Analysis of Risk Factors for Cytomegalovirus Corneal Infection

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Research Article

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Abstract

Objectives: The present study assessed the risk factors for cytomegalovirus (CMV) corneal infection and compared the odds ratios.

Methods: This study was a retrospective case-control study (2014.12–2021.1) over a 6-year period. We reviewed the medical record data and compared the differences between the CMV-positive and virus-negative groups with regard to sex, age, first diagnosis, and ocular complications to identify factors that may be associated with CMV corneal infections. The risk factors for CMV corneal infection were analysed using the chi-squared test and binary logistic regression models.

Results: Ninety CMV-positive cases and 151 virus-negative controls were involved in this study. The risk factors for CMV corneal infection were Stevens-Johnson syndrome ocular complication (OR 12.851, 95%CI, 1.435–111.111; P=0.000), a penetrating keratoplasty (PKP) (OR 4.950, 95%CI, 2.632–9.346; P=0.024, and an anterior lamellar keratoplasty (DALK) (OR 5.290, 95%CI, 1.250–22.222; P=0.022).

Conclusion: Severe corneal damage (PKP or DALK) and a severe corneal inflammatory response (SJS ocular complication) may be risk factors for CMV corneal infections.

Introduction

A Japanese ophthalmologist reported the first case of cytomegalovirus (CMV) keratitis in 2006, and there has been a constant surge of cases since this period. The available evidence showed that CMV corneal infection primarily occurred in Asian populations^{2 3}, and it primarily occurred as sporadic cases in European and American countries⁴. CMV corneal infections have gradually received widespread worldwide attention in recent years, and the pathology⁵, diagnosis⁶ and treatment^{7–9} of CMV keratitis have shown promising progress under the wisdom and work of scientists. However, the causes and mechanism of the disease remain poorly understood^{10 11}. Whether the damage to the corneal tissue caused by CMV corneal infection is a primary or secondary cause of the primary disease is not clear¹². The current hypothesis is that immune cells carrying latent CMV reactivate after entering the anterior chamber¹³. The alternative hypothesis is that the corneal tissue itself is the latent site of CMV, and the transplantation procedure reactivates the latent CMV within the cornea of the donor or recipient^{14 15}. CMV corneal infection occurs in different populations² with different anterior segment disorders^{16 17 18}. However, the risk factors for CMV corneal infection were not reported. The identification of risk factors would improve the prevention and treatment of CMV corneal infection.

CMV infection is closely related to the body's immune status¹⁹. Previous studies demonstrated that patients with immune system abnormalities often develop retinal lesions²⁰, but patients with CMV infection in the anterior segment of the eye mostly have a normal immune status²¹. Local immune factors are the primary reason for viral relapse, but the identity of the factors that activate the virus and cause lesion recurrence are not clear. This may be related to the relative independence of the immunity of

the anterior segment, and it requires further investigation. Clinical observations and previous studies reported that of CMV corneal infections occurred more often in patients after corneal transplantation and were particularly frequent after penetrating keratoplasty (PKP)^{22 23}. Our study determined whether there was any correlation between corneal transplantation and CMV corneal infection. This study was a retrospective case-control study. Cases and controls were keratopathy patients who were hospitalized in a corneal ward during the same period, and there were controllable differences in the two groups in CMV DNA PCR test results from the aqueous humour/corneal tissue. We investigated risk factors for CMV corneal infections by analysing the differences between these two groups.

Material And Methods

Hospital Cases and Controls

This study was a retrospective case-control study (2014.12–2021.1) performed over a 6-year period. It was performed according to the tenets of the Declaration of Helsinki, and the local ethics committee approved the study. All cases were collected from the cornea ward of the eye centre of Peking University Third Hospital. Viral DNA detection was routinely performed intraoperatively in patients scheduled for keratoplasty in our ward to understand ocular viral infections in that group population. The results of viral PCR were consistent with the results of intraoperative viral detection. Inpatients who were positive for aqueous humour/corneal CMV DNA were collected for the study group by reviewing the results of previous inpatient tests. The controls were selected from all inpatients admitted to our cornea ward during the same period (same month and year) and had tests within the same batch for virus detection as the cases but had negative aqueous humour/corneal viral test results. Hospitalized patients with negative virus tests must have no clinical symptoms or signs of virus infection. Cases with incomplete test results or poor case quality for various reasons unrelated to the study were excluded during the case selection process. A flowchart of the inclusion and exclusion criteria is shown in Figure 1.

