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Prevalence and predictors of cytomegalovirus retinitis in HIV-infected patients with low CD4 lymphocyte counts in Vietnam

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Abstract

Background: We describe the results of a study to determine the prevalence and characteristics of cytomegalovirus retinitis among HIV-infected patients in Vietnam.

Methods: A cross-sectional prospective study of patients with CD4 lymphocyte count $\leq$100 cells/mm^3 recruited from public HIV clinics. The diagnosis was made by a trained ophthalmologist using slit lamp biomicroscopy and corroborated on fundus photography.

Results: 201 patients were screened. The median age was 32 years, 77% were men, median CD4 count was 47 cells/mm^3, and 62% were on antiretroviral treatment. Prevalence of cytomegalovirus retinitis was 7% (14/201, 95% CI 4–11%). Cytomegalovirus retinitis was not associated with age, gender, injection drug use, CD4 count, WHO clinical stage, or antiretroviral treatment status. Blurring of vision and reduced visual acuity $<$20/40 were associated with cytomegalovirus retinitis, but only 29% of patients with the diagnosis reported blurry vision and only 64% had abnormal vision. On multivariate analysis, the sole predictor for cytomegalovirus retinitis was decreased visual acuity (OR 22.8, $p < 0.001$).

Conclusions: In Ho Chi Minh City, cytomegalovirus retinitis was found in 7% of HIV-infected patients with low CD4. HIV-infected patients with a CD4 count $<$100/mm^3 or who develop blurring of vision in Vietnam should be screened for cytomegalovirus retinitis.

Keywords

Cytomegalovirus, HIV, Vietnam, retinitis, prevalence

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Introduction

Cytomegalovirus (CMV) retinitis is a common opportunistic infection diagnosed in patients with advanced HIV infection and low CD4 lymphocyte cell counts. Before the era of highly active anti-retroviral therapy (HAART) in the USA, CMV retinitis was found in up to 30% of patients with CD4 counts less than 50 cells/mm^3 and was the most common cause of retinal infection in patients with AIDS.[1] Prevalence rates of up to 33% have been reported in developing countries, where diagnosis is more difficult and patients often present for treatment when their CD4 count is very low.[2]

Untreated CMV retinitis can result in significant loss of visual acuity and visual field.[3,4] Treatment with

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HAART to restore immune function and drugs with anti-CMV activity such as ganciclovir or valganciclovir have greatly reduced both the incidence and sequellae of CMV retinitis in developed countries.[5,6] Evidence that anti-CMV drugs can delay the progression of retinitis lesions and prevent vision loss[7] has led some western experts to recommend routine screening for asymptomatic HIV-infected patients with low CD4 counts.[8] Intravitreal ganciclovir injections have been shown to be effective at improving outcomes in resource-limited settings where other therapeutic options are unavailable or unaffordable.[9,10]

The prevalence of CMV retinitis among patients with HIV infection appears to be higher in Asia than in Africa.[2,11] Recent surveys in South Africa and Tanzania report prevalence rates of 2.6% and 1.3%, respectively.[11,12] Studies from Asia indicate a much higher burden of disease: 7.6% in AIDS patients in Shanghai, China,[13] 11% in South Korea,[14] 19.8% in Thailand,[15] and 24% in Myanmar.[16] A recent systemic review of CMV retinitis in resource-limited settings found a pooled prevalence of 14% in Asia.[17] Experts now recommend that all patients in East and Southeast Asia with CD4 <100 cells/mm^3 be screened with retinal examination, but in practice it is rarely done.[17,18]

CMV infection can also cause disseminated or extraocular disease, including pneumonitis, esophagitis, and colitis.[19,20] CMV viremia has been associated with increased mortality in Asia.[21] However, the diagnosis of extraocular CMV disease requires advanced diagnostic testing or invasive biopsies that are either not available or not accessible to HIV patients in most developing countries.

There are no data on the prevalence of CMV retinitis in Vietnam. Injection drug use continues to be the predominant mode of HIV transmission in the country.[22] The limited data available indicate that virtually all Vietnamese HIV-infected injection drug users (IDUs) have been exposed to CMV.[23] In order to assess the prevalence of CMV retinitis among HIV-infected patients in Vietnam we conducted a survey in Ho Chi Minh City (HCMC). The purpose was to inform planning for the first pilot treatment project of the disease in the country.

Methods

HIV-infected patients were recruited from public outpatient antiretroviral treatment (ART) clinics in HCMC, Vietnam, from January to April, 2010. Entry criteria were documented HIV infection, age $\geq$18 years, and CD4 $\leq$100 cells/mm^3. Recruitment was stratified to enroll an equal number of patients with CD4 $<$ and $\geq$50 cells/mm^3. Patients were excluded if they had a previous history of diagnosis or treatment for CMV retinitis. Presence or absence of eye symptoms and use of ART were recorded but were not part of the inclusion or exclusion criteria.

