Causes of Visual Acuity Loss among HIV-infected Patients with Cytomegalovirus Retinitis in the Era of Highly Active Antiretroviral Therapy in Chiang Mai University Hospital

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Objective: *To quantify the frequencies of the common causes of visual acuity loss for HIV-infected patients with cytomegalovirus retinitis (CMVR) in the era of highly active antiretroviral therapy(HAART).*

Material and Method: *The present prospective observational study comprised 113 patients (184 eyes) with newly diagnosed CMVR, from May 2008-March 2010. Each patient was followed-up every 3 months with medical history and ophthalmologic examination. Patients were divided as visual impairment and legal blindness.*

Results: *The majority of the patients were native Thai (91%), while the rest was of hill tribe origin. 55% were females with age ranged between 14 - 57 years (average of 39). The main cause of HIV infection was heterosexual contact (90%), followed by homosexual contact (7%). It was found that 68% had CD4 T-cell count less than 50 cells/μl and that 46% had bilateral CMVR. Major causes of visual impairment were CMVR zone 2&3, CMVR zone 1 and cataract, respectively. Major causes of legal blindness were CMVR zone 2&3, CMVR zone 1 and retinal detachment, respectively. Retinal detachment was a major risk factor in both groups. Even when surgery was successful, the visual acuity was not significantly improved, indicating a permanent loss of vision.*

Conclusion: *In the HAART era, immune recovery of HIV patients also helps restoring specific anti-CMV immunity. HAART reduces occurrence of visual impairment to 0.10/eye-year(EY) and legal blindness to 0.15/EY, compared to the pre-HAART figures of 0.94-0.98/EY and 0.47-0.49/EY, respectively. However, it did not completely eliminate the occurrence. CMVR and cataract remain the most common causes of visual acuity loss followed by retinitis-related retinal detachment, and optic nerve atrophy respectively.*

Keywords *Cytomegalovirus retinitis (CMVR), Visual acuity loss, Highly active antiretroviral therapy (HAART)*

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Cytomegalovirus (CMV) retinitis is the most common sight-threatening complication found in HIV patients worldwide[1-4], which can cause them to suffer from severe visual acuity loss up to complete blindness, affecting their quality of living in both the short-term and long-term[5]. Normally, CMV retinitis, (or CMVR), can be found in the patient during the last stages of their HIV infection, particularly in those with a CD4 level of less than 50 cell/cu.mm.

Prior to the highly active antiretroviral therapy (HAART) era, it was found that approximately 30% of HIV patients were infected by CMVR during their lifetime[2,6,7]. In 1994, studies of ocular complications of the AIDS Research Group found that prior to the HAART era, a CMVR patient experienced loss in visual acuity down to 20/50 (visually impaired) or worse in eight months time on average, while down to 20/200 (legally blind) or worse in 13 months time on average[7]. The incidence rate of visual impairment and legal blindness are 0.94-0.98/eye-year (EY) and 0.47-0.49/EY, respectively[7,8]. Loss in visual acuity mainly results from CMVR involving the macula or optic nerve (zone 1 retinitis) and CMVR-related retinal detachment[7].

The use of an antiretroviral drug will suppress the proliferation of HIV in human blood and so increases the immunity[9,10]. After widespread use of antiretroviral therapy in 1990, the increased immunity in HIV patients reduced the occurrence of CMVR as high as 75%[2,9,11,12].

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Furthermore, there was a report claiming a reduced rate of CMVR progression and a reduced chance of retinal detachment in CMVR patients, compared to those in the pre-HAART era[13-15]. HAART helps reduce the occurrence of visual impairment to 0.10/EY and the occurrence of legal blindness to 0.06/EY[16,17], but not to zero. The major causes of visual acuity loss are still CMV zone 1 retinitis and CMVR-related retinal detachment[8].

On the other hand, the CMVR patient, who has increased immunity after HAART, may be exposed to a higher risk of immune recovery uveitis and its complications, i.e. cataract and cystoid macular edema[19-23]. The occurrence of immune recovery uveitis is as high as 0.83/person-year (PY). At present, causes of this occurrence have not been clearly understood[23].

