for each variable in the table OR: Odds ratio CI: Confidence Interval CSF: Cerebrospinal fluid