Patients were screened by a study staff member at outpatient HIV clinics when they presented for routine follow-up appointments. All patients who met the entry criteria were given an informational brochure and invited to participate in the study. If patients agreed, they were given a referral form and instructions on where to go for the eye exam. Recruitment started at four of the largest HIV clinics in the city. When virtually all patients at a clinic were screened, the study staff began recruiting at additional HIV clinics.

Patients were examined in the retina department of the HCMC Eye Hospital, a tertiary referral center for the southern half of Vietnam. Visual acuity, external eye exam, and confrontation visual fields were assessed on all patients. Pupils were dilated with topical tropicamide 0.5% and phenylephrine hydrochloride 0.5% (Mydrin®-P; Santen OY, Tampere, Finland). Indirect ophthalmoscopy using a lit-lamp with non-contact lens (SuperField®; Volk, USA) was performed on both eyes of each patient. In addition, binocular indirect ophthalmoscopy (BIO) using a head-mounted ophthalmoscope and non-contact lens was also performed on some patients if there was a concern for retinal tear, retinal detachment, or other peripheral lesion.

The diagnosis of CMV retinitis was based on the clinical examination of the retina. Any lesion consistent with CMV retinitis, whether acutely active, regressing, or inactive, was diagnosed as a case of CMV retinitis for the study. All diagnosed or suspected cases were documented by digital retinal photography. Suspected cases were confirmed by review of the retinal photographs by an independent ophthalmologist in Singapore.

All patients gave written informed consent to participate in the survey and received 35,000 Vietnam Dong (approximately US$2) to compensate for travel and parking expenses. Medications for common eye conditions, such as topical antibiotics and anti-inflammatory drugs, were provided free to patients if indicated. Patients diagnosed with CMV retinitis were referred to a free treatment program at the HCMC Eye Hospital. All patients qualified for free ART in the public HIV treatment program. The study was approved by the ethics review committees at Beth Israel Deaconess Medical Center in Boston, USA, and the HCMC Eye Hospital.

Statistical analysis was performed using SPSS version 20 (IBM, Armonk, NY, USA). Chi square was used to test for associations between categorical variables and the outcome of CMV retinitis diagnosis. To calculate an unadjusted relative risk, CD4 count was treated as a categorical variable with two categories

defined as $<$ and $\geq$50 cells/mm^3. Age was assessed as a continuous variable using Student's t-test. Abnormal visual acuity was defined as best corrected vision of $<$20/40 in either eye on a Snellen eye chart. Independent predictors for CMV retinitis were determined in a multivariate model using backward stepwise logistic regression. All factors with a p value of $<$0.10 on bivariate analysis were included in the model, which was controlled for age, gender, CD4 count, and WHO clinical stage.

Results

Characteristics of the study sample

A total of 201 patients completed the screening examination. This represents 78% (201/259) of all patients referred from the HIV clinics to the HCMC Eye Hospital for the study. Two patients presented to the Eye Hospital but left before the examination was performed due to a long wait. The remaining 56 patients were given referrals but never arrived at the screening location. Comparison between patients who completed the study with those who were referred but did not enroll showed no differences in gender, age, WHO clinical stage, or risk factor for HIV transmission (data not shown). Non-enrollees were more likely than enrolled patients to have CD4 $<$50 cells/mm^3 (69% vs 52%, $p = 0.01$) and to have been on ART (79% vs. 61%, $p = 0.03$).

Mean age of enrolled patients was 33 years (range 21–70 years). Median CD4 was 47 cells/mm^3 (range 1–100) and mean CD4 was 48 cells/mm^3. The majority of patients (61%) were on ART a median of 12 weeks (interquartile range 4–52 weeks) and 30% of those on ART had been treated for 4 weeks or less. Other characteristics of the patient sample are shown in Table 1.

Table 1. Description of patients screened for eye disease in Ho Chi Minh City (HCMC), Vietnam (n = 201).

Characteristic	Frequency	%
Gender		
Man	154	77%
Woman	47	23%
HIV transmission category		
IDU	106	53%
Other	95	47%
WHO clinical stage		
Stage 1 or 2	57	30%
Stage 3 or 4	135	70%
Tuberculosis history		
Yes	106	54%
No	82	46%
ART		
On ART	123	61%
Not on ART	78	39%
Hepatitis C		
Anti-HCV positive	56	32%
Anti-HCV negative	120	68%
Hepatitis B		
HBsAg positive	27	15%
HBsAg negative	156	85%
Visual acuity		
$\geq$20/40 in both eyes	173	86%
$<$20/40 in either eye	28	14%
Eye symptoms		
Any symptoms	17	8%
None	184	92%

IDU: intravascular drug user; ART: antiretroviral treatment; HCV: hepatitis C virus; HBsAg: hepatitis B surface antigen.

