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Risk factors for CMV retinitis among individuals with HIV and low CD4 count in northern Thailand: importance of access to healthcare

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Abstract

Aim: To determine if poor access to healthcare is associated with increased cytomegalovirus (CMV) retinitis risk among HIV patients with CD4 counts of less than 100 cells/μl screened in a resource-limited setting.

Methods: This is a prospective cross-sectional study. Patients with known HIV and a CD4 count of less than 100 cells/μL attending an HIV clinic in Chiang Mai, Thailand completed a standardized questionnaire and underwent dilated fundus examination. Participants without CMV retinitis were invited for repeated examinations every 3 months until their CD4 count exceeded

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[*]These authors contributed equally to this work.

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100 cells/μL. The relationship between various potential risk factors and CMV retinitis was assessed with logistic regression.

Results: 103 study participants were enrolled. At enrollment, the mean age was 37.5 (95%CI 35.7 to 39.2) years, 61.2% (95%CI 51.6 to 70.7%) were male, and the mean CD4 count was 29.5 (95% CI 25.9 to 33.1). 21 eyes from 16 (15.5%) participants were diagnosed with CMV retinitis. In multivariate analyses, CMV retinitis was significantly associated with lower CD4 count (OR 1.42 per 10-cell decrement, 95%CI 1.05 – 1.93), longer travel time to clinic (OR 3.85 for those with >30-minute travel time, 95%CI 1.08 – 13.8), and lower income (OR 1.22 per US$50 less income, 95%CI 1.02 – 1.47).

Conclusion: CD4 count, low income and longer travel time to clinic were significant risk factors for CMV retinitis among HIV patients in a resource-limited setting. These results suggest that reducing blindness from CMV retinitis should focus on increasing accessibility of screening examinations to poor and hard-to-reach patients.

Keywords

cytomegalovirus retinitis; health services accessibility; HIV; poverty; risk factors

INTRODUCTION

Despite widespread use of antiretroviral therapy, cytomegalovirus (CMV) retinitis continues to be a leading cause of blindness in countries with a high burden of AIDS.[1–3] The disease burden of CMV retinitis is especially high in Southeast Asia,[4] where in some countries as many as 20% or more of AIDS patients have been found to develop CMV retinitis.[5,6] The disease causes full-thickness retinal necrosis and can lead to blindness if untreated. It has even been shown to be a risk factor for mortality in AIDS.[7] CMV retinitis is often asymptomatic at its onset, so screening for this condition is important. Experts generally recommend that HIV patients with a CD4 count below 100 cells/μL be examined with indirect ophthalmoscopy, but screening examinations are rarely done in resource-limited settings where the disease burden is highest.[1,8] Given these realities, identifying risk factors for CMV retinitis could help public health officials, HIV doctors and ophthalmologists better understand the populations for which screening examinations would have the highest yield.

In a prior study,[9] we found that individuals diagnosed with CMV retinitis at a tertiary care center in Chiang Mai, Thailand had very advanced disease at the time of diagnosis, with many patients presenting with poor vision due to large retinitis lesions, lesions affecting the macula and optic nerve, and retinal detachments. We hypothesized that the advanced state of retinitis was due to a delay in diagnosis, likely related to poor access to healthcare. We subsequently instituted a CMV retinitis screening program in an HIV clinic in the same city, and collected information about various potential risk factors for CMV retinitis to test the hypothesis that poor access to care plays a role in the development of CMV retinitis.

METHODS

This prospective cross-sectional study had approval from the Committee on Human Research at the University of California, San Francisco and the Institutional Review Board of Nakornping Hospital, Chiang Mai, Thailand, and was performed in adherence with the tenets of the Declaration of Helsinki.

