

# Cytomegalovirus Retinitis (CMVR) in HIV-infected Pediatric Patients in Chiang Mai University Hospital

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## Abstract

**Background** Cytomegalovirus retinitis (CMVR) is the most common opportunistic ocular infection in immunocompromised hosts. It affects many children in Thailand, but the data are limited for CMVR in Thai children.

**Objectives** To describe the signs, symptoms, ocular manifestations, visual acuity, T-lymphocyte CD4 level, treatment, complications of treatment and time to progression of CMVR in human immunodeficiency virus (HIV)-infected pediatric patients in Chiang Mai University Hospital.

**Design** Retrospective cohort study

**Method** The records of 36 HIV-infected pediatric patients, who had ophthalmic examinations between January 2002 and December 2012, were reviewed.

**Results** Of the 36 patients, 11 (14 eyes) had CMVR, 21 were normal and 4 (6 eyes) had other eye diseases. The average age (mean±SD) of the patients was 10.6±3.8 years and 9.5±3.6 years in the CMVR and normal group, respectively. The mean T-lymphocyte CD4 level was 23.7 cells/mm<sup>3</sup> and 232.1 cells/mm<sup>3</sup> in the CMVR and normal group, respectively. The mean log of minimum angle of resolution (MAR) in visual acuity was 1.27±1.1 and 0.11±0.1 in the CMVR and normal group, respectively. Patients receiving highly active antiretroviral therapy comprised 90.9% and 95% of the CMVR and normal group, respectively. Visual impairment was the most common presentation. Clinical manifestations showed opacification of the retina with areas of hemorrhage, exudate and necrosis, periphlebitis, frosted branch angiitis and vitritis.

**Conclusions** CMVR is associated with T-lymphocyte CD4 cells of <50 cells/mm<sup>3</sup>. Visual impairment is the most common presentation. **Chiang Mai Medical Journal 2015;54(3):121-7.**

**keywords:** Cytomegalovirus retinitis, pediatric, HIV

## Introduction

Cytomegalovirus retinitis (CMVR) is the most common opportunistic ocular infection in immunocompromised hosts, especially human

immunodeficiency virus (HIV)-infected patients<sup>[1]</sup>. It is a leading cause of blindness if left untreated. The incidence of CMVR is higher

in HIV-infected adults<sup>[2-4]</sup> than in HIV-infected pediatric patients (19-33% vs 3.4-11%)<sup>[5-8]</sup>, and this associates with T-lymphocyte CD4 cells of  $<50$  cells/mm<sup>3</sup> and  $<20$  cells/mm<sup>3</sup> in HIV-infected adults and pediatric patients<sup>[9]</sup>, respectively<sup>[10]</sup>.

In Thailand, the epidemiology of HIV infected pediatric patients is 0.43-2.9%<sup>[11]</sup>. The most common risk factor is vertical transmission (94.66%), with other risk factors including unknown causes (5.19%) and blood transfusions (0.09%)<sup>[12]</sup>.

The medications for treating CMVR are ganciclovir, foscarnet, cidofovir and fomivirsen. Cidofovir and fomivirsen are new drugs, and their efficacy and side effects have not been studied sufficiently. Consequently, ganciclovir and foscarnet are suitable choices for treating CMVR<sup>[13-14]</sup>.

At present, many children in Thailand suffer from CMVR. This condition affects their health, psychology, and quality of life, but data from previous studies are limited.

The objectives of this study were to describe the signs, symptoms, ocular manifestations, visual acuity, T-lymphocyte CD4 level, treatment, complications of treatment and time to progression of CMVR in HIV-infected pediatric patients in Chiang Mai University Hospital.