When comparing the occurrences and causes of visual acuity loss before and after HAART from the above findings, it can be seen that the post-HAART visual acuity loss has been mitigated but not completely. So in the authors' opinion, it is of great clinical benefit to study various common causes and their effects. Moreover, there are very few studies on the occurrence and causes of CMVR-related visual acuity loss in Thailand compared to those overseas. So there is no clear evidence to justify the actual causes of visual acuity loss in CMVR patients in Thailand.

The research objective for the present study was to quantify the frequencies of the common causes of visual acuity loss for CMVR-infected HIV patients in the era of HAART.

Material and Method

Participants

The present research is focused on the causes of visual acuity loss in HIV patients with CMVR during the HAART application at Chiang Mai University Hospital. It is a descriptive observational study undertaken on the patients who attended the CMV Retinitis Clinic, Department of Ophthalmology, Chiang Mai University Hospital during May 2008 to March 2010, including those patients who incurred newly diagnosed retinitis during the course of diagnosis. It was also approved by the ethic committee of ChiangMai University. All patients gave written informed consent prior to participating in the present study. Inclusion criteria included new HIV-infected patients with CMVR during the active and inactive phase. All patients were given HAART (defined as a combination of antiviral drugs$\geq$ 3 drugs including at least one protease inhibitor or non nucleoside reverse transcriptase inhibitor[32]). If the active phase was presented, intravitreal Gancyclovir injection was performed. No history of trauma, ocular surgery or other ocular co-infections were present.

Data collection

Data collection at baseline and follow-up visits included medical and ophthalmologic histories, complete ophthalmic examination, CD4 T-cell counts. Patients were examined every three months during the follow-up period.

Ophthalmic examination included a measurement of visual acuity using the ETDRS chart, measurement of intraocular pressure, slit-lamp examination, and dilated indirect ophthalmoscopy.

CMVR was diagnosed by an ophthalmologist based on its characteristic presentation using the standard classification system[13,28-30] . The location of the CMVR lesion in each eye was categorized into three zones. Zone one is defined as the area within 1500 mm of the optic nerve or within 3000 mm of the center of the macula. Zone two extends from zone one to the vortex veins and zone three lies anterior to the vortex veins[30]. Immune recovery was defined as increase of CD4 T-cell count 50-100 cells/ul from a nadir CD4 T cell count[13-16,22,28]. The nadir CD4 T cell count was defined as the patient's lowest recorded CD4 T-cell count at or before enrollment determined from the patient's medical record[13]. Immune recovery uveitis was diagnosed clinically as the presence of intraocular inflammation in a patient who had undergone immune recovery. A cataract was defined as lens opacity equal to or greater than 1+.

Main Outcome Measures

Best-corrected visual acuity (BCVA) was measured using the EDTRS chart and the patients were divided in two groups, visual impairment and legal blindness. Visual impairment was defined as BCVA between 20/50 and < 20/200, and legal blindness 20/200 or worse.

Causes of visual loss, defined as ocular characteristics which were reported to be related to decreased vision, were quantitated.

Statistics

Frequencies of causes of visual loss were calculated and compared using the Chi-square test and Fisher exact test. P-value of less than 0.05 were nominal and 2-sided. Incidence rates were calculated as the numbers of events per EYs at risk. Analysis was performed with the SPSS version 12.

Results

The results from the analysis can be summarized as follows:

Population characteristics

The number of patients who were diagnosed as "newly diagnosed retinitis" and satisfied the inclusion criteria was 113 persons (165 eyes) (Table1).

Of 165 eyes, 122 eyes were in the visual impairment group, in which 62 eyes were classified as legal blindness group. (The remaining 43 eyes were diagnosed as CMVR but the visual acuity were better than 20/50).

Cause of visual acuity loss in HIV patients with CMVR

The incidence of visual acuity loss of the CMVR patients to visual impairment and legal blindness are 0.10/EY and 0.15/EY, respectively. Various factors that cause incidental visual acuity loss in HIV patients with CMVR are listed in Table 2,3. The findings revealed the following information.The main causes of visual impairment in order of prevalence were CMVR zones 2&3, CMVR zone 1, and cataract, respectively. On the other hand, the main causes of legal blindness in order of prevalence were CMVR zones 2&3, CMVR zone 1, and retinal detachment, respectively. Optic nerve disease was the next common cause, usually characterized as optic nerve atrophy, resulting from diffuse CMVR and retinal detachment.