In-hospital patients were included in the case and control groups of this study, and outpatients were excluded due to the lack of more complete inpatient data. During the control group selection process, patients with negative results from the same period and the same virus detection batch as the CMV-positive patients who underwent viral testing were selected.

CMV DNA detection

Cornea tissues/aqueous humour samples were obtained during cornea transplantation procedures. Sufficient aqueous humour was drawn from the patient using a 1-ml syringe before removing the patients' diseased corneal tissues. The removed corneal tissues and aqueous humour were placed into 1.5-ml EP tubes. Fresh tissues were sent to the ophthalmic clinical testing laboratory of Peking University Third Hospital for viral detection. We extracted DNA using a Liferiver CMV Real Time PCR Kit (catalogue no. Z-OD-0022_02; Shanghai, China) according to the manufacturer's instructions. The limit of detection of viral DNA was 10 copies per sample size. Each sample was processed with the addition of an internal

control for the assessment of the isolation and amplification efficacy. Positive, negative and internal controls were provided by the kit manufacturer.

CMV corneal infection²⁴

A CMV corneal infection was defined as patients who had a lesion in the cornea (active or stationary phase) and positive CMV DNA PCR detection results from the corresponding corneal tissue or aqueous humour. All patients intended to undergo corneal keratoplasties, and the corneas all had varying degrees of pathological changes (diagnosis). Therefore, the definition of CMV corneal infection was positive CMV DNA detection in corneal tissue or aqueous humour.

Observation procedures and data analysis

Information on all cases, including sex, age, diagnosis and ocular-related diseases, was collected for the study group and controls. The diagnosis included endothelial decompensation, graft rejection, congenital corneal leucoma, limbal stem cell deficiency, corneal ulcer and graft melting. Ocular-related conditions included history of glaucoma/glaucoma surgery, history of corneal transplantation, vitrectomy surgery, IOL eye/aphakia, eye trauma, Stevens-Johnson syndrome, ocular graft-versus-host disease (oGVHD) and uveitis history. Corneal endothelial decompensation was divided into bullous keratopathy, corneal endothelial dystrophy and iridocorneal endothelial syndrome (ICE syndrome) based on the aetiology. The diagnosis of graft rejection was classified based on the case data as graft rejection after Descemet's Stripping Automated Endothelial Keratoplasty (DSAEK), PKP and anterior lamellar keratoplasty (DALK). Corneal ulcers were classified as bacterial, fungal and immunological based on the preoperative or intraoperative smears of the lesion and the culture results. Systemic diseases were based on the diagnosis of hypertension, diabetes, heart disease, surgical history, neoplasm, hemopathy, allergic history, thyroopathy, rheumatic immune disease and cerebral infarction in the patients. The medication history included whether the patient received topical immunosuppressive agents. The description of the history of corneal transplantation included the surgical approach and the number of procedures.

Statistical analysis

Continuous variables are expressed as the means±standard deviation. The independent samples t-test was used to compare the difference in age between the two groups. Chi-squared tests were used for comparisons between two groups. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were initially filtered by the chi-squared test. A binary logistic regression model using a backward stepwise selection method was used to further study the possible risk factors associated with CMV corneal infection. P values less than 0.05 (two-tailed) were considered statistically significant. SPSS 23.0 (SPSS, Chicago, Illinois, USA) was used for statistical analysis.