## Methods

This retrospective cohort study was approved by the Institutional Review Board of the Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand (No. 129/2013). All HIV-infected pediatric patients, who were examined from 1 January 2002 to 31 December 2012 at the Ophthalmology Clinic of Chiang Mai University Hospital, were included in this study. CMVR patients, who were immunocompromised from other causes besides HIV infection, were excluded. The data were reviewed from a digital electronic card. The data records included age, sex, affected eye, best corrected visual acuity (BCVA), T-lymphocyte CD4 level at initial ophthalmic examination, signs, symptoms, route of HIV transmission, highly active antiretroviral therapy (HAART), anti-CMV treatment and complications of treatment. Visual acuity assessment was based on the age and cooperation of the child.

BCVA was measured by the Central, Steady, Maintain technique in patients  $<2$  years old. The Allen picture chart was used in patients of 2-3 years old. The Snellen acuity chart was used to measure BCVA in patients aged  $>4$  years. BCVA was converted to the logarithm of the minimum angle of resolution (log MAR) for statistical analysis.

BCVA was tested before an eye examination on every visit. Visual acuity (VA) was examined in each patient at the first time of pre treatment in order to determine the BCVA, and again post treatment to ascertain the BCVA after the last time of treatment. An indirect ophthalmoscope was used for the fundus examination after the eye had been dilated with 1% Tropicamide and 2.5% Phenylephrine. The patients were examined by ophthalmologists and diagnosed clinically. The treatment was recorded, including medication, doses, route of drug administration and complication of treatment. Follow-up examinations were performed weekly during antiviral therapy induction until CMVR was inactive, and then biweekly for maintenance.

Statistical analysis was performed using SPSS 16.0 software. Descriptive statistics were used (significance level  $p < 0.05$ ) including the Wilcoxon's Signed Ranks test (pre-treatment/post-treatment comparisons) and Kruskal-Wallis test (comparison of independent groups). The Chi-Square and Fisher's Exact test were used independently for the CMVR and normal group.

## Results

Thirty-six patients were enrolled in this study from 1 January 2002 to 31 December 2012. Baseline characteristics are shown in Table 1. There were 11 patients (14 eyes) in the CMVR group, 21 in the normal group and 4 (6 eyes) with other eye diseases (optic nerve atrophy, papilledema, toxoplasmosis, and HIV retinopathy). The average ages (mean $\pm$ SD) were  $10.6\pm 3.8$  years,  $9.5\pm 3.6$  years and  $10.4\pm 1.7$  years in the CMVR, normal and other eye disease group, respectively ( $p = 0.302$ ). The mean T-lymphocyte CD4 level was 23.7 (range 5-49) cells/mm<sup>3</sup>, 232.1 cells/mm<sup>3</sup> and 191.0 cells/mm<sup>3</sup> in the CMVR, normal and other eye disease group, respectively. The mean log MAR in visual acuity was  $1.27\pm 1.1$ ,  $0.11\pm 0.1$  and  $1.07\pm 1.1$  in the CMVR, normal and other eye disease group, respectively ( $p = 0.018$ ). The ratio of males to females was 4:7, 15:6 and 3:1 in the CMVR, normal and other eye

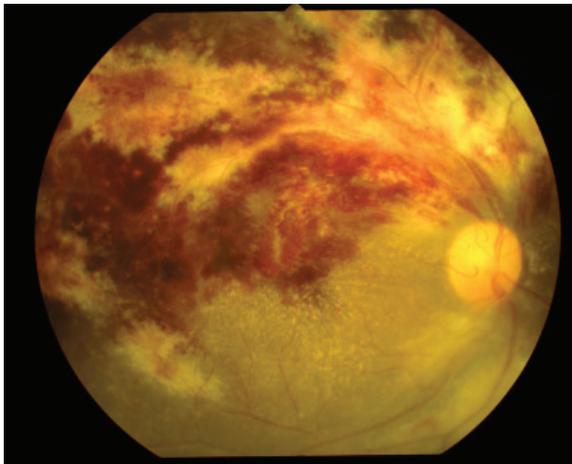
**Table 1.** Baseline characteristics of patients