Table 4 shows that among the 17 eyes developing CMVR during the follow-up period, 65% incurred visual impairment, whereas 41% incurred legal blindness after the course of one year.

Among the 20 eyes developing retinal detachment during the follow-up period, all incurred

Table 1. Demographic data of the patients (n = 133)

Patient specific characteristic	n = 113 persons	
Demographics	No.	Percentage
Age(year) mean=39, range 14-57		
< 39 years old	56	49.6
≥39 years old	57	50.4
Race		
Thai	103	91.2
Hill tribe	10	8.5
Gender		
Male	51	45.1
Female	62	54.9
HIV risk factor		
Men having sex with men	8	7.1
Heterosexual contact	102	90.3
Blood transfusion	1	0.9
Maternal infection	2	1.8
Bilateral CMVR	52	46.0
CD4-T cell count		
< 50 cells/µl	77	68.1
50-99 cells/µl	14	12.4
≥100 cells/µl	18	15.9
unknown	4	3.5

Table 2. Characteristics of CMVR at baseline (n=165)

Characteristic	No.	Percentage
Most posterior zone of CMVR		
Zone 1	114	69.1
Zone 2 or 3	145	87.9
Retinal detachment	9	5.5
Cataract	77	46.7
Immune recovery uveitis	6	3.6
Cystoid macular edema	6	3.6
Epiretinal membrane formation	2	1.2
Optic nerve disease	26	15.8

Table 3. Factors causing incident visual acuity loss in eyes affected with CMVR

Cause	Visual impairment Group%	Legal blindness Group%
	n = 19[i]	n = 26[ii]
CMVR zone 2, 3	84.2	88.5
CMVR zone 1	68.4	84.6
Retinal detachment	10.5	26.9
Cataract	26.3	15.4
Optic nerve disease	5.3	19.2
IRU	5.3	3.9
CME	5.3	3.9
ERM	10.5	3.9
Rate (/ EY)	0.10/EY	0.15/EY

NOTE Numbers add to greater than 100% because eyes may have >1 cause for vision loss.

(i) Number of eyes that initially had a good visual acuity but subsequently became visually impaired during the course of the present study

(ii) Number of eyes that subsequently became legally blind during the course of this study

CMVR = Cytomegalovirus retinitis, IRU = Immune recovery uveitis, CME = Cystoid macular edema, ERM = Epiretinal membrane, EY = Eye year

Table 4. Risk factors of visual acuity loss in eyes developing vision-threatening complications of CMVR

Characteristic	n/N	Percent with visual acuity loss			
		20/50 or worse		20/200 or worse	
		%, 6 mos	%, 12 mos	%, 6 mos	%, 12 mos
CMVR zone1	17/113	58.8	64.7	29.4	41.2
CMVR zone2 &3	21/141	52.4	52.4	28.6	33.3
RD	20/26	100.0	95.0	90.0	90.0
Cataract	22/80	72.7	72.7	36.4	54.6
CME	3/8	33.3	100.0	33.3	66.7
Optic nerve disease	15/32	93.3	93.3	66.7	73.3
IRU	3/8	33.3	100.0	33.3	66.7
ERM	4/5	75.0	75.0	50.0	50.0

n/N = Number of eyes with event/number of eyes at risk, CMVR = Cytomegalovirus retinitis, RD = Retinal detachment, IRU = Immune recovery uveitis, CME = Cystoid macular edema, ERM = Epiretinal membrane

visual impairment after a 6-month period, and even after the retinal re-attachment operation, the occurrence of visual impairment was just slightly reduced. Moreover, retinal detachment is the major risk factor causing legal blindness, including up to 90% of the eyes after the 6-month period, and no vision improvement was found after the retinal re-attachment operation.

