

The Utility of Nonroutine Intraocular Fluid Polymerase Chain Reaction for Uveitis in Indonesia

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Purpose: To investigate the utility of nonroutine polymerase chain reaction analysis of intraocular fluid to guide the diagnosis of infectious uveitis.

Patients and Methods: A retrospective cohort study was conducted by reviewing medical record data from intraocular fluid samples of uveitis patients who underwent single-plex real-time polymerase chain reaction analysis at the Department of Ophthalmology, Faculty of Medicine, Universitas Indonesia – Cipto Mangunkusumo Kirana Eye Hospital between January 2014 and December 2018.

Results: The positivity rate of nonroutine polymerase chain reaction analysis was 17.2%. The vitreous sample tended to show a higher positive outcome (28.6%) than the aqueous sample (16.2%), even though the outcome was not statistically significant. *Mycobacterium tuberculosis* and *Toxoplasma gondii* were the most frequently observed microorganisms in the polymerase chain reaction analysis among uveitis patients in our setting. The duration of symptoms, type of sample fluid (aqueous/vitreous), or presence of anterior chamber cells ≥ 2 were not significantly associated with polymerase chain reaction positivity ($p > 0.05$).

Conclusion: Nonroutine polymerase chain reaction analysis of intraocular fluid among a cohort of Indonesian patients demonstrated low positivity. The sensitivity and specificity of nonroutine single-plex polymerase chain reaction could not be estimated due to limitations such as lost to follow-up patients and incomplete monitoring data. The use of multiplex polymerase chain reaction in the future may be beneficial in our setting.

Keywords: aqueous humor, vitreous humor, infection, ocular inflammation, *Mycobacterium tuberculosis*, epidemiology

Introduction

Uveitis is a sight-threatening ocular inflammation with both infectious or non-infectious etiology. Infectious uveitis accounts for a higher proportion (often up to 50%) of uveitis cases in developing countries than in developed countries.^{1,2} Further, the causative organism varies by geographic location. In addition to *Toxoplasma gondii* (46%), the herpes simplex (HSV; 24%) and varicella-zoster (VZV; 30%) viruses were identified as the most frequent agents in the United States.³ A Thai study revealed that cytomegalovirus (CMV) was dominant because of a high proportion of anterior uveitis patients.⁴ In contrast, our previous report of a one-year study revealed that one-third of uveitis cases were classified as infectious uveitis with *T. gondii* and *Mycobacterium tuberculosis* as the common causes based primarily on corroborative evidence or clinical diagnosis.⁵

The diagnosis of infectious uveitis is typically based on clinical pattern recognition, and outcome depends on the appropriateness of the antimicrobial or antiviral treatment administered. Polymerase chain reaction (PCR) from intraocular aqueous or vitreous humor fluid samples is considered an adjunct modality to confirm an uncertain diagnosis.⁶ Even though a previous study has proposed that routine intraocular fluid PCR in suspected cases of infectious uveitis is beneficial because a clinical phenotype alone may be insufficient,⁷ not all facilities can provide this examination. In Indonesia, intraocular fluid PCR is not included in the national health service payment scheme, thus limiting its use in selected cases because many patients cannot afford the procedure. Given a lack of previously published data from Indonesia that

specifically address the utility of PCR in infectious uveitis, this study aims to present results of intraocular fluid PCR analysis conducted in our center over five years.

Patients and Methods

Records of patients who underwent PCR testing of intraocular fluids (vitreous or aqueous) for suspected infectious uveitis at the Department of Ophthalmology, Faculty of Medicine, Universitas Indonesia - Cipto Mangunkusumo Kirana Eye Hospital between January 1st, 2014 and December 31st, 2018 were retrospectively reviewed. Cipto Mangunkusumo Kirana Eye Hospital is a government tertiary-care eye institution located in Jakarta. All patients with uveitis had undergone a tailored diagnostic work-up that included chest X-ray and various laboratory tests. Anatomical involvement was determined according to the Standardization of Uveitis Nomenclature system.⁸ Intraocular fluid PCR was performed in patients with active uveitis at presentation. The standard ocular PCR in our center is real-time probe-based, with a testing price range of Rp 500,000 to 700,000 (US \$35–50) per pathogen. The pathogen tested was based on the clinical judgment of the attending ophthalmologist, as discussed with the patient. We prioritized patients with atypical presentation or recurrent uveitis with suspicion of infection for intraocular fluid PCR. In some patients, real-time PCR was performed as a part of another study, and thus the cost was covered by our institution.