Results

The study design resulted in 90 CMV-positive cases and 151 virus-negative controls from the Department of Ophthalmology, Peking University Third Hospital, Beijing, China. The study group consisted of 45 males and 45 females with a mean age of 38 ± 29 years (range 0.33–82). The control group consisted of 81 males and 70 females with a mean age of 46 ± 27 years (range 0.33–81). The number of study cases and controls that initially presented with bullous keratopathy was 5 (5.6%) and 27 (17.9%), respectively, ($\chi^2 = 7.439$, $P = 0.006$), the number of cases that had graft rejections was 36 (40%) and 37 (24.5%), respectively, ($\chi^2 = 6.413$, $P = 0.011$), and the number of cases that had graft melting was 9 (10.0%) and 4 (2.6%), respectively, ($\chi^2 = 5.971$, $P = 0.015$). The study cases and controls differed in history of corneal transplantation, and 51 (56.7%) and 43 (28.5%) of the cases and controls had corneal transplantation, respectively, ($\chi^2 = 18.835$, $P = 0.000$). Stevens-Johnson syndrome (SJS) ocular complications were present in 6 (6.7%) and 1 (0.7%) patients and controls, respectively, ($\chi^2 = 7.209$, $P = 0.007$). The numbers of cases and controls who used topical immunosuppressants were 61 (67%) and 55 (36%) ($\chi^2 = 22.205$, $P = 0.000$), respectively, which were significantly different. In general, with regard to the There were no significant differences in underlying condition and other complications between cases and controls. Specific results are shown in Table 1.

Table 1. Clinical and demographic characteristics of CMV-positive cases and controls

Patients	Study group (cases)	Control group (cases)	P
Age	38±29	46±27	t=-1.953, P=0.052
Sex	M45, F45 (90)	M81,F70 (151)	$\chi^2=0.300$, P=0.584
Ocular diagnosis			
Endothelial decompensation	20 (22.2%)	62 (41.1%)	$\chi^2=8.914$, **P=0.003
Bullous keratopathy	5 (5.6%)	27 (17.9%)	$\chi^2=7.439$, **P=0.006
Endothelial dystrophy	5 (5.5%)	4 (2.7%)	$\chi^2=1.325$, P=0.250
ICE syndrome	1 (1.1%)	3 (2.0%)	$\chi^2=0.265$, P=0.607
Graft rejection after keratoplasty	36 (40%)	37 (24.5%)	$\chi^2=6.413$, *P=0.011
Congenital cornea leucoma	16 (17.8%)	19 (12.6%)	$\chi^2=1.226$, P=0.268
Limbal stem cell deficiency	10 (11.1%)	10 (6.6%)	$\chi^2=1.493$, P=0.222
Corneal ulcer	8 (8.9%)	20 (13.2%)	$\chi^2=1.042$, P=0.307
Bacterial	3 (3.3%)	13 (8.6%)	$\chi^2=2.532$, P=0.112
Fungal	1 (1.1%)	4 (2.6%)	$\chi^2=0.656$, P=0.418
Immunity	4 (4.4%)	3 (2.0%)	$\chi^2=1.208$, P=0.272
Graft melting	9 (10.0%)	4 (2.6%)	$\chi^2=5.971$, *P=0.015
Ocular-related conditions			
Glaucoma/glaucoma surgery	24 (26.7%)	31 (20.5%)	$\chi^2=1.206$, P=0.272
Corneal transplantation history	51 (56.7%)	43 (28.5%)	$\chi^2=18.835$, **P=0.000
Vitrectomy history	1 (1.1%)	9 (6.0%)	$\chi^2=3.334$, *P=0.068
IOL eyes/aphakic eyes	29 (32.2%)	56 (37.1%)	$\chi^2=0.584$, P=0.445
Ocular trauma	6 (6.7%)	13 (8.6%)	$\chi^2=0.293$, P=0.588
SJS ocular complication	6 (6.7%)	1 (0.7%)	$\chi^2=7.209$, **P=0.007
oGVHD	3 (3.3%)	2 (1.3%)	$\chi^2=1.120$, P=0.290
Uveitis	4 (4.4%)	5 (3.3%)	$\chi^2=0.201$, P=0.654
System disease			
High blood pressure	13 (14.4%)	20 (13.2%)	$\chi^2=0.069$, P=0.793
Diabetes	4 (4.4%)	4 (2.6%)	$\chi^2=0.566$, P=0.452
Cardiac disease	3 (3.3%)	5 (3.3%)	$\chi^2=0.421$, P=0.516
Surgical operation	9 (10.0%)	12 (7.9%)	$\chi^2=0.299$, P=0.585
Tumour	5 (5.6%)	5 (3.3%)	$\chi^2=0.714$, P=0.398
Hemopathy	3 (3.3%)	2 (1.3%)	$\chi^2=1.120$, P=0.290
Allergic history	9 (10%)	6 (4.0%)	$\chi^2=3.509$, P=0.061
Thyropathy	2 (2.2%)	1 (0.7%)	$\chi^2=1.116$, P=0.291
Rheumatic immune disease	2 (2.2%)	2 (1.3%)	$\chi^2=0.278$, P=0.598
Cerebral infarction	1 (1.1%)	3 (2.0%)	$\chi^2=0.265$, P=0.607
medication history			
Topical Immunosuppressant	61 (67%)	55 (36%)	$\chi^2=22.205$, **P=0.000