In eyes with cystoid macular edema and immune recovery uveitis, it was found that both conditions were also the major risk factors for visual impairment after the one-year follow-up period.

Discussion

CMVR is often found in patients with an immune deficiency such as in HIV patients, cancer patients receiving chemotherapy, patients undergoing organ transplant and those receiving an immunosuppressive drug. Nowadays there are a number of HIV patients in Thailand, posing a big issue to Thailand's public health. CMVR is the most common opportunistic infection of eye in HIV patients[1-4], with the possibility of occurrences as high as 30%[3,6,7]. The infection mechanism of CMVR is from the diffusion of the virus in blood to the retina[33]. Therefore, the CMVR treatment can be done by intravitreous injection of the antiretroviral, i.e. gancyclovir, which is one of the virostatic agents[34]. Even though the HAART application and the subsequent immune recovery will help reduce the symptoms of visual impairment and legal blindness, their occurrences are not essentially down to zero. From the present study, the former and the latter are 0.10/EY and 0.15/EY, respectively, which are in agreement with the findings from the study of Thorne et al, i.e. 0.10/EY and 0.06/EY, respectively[32]. The only obvious difference is a higher occurrence of legal blindness in this research.

The present study shows that the main causes of visual acuity loss in HIV patients with CMVR complication after HAART application were as follows. The main cause of the visual impairment is CMVR zone 2 and 3, followed by CMVR zone 1 and cataract, respectively. On the other hand, the main cause of the legal blindness is CMVR zone 2 and 3, followed by CMVR zone 1 and retinal detachment, respectively. The results are slightly different from those of Thorne et al, which indicate that in both pre- and post- HAART eras, the main cause of visual acuity loss is the CMVR zone 1, followed by CMVR-related retinal detachment and cataract, respectively[18]. A possible explanation for the prevalence of CMVR zone 2 and 3 in the present study is that most of the patients incurred CMVR zone 1,2 and 3 in the same eye and some developed a lesion in zone 2 and 3 first, the condition of which results in the permanent loss of vision due to full retinal necrosis. Therefore, even though an immune recovery after HAART helps subdue progression of CMVR, the serial of follow-up examinations will still be indicated.

Optic nerve disease is the less common cause and is often found as optic nerve atrophy, which results from diffuse CMVR and retinal detachment. Retinal detachment is the significant risk factor that causes a 100% chance of visual impairment and a 90% chance of legal blindness after a 6 month follow-up period. Even after the retinal re-attachment operation, the level of

visual acuity was not improved. Overall, retinal detachment was found in 10% of patients with visual impairment and 27% of patients with legal blindness. Accordingly, retinal detachment is one of the most important risk factors that requires monitoring and thorough examination. The detachment usually starts at the periphery and propagates to the fovea, resulting in the permanent loss of vision.

Among patients with immune recovery from HAART, some incurred immune recovery uveitis, which caused visual impairment after the one year follow-up period. Level of the visual impairment was related to cystoid macular edema and cataract, both of which are essentially the common complications of immune recovery uveitis.

Regarding a complication incurring from the treatment, endophthalmitis was reported as occurring approximately 0.2-0.6%[35]. During the course of the present study, there were three patients, accounting for three eyes in total, incurring endopthalmitis from intravitreous injection. Apart from that, there was no other complication, such as an increase in intraocular pressure, found.

The outcomes from this research shall explain various causes that impair visual acuity in CMVR patients despite the HAART application. Accordingly, it can pave a way to prevent, monitor, or even remedy those causes as effectively as possible. Moreover, these outcomes can provide the reference information to those researchers who are pursuing a CMVR research study in Thailand in the future.

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Potential conflicts of interest

None.