Aqueous humor tap was performed in a procedural room. In the case of bilateral involvement, the eye with more severe inflammation based on presenting anterior chamber cells was chosen. Roughly 0.2 mL of aqueous sample was obtained using a 30-gauge needle on a 1 mL syringe while administering tetracaine topical anesthesia and topical 5% povidone-iodine solution. A solution containing hexamidine diisethionate 0.05% was used as another option for ocular surface disinfection.⁹ A vitreous sample was considered if the patient planned to undergo diagnostic vitrectomy in the operating theatre. Samples were transported immediately to the diagnostic laboratory (Department of Microbiology, Faculty of Medicine, Universitas Indonesia – Cipto Mangunkusumo General Hospital) within four hours.

DNA/RNA extraction of the aqueous or vitreous humor was then immediately initiated. The extraction was performed with the QIAamp DNA Mini Kit (Qiagen, Cat. No: 51304) or QIAamp Viral RNA Kit (Qiagen, Cat. No: 52904) according to the manufacturer's protocol with final elution of 40 µL (DNA) and 60 µL (RNA), and was stored at –80°C for not more than 48 hours. The elution was used as a template for single-plex real-time PCR targeted to each *Mycobacterium tuberculosis* (primer: forward 5'- CCT GCG AGC GTA GGC GTC GG-3', reverse 5'- CTC GTC CAG CGC CGC TTC GG - 3'), *Toxoplasma gondii* (primer: forward 5'- CTA GTA TCG TGC CGC AAT GTG - 3', reverse 5'- GGC AGC GTC TCT TCC TCT TTT - 3'; probe: 5'- FAM-CCA-CCT-CGC-CTC-TTG-G-3'), CMV (primer: forward 5'- CAT GAA GGT CTT TGC CCA GTA C - 3', reverse 5'- GGC CAA AGT GTA GGC TAC AAT AG - 3; probe: 5'-TGG CCC GTA GGT CAT CCA CAC TAG G-3'), HSV (primer: forward 5'- CCG TCA GCA CCT TCA TCG A - 3', reverse 5'- CGC TGG ACC TCC GTG TAG TC - 3'; probe: 5'- CCA CGA GAT CAA GGA CAG CGG CC -3'), VZV (primer: forward 5'- TCT TTC ACG GAG GCA AAC AC -3', reverse 5'- TCC AAG GCG GGT GCA TAT CT - 3'; probe: 5'-FAM-TAA CGT GGC TCG AGA ACG GTT TGG GTT T-3'), EBV (primer: forward 5'- CGG AAG CCC TCT GGA CTT C - 3', reverse 5'- CCC TGT TTA TCC GAT GGA ATG - 3'; probe: 5'-TGT ACA CGC ACG AGA AAT GCG CC-3'), and *Rubella* (primer: forward 5'- CCT AHY CCC ATG GAG AAA CTC CT - 3', reverse 5'- AAC ATC GCG CAC TTC CCA - 3'; probe: 5'- CCG TCG GCA GTT GG -3'). The PCR reaction mix was prepared according to the manufacturer's instructions for each pathogen. In addition, a negative control with nucleic acid-free water was applied. A PCR result with cycle quantification < 40 was considered positive.

Results

Patient Characteristics

The medical records of 87 patients suspected of having infectious uveitis based on intraocular fluid PCR analysis were included. The proportion of patients with anterior, intermediate, posterior, and panuveitis was 12.6% (11), 3.4% (3), 39.1% (34), and 44.8% (39), respectively. Forty-two patients (48.3%) had visual acuity hand movement or worse, with 22 patients (out of 42; 52.4%) and 13 patients (out of 42; 31.0%) diagnosed with panuveitis and posterior uveitis, respectively. Positive test results were obtained in 15 patients (17.2%). Detailed patient characteristics are provided in Table 1. Among seven HIV-positive patients, only one had a positive PCR test. This was a 54-year-old male with