	CMVR gr. (N=11)	Normal gr. (N=21)	Other gr. (N=4)	p-value
Age (months) (mean±SD)	128.0±45.9	114.3±43.2	125.5±20.9	0.302*
CD4 (cell/mm <sup>3</sup> ) (mean±SD)	23.7±6.0	232.1±53.3	191.0±85.6	0.151*
Log MAR VA (mean±SD)	1.27±1.1	0.11±0.1	1.07±1.1	0.018*
Sex (male: female)	4:7	15:6	3:1	-
HAART (%)	90.9	95	100	1.000**

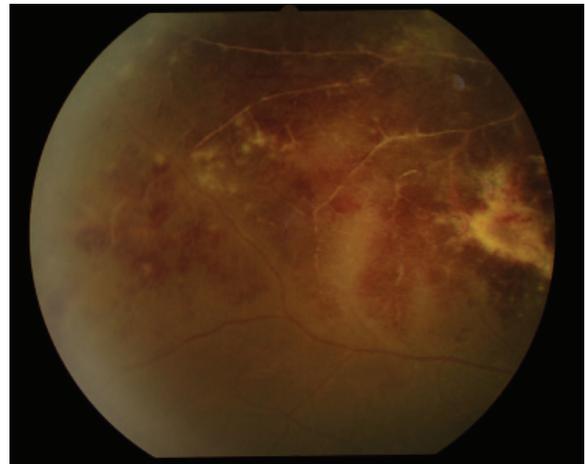
HAART = Highly active antiretroviral therapy

Other group; optic nerve atrophy, papilledema, toxoplasmosis, HIV retinopathy

\*Kruskal–Wallis test, \*\*Fisher's exact test



**Figure 1.** Fundus photograph of the patient No.3. The retina with areas of hemorrhage, exudate and necrosis or pizza pie retinopathy



**Figure 2.** Fundus photograph of the patient N0.3 showed frosted branch angiitis

disease group, respectively. The patients receiving HAART comprised 90.9%, 95% and 100% in the CMVR, normal and other eye disease group, respectively ( $p = 1.000$ ).

Visual impairment was the most common presentation. Clinical manifestations were opacification of the retina with areas of hemorrhage, exudate and necrosis (Figure 1). Other manifestations were periphlebitis, frosted branch angiitis (Figure 2) and vitritis. The route of HIV transmission was vertical for all of the patients.

The initial treatment of CMVR consisted of two groups: intravenous (IV) ganciclovir in 8 eyes (6 patients) and intravitreal (IVT) ganciclovir in 2 eyes (2 patients). Four eyes (3 patients) were observed due to old CMVR. The induction doses were 5 mg/kg of IV ganciclovir

twice daily and 2 mg/0.05 of IVT ganciclovir weekly. Maintenance therapy was continued in both groups. Four of the 6 patients in the IV ganciclovir group received 5 mg/kg of IV ganciclovir once daily, but one of them changed to IVT ganciclovir because of systemic side effects of cytopenia, agitation and change in alertness and behavior. Patients in the IVT ganciclovir group received maintenance therapy with 2 mg/0.05 mL of IVT ganciclovir every two weeks. Mean log MAR visual acuity post treatment ( $0.94 \pm 1.0$ ) was better than that pre-treatment ( $1.49 \pm 1.2$ ), but without statistical significance ( $p = 0.141$ ). The mean follow up time of this study was 2.9 years.

CMVR reactivated in only one patient (pt. No.7). The time to progression was 77 months with a T-lymphocyte CD4=24 cell/mm<sup>3</sup> and log