ICE syndrome: iridocorneal endothelial syndrome; IOL eyes: intraocular lens eyes; SJS ocular complication: Stevens-Johnsons syndrome ocular complications; oGVHD: ocular graft-versus-host disease.

The independent samples t-test was used to compare the difference in age between the two groups. The chi-squared test was used to compare the other factors in the study and control groups. P values less than 0.05 (two-tailed) were considered statistically significant.

?: As a percentage of the total number of study cases or controls

* $P \leq 0.05$, ** $P \leq 0.01$

Further refinement of the analysis of differences in the history of corneal transplantation between study cases and controls is summarized in Table 2. The number of patients having graft rejection after penetrating keratoplasty between the study cases and controls was 27 (30%) and 22 (14.6%) ($\chi^2 = 11.511$, $P = 0.001$), respectively. There were significant differences between the study cases and controls in a history of keratoplasty after PKP, and there were 39 (43.3%) and 22 (14.6%) cases who had keratoplasty, respectively ($\chi^2 = 24.679$, $P = 0.000$). The numbers of study cases and controls who were seen after a DALK were 4 (4.4%) and 2 (1.3%), respectively ($\chi^2 = 4.755$, $P = 0.029$), and the number of study cases and controls who had DSAEK were 9 (10.0%) and 22 (14.6%), respectively ($\chi^2 = 1.051$, $P = 0.305$). The number of study cases and controls with a limbal stem cell transplantation (LSCT) was 9 (10.0%) and 6 (4.0%), respectively ($\chi^2 = 3.509$, $P = 0.061$), which was not significantly different between the two groups. The numbers of study cases and controls who had corneal keratoplasty were 37 (41.1%) and 39 (25.8%), respectively ($\chi^2 = 6.101$, $P = 0.014$), and 14 (15.6%) and 4 (2.6%), respectively ($\chi^2 = 13.592$, $P = 0.000$).

The chi-squared test was used to analyse factors that were different between the study cases and controls, and the results were shown in Table 3. The ORs for graft rejection post-PKP were 2.513 (95%CI, 1.327–4.759), 4.083 for graft melting (95%CI, 1.219–13.674), 10.714 for Stevens-Johnson syndrome ocular complication (95%CI, 1.268–90.501), 3.180 for corneal transplantation history (95%CI, 1.844–5.484), 4.484 for PKP (95%CI, 2.424–8.294), 4.161 for DALK (95%CI, 1.048–16.521), 2.005 for one keratoplasty (95%CI, 1.150–3.4996), and 6.770 for two keratoplasties (95%CI, 2.154–21.277). A binary logistic regression model was established for further analysis, and the final significant risk factors for CMV corneal infection were shown in Table 4. The ORs for Stevens-Johnson syndrome ocular complications were 12.851 (95% CI, 1.435–111.111), 4.950 for PKP (95% CI, 2.632–9.346), and 5.290 for DALK (95% CI, 1.250–22.222). The application of topical immunosuppression was excluded as a confounding factor during the analysis. We compared the risk factor efficacy of PKP, DALK and SJS ocular complications (Figure 2). To assess the efficacy of these risk factors, the area under the curve (AUC) was calculated using receiver operating characteristic (ROC) regression. The overall AUC of the risk factors was 0.686 (95% CI: 0.613–0.758). The AUC of SJS ocular complications was 0.530 (95% CI: 0.454–0.606). The AUC for PKP was 0.644 (95% CI: 0.569–0.718), and the AUC for DALK was 0.529 (95% CI: 0.453–0.605).