Table 1 Characteristics of Patients

Characteristics	All Patients (n= 87)	Patients with Any Positive PCR Result (n=15)	Patients with Negative PCR Result (n=72)
Age	40.93 ± 15.0	37.07 ± 11.8	41.74 ± 15.5
Gender			
Male	49 (56.3%)	8 (16.3%)	41 (83.7%)
Female	38 (43.7%)	7 (18.4%)	31 (81.6%)
Laterality			
Unilateral	39 (44.8%)	7 (17.9%)	32 (82.1%)
Bilateral	48 (55.2%)	8 (16.7%)	40 (83.3%)
Presenting visual acuity (LogMar; median, IQR)	1.77 (IQR 1.48)	2.48 (IQR 1.18)	1.77 (IQR 1.43)
Onset			
Acute (≤ 90 days)	49 (56.3%)	7 (14.3%)	42 (85.7%)
Chronic (> 90 days)	35 (40.2%)	8 (22.9%)	27 (77.1%)
Unclear	3 (3.4%)	0	3 (100%)
Fluid samples			
Aqueous	80 (92.0%)	13 (16.2%)	67 (83.8%)
Vitreous	7 (8.0%)	2 (28.6%)	5 (71.4%)
Anterior chamber cells*			
< +2	52 (57.8%)	8 (15.4%)	44 (84.6%)
≥ +2	20 (22.2%)	4 (20.0%)	16 (80.0%)

Note: *Anterior chamber cells data in 15 patients were not available or could not be evaluated.

Abbreviations: PCR, polymerase chain reaction; IQR, interquartile range.

bilateral panuveitis with exudative retinal detachment and a positive result for *T. gondii*. In addition, one non-HIV patient with posterior uveitis tested positive for both *T. gondii* and VZV.

PCR Results

Overall, *M. tuberculosis* was the most-ordered PCR test, and five patients (6.9%) were positive for this agent. None of the samples showed a positive result for the Epstein-Barr virus (EBV). The percentage of PCR positivity for each microorganism is displayed in Table 2. Duration of symptoms, sample type (aqueous/vitreous), or the presence of anterior chamber cells ≥ 2+ were not significantly associated with PCR positivity ($p > 0.05$). Among the 15 patients with at least one pathogen identified with PCR, six (40%), six (40%), and three (20%) patients had posterior uveitis, panuveitis, and anterior uveitis, respectively. Finally, positive PCR results from 10/12 (83.33%) patients with panuveitis or posterior uveitis were based on aqueous humor analysis (Table 3).

Table 2 Positivity of Intraocular PCR Based on Microorganism and Anatomical Involvement

Microorganism	N Tested	N positive (% From N Tested)	N (Eyes) Positive Based on the SUN Anatomical Classification / N (Eyes Assessed)			
			Anterior	Intermediate	Posterior	Panuveitis
<i>M. tuberculosis</i>	72	5 (6.9%)	1/11 (9.1%)	0/3 (0%)	1/28 (3.6%)	3/30 (10.0%)
<i>T. gondii</i>	37	3 (8.1%)	0/3 (0%)	0/2 (0%)	2/15 (13.3%)	1/17 (5.9%)
CMV	55	3 (5.5%)	2/5 (40.0%)	0/3 (0%)	1/23 (4.3%)	0/24 (0%)
HSV	41	1 (2.4%)	0/3 (0%)	0/2 (0%)	0/15 (0%)	1/21 (4.8%)
VZV	29	2 (6.9%)	0/1 (0%)	0/2 (0%)	2/12 (16.7%)	0/14 (0%)
Rubella	27	1 (3.7%)	0/1 (0%)	0/1 (0%)	0/9 (0%)	1/16 (6.3%)
EBV	24	0 (0)	0/1 (0%)	0/1 (0%)	0/9 (0%)	0/13 (0%)

Abbreviations: SUN, Standardization of Uveitis Nomenclature; CMV, cytomegalovirus; HSV, herpes simplex virus; VZV, varicella-zoster virus; EBV, Epstein-Barr virus.