Details of the study population and enrollment process have been described elsewhere.[9] Briefly, from June 18, 2010 through June 15, 2012, patients with a CD4 cell count of less than 100 cells/μL who presented to the HIV clinic at Nakornping Hospital, a tertiary medical center, were offered enrollment in the study. Of note, Nakornping Hospital also provides primary HIV care, and patients do not need referrals to come to the HIV clinic at this facility. Although CMV screening would ideally occur at any health care facility providing HIV care, this tertiary care hospital was chosen for our study because of its dedicated HIV clinic and because of the presence of an Ophthalmology service with a fellowship-trained retina specialist. Patients who were pregnant, younger than 18 years, or had a diagnosis of CMV retinitis were excluded. After informed consent, a designated nurse in the HIV clinic administered a standardized risk factor questionnaire. Included in the questionnaire was monthly income, which was defined as the enrollee's average income over the past one month. Participants subsequently had dilated fundus examinations with indirect ophthalmoscopy by a retina specialist (CJ). The ophthalmologist determined the presence or absence of CMV retinitis for each eye using a standardized form. Study participants without CMV retinitis were offered repeated screening every 3 months until their CD4 cell count increased to 100 cells/μL or greater; the same questionnaire and examinations were conducted at each study visit. Patients who were found to have CMV retinitis received repeated intravitreal ganciclvoir injections according to a standard treatment protocol.

All statistical analyses were performed using Stata/SE 14.0 (StataCorp LP, College Station, Texas). Descriptive statistics were calculated for each of the potential risk factors, stratified by disease status. Cost and income were collected in Thai baht and converted into United States dollars based on the currency exchange rate of June 2011, the mid-point of the study (1 Thai baht = 0.0326 US dollar).[10]

Bivariate logistic regression models were constructed to determine statistically significant predictors for the outcome of CMV retinitis, using patient-visit as the unit of analysis. All study visits for each participant were included in regression models until the participant developed CMV retinitis in either eye, when further participant-visits were censored. Cluster-correlated variance estimates were used to account for non-independence of multiple visits from the same participant.[11] When a potential risk factor occurred either in all or none of the cases of CMV retinitis, penalized maximum likelihood regression was used (*firthlogit* command in Stata). Continuous predictors were tested for specification error (*linktest* command in Stata) and transformations applied as needed. For HIV behavioral risk factors, logistic regression analyses were conducted using the entire study population and also separately for each sex subgroup (male vs. female); the results were similar so only the analysis of the entire population was included here. The use of a quadratic term and cubic splines were explored for continuous variables but these did not significantly improve model

fit and were not used in any of the final models. All patient-level factors with a bivariate $P<0.1$ were included in a multivariate logistic regression model adjusted for age and sex, and a backward stepwise selection algorithm employed until covariates had a $P<0.05$.

RESULTS

The characteristics of the participants included in the study have been described previously.[9] A total of 103 subjects were enrolled; 23 of these underwent one follow-up visit for additional CMV retinitis screening 3 months after the initial screening, and 5 underwent 2 follow-up visits at 3 and 6 months after the initial screening (Table 1). Overall, the mean age of study participants at the time of enrollment was 37.5 (95%CI 35.7 to 39.2) years and 61.2% (95%CI 51.6 to 70.7%) were male. Most participants were of Thai ethnicity, although 5.8% identified as hill tribe, 1.0% as Chinese, and 8.7% as other. Almost half of participants (43.7%, 95%CI 34.1 to 53.3%) were unemployed. Most participants had very low CD4 counts; on average, the most recent CD4 count was 29.5 cells/μL (95%CI 25.9 to 33.1). Of the 103 subjects, 21 eyes (10.2% of 206 examined eyes) from 16 (15.5%) participants were diagnosed with CMV retinitis at some point during the study.

Descriptive statistics for each of the potential risk factors elicited in the study are shown in Table 1, stratified by CMV retinitis status. The most significant factors associated with CMV retinitis from bivariate logistic regression analyses were travel time of greater than 30 minutes to the HIV clinic, lower income, and IV drug use (Table 2). CD4 counts were lower in participant-visits where CMV retinitis was diagnosed (mean CD4 count 22.1 cells/μL, 95%CI 12.2 – 31.9; range 5 to 79) compared to those visits where CMV retinitis was absent (mean CD4 count 36.4, 95%CI 32.3 – 40.4; range 1 to 98).