Table 2. Differences in corneal transplantation history between study cases and controls

Risk factor	OR (Odds ratio)	95%CI	P value
Bullous keratopathy	0.270	0.100–0.729	**P=0.006
Graft failure postkeratoplasty	2.513	1.327–4.759	**P=0.001
Graft dissolution	4.083	1.219–13.674	*P=0.015
SJS ocular complication	10.714	1.268–90.501	**P=0.007
Keratoplasty history	3.180	1.844–5.484	**P=0.0070
PKP	4.484	2.424–8.294	**P=0.000
DALK	4.161	1.048–16.521	*P=0.029
Number of keratoplasty			
1	2.005	1.150–3.496	*P=0.014
2	6.770	2.154–21.277	**P=0.000
Immunosuppressant	3.671	2.133–6.594	**P=0.000

PKP: penetrating keratoplasty; DALK: anterior lamellar keratoplasty; DSAEK: Descemet's Stripping Automated Endothelial Keratoplasty; LSCT: limbal stem cell transplantation.

The chi-squared test was used to compare other factors in the study and control groups. P values less than 0.05 (two-tailed) were considered statistically significant.

‰: As a percentage of the total number of study cases or controls

*P<0.05, **P<0.01

Table 3. Preliminary Prediction of CMV corneal infection

Patients	Study cases	controls	P
Graft rejection postkeratoplasty	36 (40%)	37 (24.5%)	$\chi^2=6.413$, *P=0.011
PKP	27 (30%)	22 (14.6%)	$\chi^2=11.511$, **P=0.001
DALK	4 (4.4%)	2 (1.3%)	$\chi^2=2.261$, P=0.133
DSAEK	6 (6.7%)	11 (7.3%)	$\chi^2=0.033$, P=0.856
Keratoplasty history	51 (56.7%)	43 (28.5%)	$\chi^2=18.835$, **P=0.000
PKP	39 (43.3%)	22 (14.6%)	$\chi^2=24.679$, **P=0.000
DALK	7 (7.8%)	3 (2.0%)	$\chi^2=4.755$, *P=0.029
DSAEK	9 (10.0%)	22 (14.6%)	$\chi^2=1.051$, P=0.305
LSCT	9 (10.0%)	6 (4.0%)	$\chi^2=3.509$, P=0.061
Number of keratoplasty			
1	37 (41.1%)	39 (25.8%)	$\chi^2=6.101$, *P=0.014
2	14 (15.6%)	4 (2.6%)	$\chi^2=13.592$, **P=0.000

PKP: penetrating keratoplasty; DALK: anterior lamellar keratoplasty.

*P<0.05, **P<0.01

Table 4. Binary logistic regression model predictive of CMV corneal infection

Risk factor	E(β) Odds radio	95%CI	P value
PKP	4.950	2.632–9.346	**P=0.000
DALK	5.290	1.250–22.222	**P=0.024
SJS ocular complication	12.851	1.435–111.111	**P=0.022

PKP: penetrating keratoplasty; DALK: anterior lamellar keratoplasty.

*P<0.05, **P<0.01

Binary regression analysis of risk factors for CMV corneal infection. The AUC of the total risk factors was 0.686 (95% CI: 0.613-0.758). The AUC of SJS ocular complications was 0.530 (95% CI: 0.454-0.606). The AUC for PKP was 0.644 (95% CI: 0.569-0.718) and for DALK was 0.529 (95% CI: 0.453-0.605). SJS OC Stevens Johnsons syndrome ocular complication