Spectrum of eye diseases in the study population

One or more ophthalmologic diagnosis was found in 40 (20%) of the patients. CMV retinitis was the most common diagnosis, affecting 7% (14/201, 95% CI 4–11%) of the study sample. The majority of patients had CMV retinitis in only one eye. Only 2/14 (14%) of patients had both eyes affected. In the majority (64%) of patients CMV retinitis was classified as active, 14% had regressing lesions, and 21% were inactive. Table 2 presents a complete list of concomitant diagnoses made on clinical examination.

Factors associated with CMV retinitis

The mean age of patients with CMV retinitis was 33.3 years, slightly higher than the mean age (33.0 years) of patients without CMV retinitis, but the difference was not significant ($p = 0.87$). Table 3 shows the results of bivariate analysis of categorical risk factors. Only blurring of vision and decreased visual acuity $<$20/40 were significantly associated with CMV retinitis. Although these two factors were significantly correlated (Spearman's Rho –0.339, $p < 0.001$), there was a large amount of discrepancy between patient report of abnormal vision and reduced visual acuity on examination. Of the 24 patients with measured abnormal visual acuity, only 6 (25%) reported blurring of vision. Conversely, 10 patients reported blurry vision and four (40%) of these had normal visual acuity. On multivariate logistic regression, the sole predictor for CMV retinitis was decreased visual acuity (odds ratio 22.8, 95% CI 36.7–78.2, $p < 0.001$). The outcome of the multivariate logistic regression did not change whether CD4 count was input as a categorical or a continuous

Table 2. Ophthalmologic diagnoses among patients with CD4 <100 screened in Ho Chi Minh City (HCMC), Vietnam (n = 201).

Diagnosis	Eyes (n)	Patients (n)	Patient prevalence
CMV retinitis	16	14	7%
HIV retinopathy	16	12	6%
Cataract	10	7	3.5%
Herpes keratitis (active or scar)	5	4	2%
Optic neuritis (without CMV)	4	3	1.5%
Retinal hemorrhage (without CMV)	2	2	1%
Anterior chamber uveitis	3	2	1%
Herpes zoster ophthalmicus	2	2	1%
Conjunctivitis	2	1	0.5%
Vitritis (without CMV)	1	1	0.5%
TB retinitis	1	1	0.5%
Diabetic retinopathy	1	1	0.5%

CMV: cytomegalovirus.

Table 3. Bivariate associations between risk factors and cytomegalovirus (CMV) retinitis diagnosis.

	CMV retinitis n(%)			
Risk factor	Positive	Negative	Unadjusted RR (95% CI)	*p* Value
Gender				
Woman	4 (8.5)	43 (91.5)	1.34 (0.40–4.49)	NS
Man	10 (6.5)	144 (93.5)		
Risk behavior				
IDU	7 (6.6)	99 (93.4)	0.89 (0.30–2.63)	NS
Other	7 (7.4)	88 (92.6)		
WHO clinical Stage				
Stage 3 or 4	12 (8.9)	123 (91.1)	2.68 (0.58–12.4)	NS
Stage 1 or 2	2 (3.5)	55 (96.5)		
CD4 count				
<50 cell/mm^3	8 (7.6)	97 (92.4)	1.24 (0.41–3.70)	NS
≥ 50 cell/ mm^3	6 (6.2)	90 (93.8)		
Tuberculosis history				
Yes	10 (9.4)	96 (90.6)	2.74 (0.73–10.3)	NS
No	3 (3.7)	79 (96.3)		
ART				
On ART	10 (8.1)	113 (91.9)	1.64 (0.50–5.41)	NS
Not on ART	4 (5.1)	74 (94.9)		
Visual Acuity				
$<20/40$ in either eye	9 (37.5)	15 (62.5)	20.6 (6.1–69.5)	<0.001
$\geq 20/40$ in both eyes	5 (2.8)	172 (97.2)		
Blurred vision				
Yes	4 (40)	6 (60)	12.1 (2.93–49.7)	0.001
No	10 (5.2)	181 (94.8)		

RR: relative risk; NS: not significant; IDU: intravascular drug user; ART: antiretroviral treatment.

variable or by the use of nadir vs. most recent CD4 count (data not shown).

Discussion

We found a prevalence rate for CMV retinitis of 7% among HIV-patients at outpatient clinics in Ho Chi Minh City, Vietnam. This is lower than rates found in other East Asian countries[14–16] but similar to a pooled rate of 7.7% among 21 studies that did not select patients based on symptoms or other clinical criteria.[17] It is unclear whether the prevalence rates reported in other countries represents true differences in burden of disease or merely methodological differences between the various studies. In our study we recruited ambulatory patients from HIV clinics regardless of the presence or absence of eye symptoms in order to obtain a representative sample of patients with HIV infection in Vietnam. Other studies may have recruited in eye hospitals or on inpatient units, which could have biased their results towards higher prevalence rates.

