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Polymerase Chain Reaction Analysis of Aqueous and Vitreous Specimens in the Diagnosis of Posterior Segment Infectious Uveitis

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Abstract

PURPOSE—To assess polymerase chain reaction (PCR) analysis of intraocular fluid as a test for infectious uveitis of the posterior segment in a representative patient population.

DESIGN—Retrospective, interventional case series.

METHODS—One hundred and thirty-three patients with possible infectious chorioretinitis underwent PCR testing of aqueous or vitreous in a university setting. Baseline characteristics predictive of test positivity were identified. Positive and negative predictive values were calculated.

RESULTS—Four hundred and thirty-three PCR tests of 105 aqueous and 38 vitreous specimens (mean, 3.3 tests per patient) identified 77 of the 95 patients with a final clinical diagnosis of infectious uveitis (81%). Herpes simplex virus, varicella zoster virus, and cytomegalovirus PCR analysis were performed in almost all cases, with fewer tests for toxoplasmosis or Epstein-Barr virus. Clinical features associated with positive PCR results were retinal vascular inflammation ($P < .001$), optic nerve involvement ($P = .008$), immunocompromised state ($P = .039$), and extensive retinitis ($P = .002$). Cases sampled within one week of presentation were more likely to have positive PCR results than those sampled later ($P = .071$). The predictive value of positive and negative tests was 98.7% and 67.9%, respectively, in this patient group. Alteration in treatment based on PCR and syphilis serologic results led to resolution in 25 of 26 patients after treatment was changed.

CONCLUSIONS—PCR testing is a useful adjunct in the diagnosis of infectious causes of posterior uveitis. Cases with vascular or optic nerve inflammation, extensive retinitis, or immunocompromise are more likely to have positive PCR results and may benefit from PCR testing of aqueous humor.

Infectious retinitis caused by herpes simplex virus 1 (HSV 1) and herpes simplex virus 2 (HSV 2), cytomegalovirus (CMV), varicella zoster virus (VZV), Epstein-Barr virus (EBV), or *Toxoplasmosis gondii* is potentially blinding in both immunocompetent and immunocompromised patients. Initial treatment can be based on a presumptive diagnosis

after an ophthalmologic examination; however, the clinical appearance of intraocular infections caused by viruses, bacteria, fungi, and parasites can be similar or the retinal lesions may not be well seen because of vitreous inflammation, complicating clinical diagnosis. Because institution of proper therapy is needed urgently in many cases, rapid analysis of intraocular fluid may improve outcomes by shortening the interval before effective treatment is administered.

Polymerase chain reaction (PCR) amplifies the deoxyribonucleic acid (DNA) or ribonucleic acid (RNA) of pathogens, making them easier to detect, especially when present in small quantities. The method is more rapid than culture and is highly accurate and reproducible in the laboratory. In actual clinical use, false-positive results are possible from contamination, and false-negative results are possible from polymorphism, specimen degradation, or failure to sample in the acute stages of disease.¹

Polymerase chain reaction testing for the diagnosis of viral retinitis is supported by numerous case reports and case series.^{2–7} PCR seems to have a very low false-positive rate when used on ocular fluids. Pendergast and associates reported that 75 aqueous and vitreous specimens from uninfected immunocompetent patients were negative for HSV 1 and HSV 2, VZV, CMV, and EBV by PCR.⁸ The false-negative rate is more difficult to determine because often there is no other gold standard with which to compare, other than final clinical diagnosis, because viral cultures are among the least efficient diagnostic tests for intraocular fluid⁹ and toxoplasmosis culture is performed rarely.¹⁰ For this reason, validation in consecutive patients typical of those who usually undergo the testing is needed to assess the usefulness of the method for routine diagnostic use.

The purpose of this study was to examine a single institution's experience with PCR testing of aqueous and vitreous humor samples from patients with intraocular inflammation and suspected infectious retinitis between November 1, 2001 and October 31, 2006, to assess false-positive and false-negative rates in a representative patient group and to make recommendations regarding the use of this method for the rapid diagnosis of infectious intermediate uveitis, posterior uveitis, and panuveitis.