Three risk factors remained significantly associated with CMV retinitis in the multivariate logistic regression after backward stepwise selection algorithm: most recent CD4 count, travel time to HIV clinic, and income (Table 2). Specifically, after adjusting for age and sex, the odds of CMV retinitis were increased by 1.42 (95%CI 1.05 – 1.93) for every 10 fewer CD4 cells/μL on the most recent laboratory testing, by 3.85 (95%CI 1.08 – 13.8) for a clinic travel time that exceeded 30 minutes, and by 1.22 (95%CI 1.02 to 1.47) for every US$50 less in monthly income.

DISCUSSION

In this study population with a CD4 count below 100 cells/μL being screened for CMV retinitis, the most important risk factors for CMV retinitis were lower CD4 counts, longer travel times and lower incomes—the latter two of which are likely indicators of poor access to health care.

The most important risk factor for CMV retinitis found in prior studies has been low CD4 count, and our study was no different.[12,13] On average, the most recent CD4 count at participant-visits in which CMV retinitis was diagnosed was 22.1 cells/μL, and each 10-cell decrement in CD4 count conveyed an almost 50% increased risk of CMV retinitis. Unlike some other studies, antiretroviral therapy was not associated with a reduced risk of CMV retinitis in this population.[14–17] However, the protective effect of antiretroviral therapy for

CMV retinitis is likely mediated entirely through reconstitution of the immune system (i.e., CD4 count), and therefore any effect would likely not be apparent at CD4 counts as low as those found in our study population.

Previous studies have identified genetic, laboratory, and several clinical risk factors for CMV retinitis.[17–21] Based on our experience, we suspected that poor healthcare access might be an additional contributing factor for CMV retinitis, but could not identify previous studies in which this was assessed. We studied this specific hypothesis in the present study, and found two important proxies of health care access to be associated with CMV retinitis in this northern Thai population: income and travel time to the HIV clinic.

The average monthly income per capita in Thailand in 2011 was US$236.[22] This study found a similar income among participants without CMV retinitis (mean $212 per month), but a much lower income for those with retinitis (mean $60 per month). We speculate that low incomes are an impediment to seeking health care, which causes a delay in the diagnosis and treatment of HIV, and therefore increases the risk for an opportunistic infection. However, causality cannot be assessed in this study, and it is also possible that individuals with more advanced HIV are unable to work because of their illness, and therefore have lower incomes.

The Thai government instituted the “30 Baht” program in 2001 to increase access to care for its citizens. Under this program, the fees for each healthcare visit cannot exceed 30 Baht (approximately US$1.00). However, transportation is not covered under this program, which may be a major barrier to healthcare access for some patients.[23] Our study found that the time required to travel to the HIV clinic was a significant risk factor, but the cost of travel was not. This apparent discrepancy could be explained in several ways. First, Chiang Mai has public transportation options that charge a single price regardless of the duration of the trip. Moreover, those who could afford a faster mode of transportation likely spent more money, but had shorter travel times than those who could not afford a faster type of transportation. In this setting, time is likely a more accurate estimate of the difficulty in reaching care.

CMV retinitis continues to cause significant morbidity in AIDS patients in some parts of the world, especially Southeast Asia. Recent studies have found CMV retinitis in 20–33% of AIDS patients in northern Thailand and Myanmar, despite widespread availability of antiretroviral therapy.[6,24,25] In contrast, CMV retinitis is much less common in Singapore, where only about 5% of AIDS patients were diagnosed with CMV retinitis in one study.[17] The lower incidence in Singapore may be related to its smaller geographic size and greater wealth, which likely increases access to health care. People are likely diagnosed with HIV sooner, spend less time at low CD4 counts, and are less likely to develop CMV retinitis.