HCMC has universal access to free ART through its network of public HIV clinics and 61% of patients in this survey were taking ART. Other locations with less access to ART may indeed have higher rates of opportunistic infections, including CMV retinitis. The median time on ART for patients in the study was only 12 weeks, which for most patients may not have been enough time to achieve complete viral suppression and immune restoration. However, one-quarter of the ART patients were on treatment for more than 52 weeks. Routine viral load testing is not performed in the public treatment system in Vietnam, so we could not assess whether these patients had achieved viral suppression with persistently low CD4 counts or were experiencing treatment failure.

We found that patients with lower CD4 cell counts had a higher prevalence rate of CMV retinitis, but the difference was not statistically significant. This finding contradicts many previous studies,[13,24] which have found significantly higher rates of CMV retinitis among patients with CD4 <50 cells/mm^3.

The sole factor that was an independently significant predictor for CMV retinitis was abnormal visual acuity. However, poor visual acuity was only 64% sensitive in screening for CMV retinitis; 5/14 (36%) of patients with CMV retinitis had normal visual acuity. Specificity of visual acuity was higher; 90% of patients without CMV retinitis had normal visual acuity. Eye symptoms were even worse predictors of CMV retinitis. Blurring of vision was the most common eye symptom experienced by patients with the disease, yet only 4/14 (29%) of patients reported this symptom.

No symptom or sign in our survey proved highly sensitively in screening for CMV retinitis. This would support calls for universal eye examination of patients with low CD4 counts <100 cells/mm^3 as the only method to ensure early detection and treatment of this sight-threatening disease.[2,17,18] In Vietnam, as in most other developing countries, the expertise in diagnosing CMV retinitis is limited to a few trained ophthalmologists in the largest cities. More training is needed for ophthalmologists in smaller cities and rural areas to accurately screen for CMV retinitis, which can be done without the need for expensive machinery or laboratory testing.

In developing countries that lack ophthalmologists, task shifting to other physicians can provide an alternative method for screening, diagnosing, and treating CMV retinitis. In Myanmar, primary care HIV physicians have successfully been trained in indirect ophthalmoscopy to diagnose CMV retinitis and in providing appropriate treatment.[16] In this study, 22% of referred patients never made it to the screening exam. Providing the service in HIV clinics rather than in specialized centers would increase the numbers of patients that could access appropriate screening for CMV retinitis. Telemedicine may be an option for bringing accurate diagnosis to patients outside of major urban areas: a study in Thailand found a 90% sensitivity in screening for CMV retinitis using digital retina images sent electronically to distant ophthalmologist readers.[25]

Our study has certain limitations. All patients were screened with a slit-lamp exam but not all patients were examined by BIO with a head-mounted ophthalmoscope. It is possible that some peripheral CMV retinitis lesions might have been missed using this examination methodology. We recruited only outpatients and therefore may have excluded patients with the lowest CD4 counts who were admitted to the hospital or were too ill to go to the clinic. We know that patients who were referred but did not present for the eye examination had lower mean CD4 counts than patients who participated in the study. If the sample was biased to patients who had higher CD4 counts, and if any peripheral retinitis lesions were missed, then we may have underestimated the true prevalence rate of CMV retinitis in Vietnam.

Patients with CMV retinitis in Vietnam are able to access effective treatment with intravitreal injections of ganciclovir, which cost less than US$10 per month. The affordability of intravitreal ganciclovir has made it the most widely used treatment modality in developing countries.[9,10] However, it should be noted that intravitreal injections do not treat extraocular CMV disease and do not prevent CMV disease in the contralateral eye. Systemic treatment for CMV disease has been shown to reduce mortality in patients with CMV retinitis.[26] Systemic treatment with oral valganciclovir is

now the standard of care for CMV retinitis in western countries[27]: this medication should be made more affordable and more available in developing countries as well.

In summary, we found a 7% prevalence of CMV retinitis among patients with low CD4 count in Vietnam. Since many patients are asymptomatic and the risk of visual loss is high without treatment, we recommend routine eye examination as screening for all HIV-infected patients with CD4 counts <100 cells/mm^3 and in any patient with eye symptoms. A simple and quick clinical examination by a trained ophthalmologist can provide an early diagnosis, allow early referral for treatment, and prevent visual loss or blindness.

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Conflict of Interest

Drs Donn Colby and Todd Pollack have received research grant support from Roche Molecular Systems, Inc. The other authors report no conflict of interest.

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