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สาเหตุของระดับการมองเห็นลดลงในผู้ป่วยติดเชื้อ HIV ที่มีโรคจอตาอักเสบจากเชื้อ Cytomegalovirus ในช่วงที่ได้รับยาต้านไวรัสที่มารับการรักษาในโรงพยาบาลมหาราชนครเชียงใหม่

จุฬาลักษณ์ ตั้งมั่นคงวรกูล, สมสงวน อัษญคุณ

วัตถุประสงค์*: เพื่อศึกษาสาเหตุของการสูญเสียสายตาในผู้ป่วยเอดส์ ที่มีการติดเชื้อ Cytomegalovirus ที่จอตา (Cytomegalovirus retinitis, CMVR) ในยุคที่มีการใช้ยาต้านไวรัสที่มีประสิทธิภาพสูง*

วัสดุและวิธีการ*: ทำการศึกษาแบบไปข้างหน้า ในผู้ป่วยเอดส์ 113 ราย (165 ตา) ที่ได้รับการวินิจฉัยมีการติดเชื้อ CMVR ที่จอตาตั้งแต่เดือนพฤษภาคม พ.ศ. 2551 ถึงเดือนมีนาคม พ.ศ. 2553 ณ โรงพยาบาลมหาราชนครเชียงใหม่ ผู้ป่วยได้รับการตรวจทางจักษุและติดตามผลทุกๆ 3 เดือน*

ผลการศึกษา*: การศึกษานี้ผู้ป่วยมีอายุอยู่ในช่วง 14 -57 ปี โดยอายุเฉลี่ยคือ 39 ปี ผู้ป่วยมีเชื้อชาติไทย 103 คน (ร้อยละ 91) และเป็นชาวไทยภูเขา 10 คน พบผู้ป่วยเพศหญิงมากกว่าชาย ปัจจัยเสี่ยงของการติดเชื้อ HIV ที่พบมากที่สุดคือ การมีเพศสัมพันธ์กับเพศตรงข้ามคิดเป็นร้อยละ 90 รองลงมาคือเพศชายมีเพศสัมพันธ์กับเพศชายคิดเป็นร้อยละ 7 ผู้ป่วยส่วนใหญ่จำนวนร้อยละ 68 มีจำนวน CD4 T-cell count ที่น้อยกว่า 50 เซลล์/ไมโครลิตร และผู้ป่วยที่มีภาวะติดเชื้อ CMVที่จอตาทั้งสองข้างมีจำนวนเกือบครึ่งหนึ่งของผู้ป่วยทั้งหมดคิดเป็นร้อยละ 46 อุบัติการณ์ของการเกิดภาวะสายตาเลือนรางและภาวะตาบอดตามกฎหมาย ในผู้ป่วย CMVR เท่ากับ 0.10/EY, 0.15/EY ตามลำดับ ปัจจัยที่ทำให้เกิดอุบัติการณ์ของระดับการมองเห็นลดลงมีดังนี้ สาเหตุหลักที่ทำให้เกิดภาวะสายตาเลือนรางมากที่สุดเรียงตามลำดับได้แก่ ภาวะ CMVR zone 2&3, ภาวะ CMVR zone 1 และ ภาวะต้อกระจกตามลำดับ ในขณะที่สาเหตุหลักที่ทำให้เกิดภาวะตาบอดตามกฎหมายมากที่สุดเรียงตามลำดับได้แก่ ภาวะ CMVR zone 2&3, ภาวะ CMVR zone 1 และ ภาวะจอตาลอกตามลำดับ ภาวะจอตาลอกเป็นปัจจัยเสี่ยงที่สำคัญที่ทำให้เกิดสายตาเลือนรางและตาบอดตามกฎหมาย ถึงแม้ว่าผู้ป่วยจะได้รับการผ่าตัดจอตาให้ติดได้ดังเดิม แต่ระดับการมองเห็นก็ยังไม่ดีขึ้นมากนัก ซึ่งแสดงถึงการสูญเสียสายตาอย่างถาวร*

สรุป*: หลังการใช้ยาต้านไวรัส ภูมิคุ้มกันของร่างกายที่เพิ่มขึ้นในผู้ป่วยเอดส์ช่วยลดอุบัติการณ์ของการติดเชื้อ CMVR การใช้ยาต้านไวรัสช่วยลดอุบัติการณ์ของสายตาเลือนรางและตาบอด การเกิดการอักเสบของจอตา การเกิดต้อกระจก จอตาลอก และขั้วประสาทตาฝ่อ เป็นสาเหตุที่ทำให้เกิดการสูญเสียของสายตา*