**Table 2.** Clinical features of 11 patients with CMVR

Pt No. /Sex	Laterality	Age	CD4	HAART	Log MAR VA (before)	Eye exam	Induction	Maintenance	Log MAR VA (after)
1/F	RE	107	49	yes	0.00	Exudate	IVT Ganc x 6	IVT Ganc x 6	0.00
2/M	LE	169	14	yes	2.30	Exudate, hemorrhage, frosted branch angiitis	IVT Ganc x 7	IVT Ganc x 6	2.30
3/M	BE	174	5	yes	2.30, 0.60	Exudate, hemorrhage, optic disc swelling	IV Ganc x 25	IVT Ganc x 8	2.30, 1.00
4/F	RE	136	16	yes	2.80	Exudate, hemorrhage	IV Ganc x 20	IV Ganc x 36	2.30
5/F	BE	154	NA	yes	2.80, 2.30	Exudate	IV Ganc x 29	-	1.00, 0.48
6/F	LE	124	39	yes	1.80	Exudate, hemorrhage, vitreous clumping, sheathing vessels	IV Ganc x 14	IV Ganc x 48	2.30
7/F	LE	8	13	yes	0.00	Exudate, sheathing vessels	IV Ganc x 14	IV Ganc x 4	0.00
8/M	RE	111	NA	yes	No PL	Exudate, retinal detachment	observe	observe	-
9/M	RE	125	30	no	0.00	Exudate, hemorrhage, sheathing vessels	IV Ganc x 15	IV Ganc x 43	0.00
10/F	BE	135	482	yes	1.20, 0.18	Chorioretinal scar	observe	observe	-
11/F	LE	165	13	yes	0.18, 0.18	Dry exudate	observe	observe	-

IV Ganc; intravenous Ganciclovir, IVT Ganc; intravitreal Ganciclovir, NA; not available, RE; right eye, LE; left eye, BE; both eyes

MAR VA of 0.00, 1.85. The patient received IV ganciclovir as induction therapy for 14 days.

**Discussion**

Cytomegalovirus (CMV) is the largest and most complex member of the herpes virus family that infects humans<sup>[15]</sup>. It is named for

its cytopathic effect of producing enlarged cells with intranuclear and cytoplasmic inclusions, which often give the cells their classic ‘owl’s eye’ appearance<sup>[16]</sup>. The prevalence of infection is greater in developing countries and among lower socioeconomic groups of developed nations<sup>[17]</sup>. In adults with AIDS, CMVR is

associated typically with a CD4 T-lymphocyte count of  $<50$  cells/mm<sup>3</sup><sup>[18,19]</sup>, and this condition is associated with T-lymphocyte CD4 cells of  $<20$  cells/mm<sup>3</sup> in HIV-infected pediatric patients. A retinal infection can develop in immunosuppressed patients, or those who have lost their cellular immunity specifically against CMV. In this study, average CD4 T-lymphocyte counts were 23.7 cells/mm<sup>3</sup>.

In this study, decreased vision was evident in most patients, and some children were preverbal and unable to describe visual changes, which may lead to delayed diagnosis and treatment. Opacification of the retina was the common clinical manifestation of CMVR. Initially, infected retinal tissue was transparent, but as viral replication increased within infected cells, translucency was lost and replaced by a white lesion. When CMV retinitis starts adjacent to a blood vessel, it can either cause vascular occlusion with typical hemorrhages or present as a frosted branch angiitis. Other manifestations include areas of retinal exudate, necrosis and vitritis. In this study, clinical manifestations of CMVR in pediatric patients were the same as those in adult patients.

The medications for treating CMVR are ganciclovir, foscarnet, cidofovir and fomivirsen, but only ganciclovir was available in this study. Ganciclovir is an acyclic nucleoside analogue of 2-deoxyguanosine, with potent anti-CMV activity *in vitro* and *in vivo*. Its mechanism of action is selective inhibition of CMV DNA polymerase, thus inhibiting viral replication effectively<sup>[20,21]</sup>. IV ganciclovir was effective, but systemic toxicity, cytopenia and behavioral changes were found. Local therapy with IVT ganciclovir, which has not been approved by the Food and Drug Administration (FDA), was cost-effective without complication in this study.