Discussion

The results of this study showed that CMV corneal infections mostly occurred after corneal transplantation, which is similar to CMV infection in other organs throughout the body. In contrast, a CMV corneal infection after a corneal transplantation only had ocular manifestations, unlike CMV systemic infections with CMV positivity in serum that occur after the transplantation of other organs²⁵. Unlike systemic CMV infections, CMV corneal infections were not associated with the systemic immune status but only with the anterior segment immune status²⁶. The results of this study also confirmed that systemic factors were not risk factors for CMV corneal infections. CMV corneal infections may be the result of localised reactivation of latent CMV from recipients²⁷ or donors¹⁵. The final results of this study revealed that the risk factors for CMV corneal infections were PKP, DALK and SJS ocular complications. The results were most striking for PKP, which had the smallest range of 95% confidence intervals. PKP and DALK caused greater damage to the corneal tissue due to the 360° annular incision involving the corneal stromal layers. The complexity of the preoperative primary disease²⁸, the intense inflammatory response and corneal neovascularisation²⁸ exacerbated the immune damage secondary to PKP and DALK in the anterior segment of the eye. DSAEK surgery was less traumatic, had a significantly better postoperative recovery than PKP, and had a milder inflammatory response²⁹. CMV may be latent in the stromal layer of the cornea²⁴, and the DSAEK procedure did not contain latent CMV from a donor because there were few antigen-presenting cells (APCs) in the grafts³⁰.

Topical immunosuppression and glucocorticoids after keratoplasties may render the anterior ocular segment immunocompromised and contribute to CMV reactivation^{31 32}. Local or systemic immunosuppressive agents with stronger effects tended to be applied, especially after keratoplasty, after

considering the higher odds of rejection³⁰. However, novel conclusions were made in studies of other organ transplants, and early tacrolimus application after transplantation plays a protective role against CMV infection³³, which may involve the relationship between CMV latent cells and killer cells^{34 35}. However, more evidence is needed to make an accurate conclusion. Immunosuppressants in this study were excluded as confounders in the binary logistic model analysis and were not analysed in detail.

SJS ocular complication is a typically intense inflammatory disease of the ocular surface that manifests as a defect in the corneal epithelium in the acute phase and nonspecific keratitis and corneal lysis in the chronic phase due to the presence of ongoing inflammation. The present study revealed SJS ocular complications as a risk factor for CMV corneal infections, but this factor had a large confidence interval range. The reason for this result may be that the disease caused persistent inflammatory reactions on the ocular surface³⁶, but the severities and treatments varied greatly between individuals. There have been no studies of ocular SJS manifestations associated with CMV corneal infections. Most SJS ocular complication patients in this study presented with a CMV corneal infection that did not have a history of corneal transplantation, which suggests that a CMV corneal infection may also result from reactivation of a recipient CMV infection under corneal inflammation and lesions²⁶. oGVHD with ocular surface damage was not a risk factor in this study for several possible reasons. 1) The sample size of hospitalised oGVHD patients included in this study was small. 2) The corneal inflammation caused by oGVHD was superficial, had timely follow-up and treatment, and few involved the stromal layer³⁷.

In conclusion, severe corneal damage (PKP or DALK) and a severe corneal inflammatory response (SJS ocular complication) may be risk factors for CMV corneal infections. This study preliminarily identified the possible risk factors for CMV cornea infection in a limited retrospective cohort study. The results provide a method to analyse the mechanism of CMV corneal infection.

Declarations

Funding

The study was supported by a National Natural Science Foundation (81970768). Dr. Hong had full access to all of the data and takes responsibility for the data integrity and accuracy of data analyses.

Conflicts of interest

None of the authors have any conflicts of interest related to this study.

Availability of data and materials

Some or all data and materials generated or used during the study are available from the corresponding author upon request. (List items)

Code availability

Some or all codes generated or used during the study are available from the corresponding author by request. (List items)

Authors' contributions

Yunxiao Zang performed the studies and drafted the manuscript. Rongmei Peng and Jinghao Qu participated in the design of the study and performed the statistical analyses. Gege Xiao and Lixue Shuai conceived the study, participated in its design and coordination and helped draft the manuscript. Linhui He and Xuanjun Zhang collected aqueous humour/cornea tissue viral DNA PCR detection results. The corresponding author Jing Hong is responsible for ensuring that the descriptions are accurate and agreed upon by all authors. All authors read and approved the final manuscript.

Ethics approval

The present study was performed in accordance with the Declaration of Helsinki and approved by the Medical Ethics Committee of Peking University Third Hospital (201729901).

Consent to participate

These patients were contacted by telephone to obtain verbal informed consent.

Disclosure statement.

The authors report no conflicts of interest.

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Figures

Figure 1

Selection method of the control group and the study flowchart.

Figure 2

ROC curve for SJS ocular complications, PKP and DALK