Table 3 Positivity of Intraocular PCR Based on Anatomical Involvement and Fluid Sample Type

SUN Anatomical Involvement	Fluid Sample	Total N (Patient) Tested	N (Patient) Positive/N Total (%)	Distribution of Positive Pathogen Findings (N)						
				M. <i>tuberculosis</i>	<i>T. gondii</i>	CMV	EBV	HSV	VZV	Rubella
Anterior	Aqueous	11	3/11 (27.3%)	1	–	2	–	–	–	–
	Vitreous	0	0/0 (0%)	–	–	–	–	–	–	–
Intermediate	Aqueous	3	0/3 (0%)	–	–	–	–	–	–	–
	Vitreous	0	0/0 (0%)	–	–	–	–	–	–	–
Posterior	Aqueous	29	5/29 (17.2%)	1	2	–	–	–	2	–
	Vitreous	5	1/5 (20%)	–	–	1	–	–	–	–
Panuveitis	Aqueous	37	5/37 (13.5%)	2	1	–	–	1	–	1
	Vitreous	2	1/2 (50%)	1	–	–	–	–	–	–

Abbreviations: SUN, Standardization of Uveitis Nomenclature; CMV, cytomegalovirus; HSV, herpes simplex virus; VZV, varicella-zoster virus; EBV, Epstein–Barr virus.

Discussion

In general, the intraocular fluid PCR positivity rate that we observed is considered low. Nonroutine intraocular fluid PCR analysis in uveitis yielded 17.2% positivity in our population. Interestingly, analysis from the vitreous sample showed higher positivity (28.6%) compared to the aqueous sample (16.2%), even though the difference was not statistically significant. This finding is consistent with Dos Santos et al's observation that a higher number of positive vitreous samples detected and identified infectious agents compared to aqueous humor samples.¹⁰ However, a multiple regression analysis by Balne et al revealed no significant association between positive PCR outcome and the type of sample (aqueous/vitreous) used.¹¹ Another interesting study finding is that even in cases of posterior uveitis, aqueous fluid (17.2% positivity) analysis was still representative for diagnosing intraocular infection (compared to 20% positivity in vitreous fluid analysis). However, the positivity of vitreous fluid samples (50%) was considerably higher compared to aqueous samples (13.5%) in the context of panuveitis cases (Table 3). This finding is in line with a previous study that corroborates the usefulness of initial aqueous humor analysis in posterior uveitis,¹² and with Oahalou et al finding that panuveitis and posterior uveitis were associated with an increased diagnostic yield of pars plana vitrectomy.¹³

M. tuberculosis and *T. gondii* were significant causative pathogens in our setting, especially in patients with atypical presentation. This may be attributed to the high proportion of patients with posterior uveitis or panuveitis. Our finding is consistent with results from our previous cohort, which indicated that 68% and 20% of all infectious uveitis was caused by toxoplasmosis and tuberculosis, respectively.⁵ The percentage of *M. tuberculosis* detected in vitreous analysis in our study (16.67%; 1/6) was higher than that found in aqueous analysis (6.1%; 4/66). This finding may be due to the microorganism's localization in retinal pigment epithelium (RPE).¹⁴ Thus, the vitreous humor, which is anatomically closer to RPE than the aqueous humor, yielded more positive results. However, in the context of *T. gondii*, our study found positive results only in aqueous samples (3/33; 9.1% versus 0/4; 0% in vitreous samples). Although the previous study showed that parasites were more localized in the inner layers of the retina—mainly in the posterior pole of the eye¹⁵—and the DNA burden in the aqueous humor was considered low,¹⁶ Matos et al also revealed that PCR examination using the aqueous humor was precise in ocular toxoplasmosis, with a sensitivity of 75%.¹⁷

We found that the highest proportion of patients undergoing intraocular PCR analysis had panuveitis. As the ocular condition worsened, clinical pattern recognition alone was insufficient to guide appropriate diagnosis in significant panuveitis patients with visual acuity equal or worse than hand movement. In the Indonesian population, toxoplasmosis should be considered as a cause of atypical posterior uveitis or panuveitis.¹⁸ However, the timing of PCR analysis appeared to significantly affect the positivity of *T. gondii* PCR. De Groot-Mijnes et al observed that the positivity of *T. gondii* declined if samples were collected and analyzed at four weeks after onset. The authors observed that at a later time, the Goldmann–Witmer coefficient (GWC) was more accurate for guiding ocular toxoplasmosis diagnosis.¹⁹ Unfortunately, GWC examination is not available in our center, and patients inconclusive after PCR analysis could not be confirmed with the disease.