In Thailand, sex worker, man who have sex with men (MSM) and intravenous drug use are known risk factors for HIV; year 2011 estimates of the prevalence of HIV in these groups were 2.5%, 11.3% and 21.8%, respectively, compared with 1.3% for the general population in the same year.[26] Given the importance of these behavioral risk factors, we sought to determine if they also played a role in the development of CMV retinitis. Overall, less than

10% of our study population identified as a man who has sex with men (MSM), as being a sex worker, or as having sex with a sex worker. These findings are consistent with results from a prior study from Chiang Mai that showed that 90% of HIV cases from this area were contracted through heterosexual sex.[24] We did not find significant associations between CMV retinitis and sex with a sex worker, being a sex worker, or being an MSM. Intravenous drug use was associated with CMV retinitis in bivariate analysis, but the association was not maintained in the multivariate model.

This study has several limitations. We performed a cross-sectional survey of risk factors, so cannot comment on causality. A relatively low number of participants were diagnosed with CMV retinitis, reducing the power of the study. However, despite the low number of cases, we found several significant risk factors in multivariate analyses, suggesting that these factors are strongly associated with CMV retinitis. Socioeconomic status and access to health care are complicated constructs and difficult to capture in a relatively brief self-reported questionnaire. Sexual behaviors are difficult for patients to talk about in this area of Thailand. A lengthier questionnaire or qualitative approaches may have provided more detail but were not possible given resource constraints. Finally, the study was conducted at a tertiary care medical center because of the presence of HIV and Ophthalmology services, which increased the sample size for the study and allowed us to provide care for patients with CMV retinitis. In reality, HIV-infected persons in Thailand are able to access HIV care also at primary and secondary health care facilities, and the generalizability of the study findings to those settings is unclear.

In conclusion, this cross-sectional analysis showed that poor access to healthcare, specifically lower income and longer travel time to the HIV clinic, were significantly associated with developing CMV retinitis. Reducing blindness from CMV retinitis should focus on increasing accessibility of screening examinations to poor and hard-to-reach patients.

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Table 1.

Characteristics of individuals screened for cytomegalovirus (CMV) retinitis, stratified by whether CMV retinitis was detected in either eye.

Characteristic	Number (%) or Mean (95% Confidence Interval) No CMV Retinitis N=87	CMV Retinitis N=16
Number of screening visits[a]		
Baseline only	62	13
Baseline and 3 months	20	3
Baseline, 3 and 6 months	5	0
Enrollment characteristics		
Demographics		
Age, years	36.8 (34.9 – 38.7)	41.1 (36.5 – 45.7)
Male	54 (62.1%)	9 (56.3%)
Single	42 (48.3%)	9 (56.3%)
Ethnicity		
Thai	72 (82.8%)	15 (93.8%)
Hill tribe	6 (6.9%)	0 (0%)
Chinese	1 (1.1%)	0 (0%)
Other	8 (9.2%)	1 (6.2%)
Unemployed	35 (40.2%)	10 (62.5%)
Access to healthcare		
No caretaker	29 (33.3%)	4 (25.0%)
Not on antiretroviral therapy	21 (24.1%)	3 (18.8%)
More than 30 min to clinic	30 (34.5%)	10 (62.5%)
Round trip cost, USD	4.76 (3.19 – 6.36)	4.43 (2.78 – 6.10)
Monthly income, USD	212 (144 – 280)	60 (14 – 106)
HIV risk factor exposure[b]		
Among men		
Man who has sex with men	9 (16.7%)	1 (11.1%)
Sex with sex worker	6 (11.1%)	1 (11.1%)
Sex worker	6 (11.1%)	0 (0%)
IV drug use	3 (5.6%)	4 (44.4%)
Among women		
Sex with sex worker	0 (0%)	0 (0%)
Sex worker	1 (3.2%)	0 (0%)
IV drug use	0 (0%)	0 (0%)
Past Medical History		
History of STI[c]	20 (23.0%)	4 (25.0%)
History of opportunistic infection[d]	37 (42.5%)	9 (56.3%)
CD4 count, cells/μl		
At HIV diagnosis	46.7 (30.4 – 63.0)	20.8 (11.5 – 30.0)