METHODS

THIS RETROSPECTIVE, INTERVENTIONAL CASE STUDY WAS approved by the Human Subjects Research Subcommittee of the University of Miami Miller School of Medicine. Sample logs of the Bascom Palmer Eye Institute Clinical Microbiology Laboratory were reviewed to identify patients undergoing PCR testing of intraocular fluids for posterior segment inflammation for diagnostic purposes. Specimens were not obtained from patients with known pathogenic diagnoses even if fluid was incidentally available, for example, from therapeutic aspiration of aqueous or nondiagnostic intraocular surgery. The charts were reviewed to determine patient characteristics, clinical history, and clinical course. All ocular fluid specimens were obtained by house staff or medical staff members of the Anne Bates Leach Eye Hospital between November 1, 2001 and October 31, 2006, in various clinical settings, including the emergency room, outpatient clinics, and operating rooms. Standard preparation for obtaining an intraocular fluid specimen included topical

anesthesia and povidone-iodine 5% and the use of a sterile lid speculum. A 30-gauge half-inch needle was used for anterior chamber paracentesis. Typical volumes recovered were 0.1 to 0.25 ml aqueous humor. Vitreous specimens were obtained in a variety of ways, including by aspiration with a vitrector at the time of diagnostic vitrectomy. In the clinic, vitreous taps usually were performed with a 23-gauge needle on a 1- or 3-ml syringe with entry through the pars plana. Aqueous humor was obtained preferentially. Specimens were transferred to small O-ring vials or Eppendorf vials for transport and remained frozen until testing was performed. Four tests were performed commonly to detect pathogens most likely to cause infectious retinitis: HSV 1 and HSV 2, VZV, CMV, and toxoplasmosis. EBV PCR was performed on some specimens. The quantity of the specimen sometimes did not permit a full panel of testing, or the ordering clinician may have ordered fewer tests based on diagnostic suspicion.

Focus Diagnostics (Cypress, California, USA) retrieved the samples by courier and performed real-time (RT) PCR analyses on a commercial basis. Results were reported as detected or not detected within 48 to 72 hours, with the proviso that the method had not been validated for eye fluid. There was a brief six-month interval from June 2001 until December 2001 in which the samples were sent to the Mayo Clinic in Rochester, Minnesota. These samples were forwarded to Focus Diagnostics; therefore, all samples were analyzed by the same reference laboratory. Limits of detection for the Focus assays are: 1) EBV RT-PCR: 100 copies/ml in whole blood and 500 copies/ml in cerebrospinal fluid (CSF) or serum; 2) HSV 1 and HSV 2 RT-PCR: 100 copies/ml in serum, CSF, transport media, or tissue; 3) *T. gondii* RT-PCR: 50 copies/ml in whole blood, CSF, amniotic fluid, or tissue; 4) CMV RT-PCR: 200 copies/ml in whole blood, CSF, urine, amniotic fluid, or tissue; and 5) VZV RT-PCR: 500 copies/ml in whole blood, CSF, or transport media.

Statistical analysis was performed by the Biostatistics Department at the Bascom Palmer Eye Institute. Descriptive statistics were computed. Comparisons of dichotomous outcomes, such as PCR results between different groups (e.g., aqueous or vitreous sampling site), were made by the Chi-square or Fisher exact test as appropriate. SPSS software for Windows version 15.0 (SPSS Inc, Chicago, Illinois, USA) and StatXact (Cytel Inc, Cambridge, Massachusetts, USA) were used.

Sensitivity and specificity were based on the final clinical diagnosis as the gold standard. A true positive or true negative result was considered to be a test or panel of tests that agreed with the final clinical diagnosis. A false positive was defined as testing that detected DNA that did not agree with the final clinical diagnosis. A false negative was defined as testing that failed to detect DNA from the predicted etiologic agent based on the final clinical diagnosis.

RESULTS

ONE HUNDRED AND THIRTY-THREE PATIENTS WERE EVAL-uated in this study, none of whom had been reported in a prior publication. Patient characteristics are listed in Table 1. There was a male predominance. The mean age was 47 years, and 60% of participants were considered to be immunocompromised. No complications of specimen

acquisition were recorded. The mean logarithm of the minimum angle of resolution visual acuity was 1.5 ± 1.1 in 128 sampled eyes at baseline and 1.3 ± 1.2 in the 72 patients achieving six months of follow-up.