Geographical variation can also influence the causative pathogen of infectious uveitis. Given the continuing lack of consensus on when to perform intraocular PCR, our study setting is different than one in which intraocular PCR is routinely performed. Pathanapitoot et al's study in the Thai population reported intraocular PCR positivity of 33%, nearly double that in our study. This may be due to a higher number of patients with anterior uveitis (41%) with positive CMV and to the routine performance of PCR in patients with an inconclusive initial work-up.⁴ In Africa, the positivity of intraocular PCR in suspected infectious posterior uveitis cases was roughly 16%, in line with our findings.⁷

As our study reported the PCR outcome on a nonroutine basis, the selection of the pathogen under examination may have affected the positivity rate of our result. In addition to the judgment of the attending ophthalmologist, patients' ability to pay for PCR analysis determined the type and number of pathogen examined. In other words, the greater the number of pathogens examined, the higher the cost. Further, we could not compare the result of these PCR findings with the treatment response of individual patients. The study was also limited by loss to follow-up and incomplete monitoring data. Thus, sensitivity and specificity could not be estimated. Given our finding, the use of multiplex PCR in the future may be beneficial in our setting. Furthermore, we suggest conducting a robust prospective study for a comparative outcome evaluation—with a focus on cost-effectiveness in our population—with and without intraocular fluid PCR analysis in patients with suspected infection. Further studies to elucidate the diagnostic value of multiplex PCR and of affordable and accessible examinations to detect the causative pathogen of suspected infectious uveitis—together with their related clinical manifestations and treatment response—appear to be warranted in our setting.

Conclusion

Nonroutine PCR analysis of intraocular fluids from an Indonesian cohort demonstrated low positivity. The two most common causative microorganisms in infectious uveitis were *M. tuberculosis* and *T. gondii*. The sensitivity and specificity of nonroutine single-plex PCR could not be estimated due to limitations such as lost to follow-up patients and incomplete monitoring data. The use of multiplex PCR to detect the etiology of suspected infectious uveitis may be beneficial in our setting.

Data Sharing Statement

The data that support the findings of this study are available on request from the corresponding author, [RLDN]. Due to the privacy of research participants, names of individuals will be provided in the form of initials, and medical record numbers will not be provided.

Ethics Statement

Ethical approval was waived by the local Ethics Committee of the Faculty of Medicine, Universitas Indonesia – Cipto Mangunkusumo Hospital, Jakarta, Indonesia in view of the retrospective nature of the study, and all procedures performed were part of routine care.

Acknowledgments

We thank Gloria P. Usodo, MD, for her help in reviewing the patient medical records.

Author Contributions

All authors contributed to the study conception and design. Material preparation, acquisition of data and analysis were performed by Ikhwanuliman Putera, Rina La Distia Nora, and Priscilla Jessica. Clinical data were interpreted by Ikhwanuliman Putera, Lukman Edwar, Made Susiyanti, Ratna Sitompul, Yulia Aziza, and Rina La Distia Nora. PCR results were interpreted by Mei Riasanti, Andriansjah Rukmana, and Andi Yasmon. Final data interpretation and analysis were performed by all authors. The first draft and revised version of the manuscript were written by Ikhwanuliman Putera and Priscilla Jessica. All authors reviewed, revised, and approved all versions of the article before first submission and before re-submission of the revised manuscript. All authors agreed to submit the article to *Infection and Drug Resistance*. All authors agreed to take responsibility and be accountable for the contents of the article.

Funding

This study was supported by Riset Inovatif Produktif - Lembaga Pengelola Dana Pendidikan (RISPRO LPDP) [grant number RISPRO/KI/B1/KOM/5/15219/4/2020]. The funding source had no involvement in the collection, analysis, and interpretation of data, in the writing of the report, and in the decision to submit the article for publication.

Disclosure

The authors report no conflicts of interest in this work.

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