	Number (%) or Mean (95% Confidence Interval)	
Characteristic	**No CMV Retinitis N=87**	**CMV Retinitis N=16**
Nadir	28.3 (24.5 – 32.1)	17.3 (9.8 – 24.8)
Most recent	31.3 (27.3 – 35.3)	19.6 (11.6 – 27.6)

HIV: human immunodeficiency virus; IV: intravenous; USD: United States dollar

[a] Study participants were offered a screening examination of each eye every 3 months until the CD4 count exceeded 100 cells/μl or until the eye developed CMV retinitis.

[b] Stratified by sex; proportions shown for 9 men with and 54 men without CMV retinitis, and for 7 women with and 33 women without CMV retinitis.

[c] Sexually transmitted infection; included gonorrhea, condyloma, syphilis, genital herpes simplex virus (HSV) infections.

[d] Included tuberculosis, penicilliosis, *Pneumocystis* pneumonia, cryptococcal meningitis, and *Mycobacterium avium* complex (MAC).

Table 2.

Analysis of risk factors for cytomegalovirus (CMV) retinitis: bivariate and multivariate analyses

	Bivariate analysis		Multivariate analysis[a]	
Patient characteristics	**Odds Ratio (95% CI)**	***P*-value**	**Odds Ratio (95% CI)**	***P*-value**
Demographics				
Age, per decade	1.52 (0.96 – 2.39)	0.07	1.70 (1.02 – 2.85)	0.04
Male	0.96 (0.32 – 2.87)	0.94	1.43 (0.44 – 4.60)	0.55
Single	1.50 (0.50 – 4.48)	0.47		
Thai	5.04 (0.29 – 88.3)	0.27		
Unemployed	2.60 (0.80 – 8.50)	0.11		
Access to healthcare				
No caretaker	0.64 (0.20 – 2.09)	0.46		
Not on antiretroviral therapy	0.62 (0.16 – 2.35)	0.48		
More than 30 min to clinic	3.52 (1.13 – 11.0)	0.03	3.85 (1.08 – 13.8)	0.04
Round trip cost, per additional USD	0.99 (0.95 – 1.04)	0.77		
Income, per 50 USD less	1.22 (1.03 – 1.45)	0.02	1.22 (1.02 – 1.47)	0.03
HIV risk factor exposure[b]				
Man who has sex with men	0.54 (0.06 – 4.70)	0.58		
Sex with sex worker	0.72 (0.12 – 4.37)	0.72		
Sex worker	0.35 (0.02 – 6.29)	0.48		
Intravenous drug use	4.58 (1.14 – 18.4)	0.03		
Past medical history				
History of STI	1.16 (0.34 – 3.93)	0.81		
History of opportunistic infection	1.64 (0.57 – 4.70)	0.36		
CD4 count, per 10 fewer cells/μL				
At diagnosis	1.36 (0.91 – 2.02)	0.13		
Nadir	1.56 (0.99 – 2.44)	0.06		
Most recent	1.48 (0.98 – 2.23)	0.06	1.42 (1.05 – 1.93)	0.02

CD4: cluster of differentiation 4; CI: confidence interval; HIV: human immunodeficiency virus; STI: sexually transmitted infection; USD: United States dollars

[a] Age- and sex-adjusted multivariate model; constructed by entering terms with $P<0.1$ from bivariate analyses then performing a backwards stepwise selection algorithm until all variables had a $P<0.05$.

[b] Results were similar when regression models were constructed separately for men and women.