## Conclusion

In this study, CMVR was associated with T-lymphocyte CD4 cells of 5–49 cells/mm<sup>3</sup>. Visual impairment was a common presentation, but there might be delayed diagnosis and treatment for some preverbal children. IVT ganciclovir is not approved by the FDA, but it was cost-effective with no complications

in this study. IV ganciclovir was effective, but systemic side effects (pancytopenia and behavioral change) were identified in one patient. Routine screening should be carried out for early diagnosis and treatment to decrease complications and improve quality of life.

The limitation of this study was a retrospective study with a small number of patients, thus a larger prospective study is recommended. Some children were preverbal and unable to describe visual changes, which might affect the result of this study.

## Ethics

This study was approved by the Institutional Review Board of the Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand (No. 129/2013).

## Acknowledgement

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## ภาวะจอตาอักเสบจากเชื้อ Cytomegalovirus ในผู้ป่วยเด็กติดเชื้อเอชไอวี

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**วัตถุประสงค์** เพื่อศึกษาอาการ อาการแสดง ลักษณะที่ตรวจพบทางตา ระดับ T-lymphocyte CD4 วิธีการรักษา ระดับการมองเห็น ภาวะแทรกซ้อนจากการรักษาและระยะเวลาการกลับเป็นซ้ำของโรคจอตาอักเสบจากเชื้อ cytomegalovirus ในผู้ป่วยเด็กติดเชื้อเอชไอวี คณะแพทยศาสตร์ มหาวิทยาลัยเชียงใหม่

**รูปแบบการศึกษา** Retrospective cohort study

**วิธีการศึกษา** ศึกษาข้อมูลจากเวชระเบียนของผู้ป่วยเด็กที่ติดเชื้อเอชไอวี จำนวน 36 ราย ที่ได้รับการตรวจตาตั้งแต่เดือนมกราคม พ.ศ. 2545 ถึงเดือน ธันวาคม พ.ศ. 2555

**ผลการศึกษา** ผู้ป่วยเด็กทั้งหมด 36 ราย พบภาวะ CMVR 11 ราย (14 ตา) ผลการตรวจตาปกติทั้งสองข้าง 21 ราย และพบโรคตาอื่น ๆ อีก 4 ราย (6 ตา) อายุเฉลี่ยของผู้ป่วยในกลุ่ม CMVR คือ  $128.0 \pm 45.9$  เดือน และ  $114 \pm 43.2$  เดือน ในกลุ่มปกติ ระดับ T-lymphocyte CD4 มีค่าเฉลี่ย  $23.7 \text{ cell/mm}^3$  ในกลุ่ม CMVR และ  $232.1 \text{ cell/mm}^3$  ในกลุ่มปกติ ระดับการมองเห็น (log MAR visual acuity)  $1.27 \pm 1.1$  ในกลุ่ม CMVR และ  $0.11 \pm 0.1$  ในกลุ่มปกติ ผู้ป่วยในกลุ่ม CMVR รับประทานไวรัสรัยละ 90.9 และในกลุ่มปกติได้รับรัยละ 95 ระดับการมองเห็นที่ลดลงเป็นอาการที่พบบ่อยของผู้ป่วย ลักษณะทางคลินิกที่สำคัญได้แก่ พบจอตาขาวขุ่นขึ้น พบตำแหน่งที่มีเลือดออก ของเหลวรั่วออกจากหลอดเลือด หรือมีเนื้อตายของจอตา นอกจากนี้ยังพบลักษณะอื่น ๆ อีก เช่น น้ำวุ้นลูกตาอักเสบ การอักเสบของหลอดเลือดที่จอตา

**สรุป** ภาวะจอตาอักเสบจากเชื้อ cytomegalovirus มีความสัมพันธ์กับระดับ T-lymphocyte CD4 ที่น้อยกว่า  $50 \text{ cell/mm}^3$  และระดับการมองเห็นที่ลดลงเป็นอาการสำคัญที่นำผู้ป่วยมาพบแพทย์ 8 เชียงใหม่ เวชสาร 2558;54(3):121-7.

**คำสำคัญ:** ภาวะจอตาอักเสบจากเชื้อ cytomegalovirus เด็ก เอชไอวี