The indications for PCR testing are listed in Table 2. Most patients had pretest diagnoses of acute retinal necrosis, toxoplasmosis, panuveitis or chorioretinitis, or CMV retinitis (CMVR). The anatomic distribution of inflammation in the patients included in this study is described in Table 3. More than two-thirds of cases were unilateral with a right eye predominance ($P = .026$). Visible retinal or choroidal lesions were present in 94% of cases.

Table 4 describes the positive results by sampling site. One hundred and one patients had primarily aqueous sampling, 32 patients had primarily vitreous sampling, and 10 patients had sampling from both sites. Overall, a higher percentage of true positive diagnoses were obtained from aqueous than vitreous; however, this difference was not statistically significant ($P = .31$). The number of patients sampled from both ocular compartments was too small to compare statistically.

Table 5 lists the number of PCR tests performed and the positive PCR results by organism. There were 433 diagnostic tests performed with a mean of 3.3 tests per patient (range, one to six). HSV 1, HSV 2, VZV, and CMV PCR were the most frequent tests and were performed in almost all patients. VZV and CMV PCR were the tests with the most frequently positive results (22% of each).

Table 6 lists the positive PCR reactions for each pretest diagnosis. A positive PCR result would be expected for the four pretest diagnoses of necrotizing herpetic retinopathy, CMVR, toxoplasmosis, and infectious chorioretinitis of uncertain origin. Of these 90 patients, 66 (73%) had positive PCR results. Four patients tested positive for more than one agent; two of these were human immunodeficiency virus (HIV) positive and one was immunocompromised from another cause.

Table 7 gives the number of patients with final diagnoses of necrotizing herpetic retinopathy, CMVR, toxoplasmosis, EBV, and chorioretinitis not otherwise specified. The percentages of tests with positive results for each diagnosis were 88%, 82%, 67%, 100%, and 33%, respectively. Human T-cell lymphotropic virus 1 (HTLV-1) PCR was ordered in one Haitian patient with panuveitis and showed positive results. One patient with a pretest and posttest diagnosis of infectious chorioretinitis of uncertain cause had positive results for both VZV and EBV PCR tests; both were counted as false positives. Forty-four patients had pretest diagnoses for which a negative PCR result would be expected; however, viral or toxoplasmic infection was confirmed in 11 (25%) by PCR.

Fewer patients were identified with necrotizing herpetic retinopathy than were suspected clinically before testing (43 vs 45). More patients with CMVR were identified than were clinically suspected (28 vs 21) and fewer cases of toxoplasmosis (18 vs 23). The other 38 final diagnoses among the 133 patients were syphilis ($n = 10$), infectious nonviral endophthalmitis ($n = 10$), noninfectious chorioretinitis of unknown origin ($n = 3$), Behçet disease ($n = 2$), vasculitis ($n = 2$), and one case each of iridocyclitis, retrolental mass, retained lens fragment, familial exudative vitreoretinopathy, serpiginous choroidopathy,

monoclonal gammopathy, human leukocyte antigen (HLA-B27) uveitis, pars planitis, rhegmatogenous retinal detachment, traumatic panuveitis, and sarcoidosis.

Table 8 compares the presence or absence of various clinical characteristics in relation to PCR testing positivity. Retinal vascular inflammation ($P < .001$), optic nerve involvement ($P = .008$), immunocompromised state ($P = .039$), and extensive retinitis involving both the posterior and peripheral retina ($P = .002$) were significantly associated with positive PCR results. Hypopyon was significantly associated with negative PCR results ($P = .041$). The likelihood of positive PCR results was not related to the presence or absence of anterior segment inflammation. Most patients were sampled within one week of presentation and were more likely to have positive PCR results than those sampled later; however, this was not statistically significant ($P = .071$). Retinal vascular inflammation had the highest relative risk of positive PCR results (2.07; 95% confidence interval, 1.42 to 3.02).

The sensitivity and specificity of PCR testing of ocular fluids from patients with suspected infectious uveitis was calculated. Using the final clinical diagnosis of the 133 patients as the gold standard, 76 cases were true positives and 38 cases were true negatives. There was one false-positive case and there were 18 false-negative cases. The sensitivity therefore was 80.9% and the specificity was 97.4%. The positive predictive value, defined as the likelihood of having disease related to the tested infectious agent given positive PCR results, was 98.7%. The negative predictive value, defined as the likelihood of not having the specified disease given negative PCR results, was 67.9%.

Treatment was altered in 26 cases (19.5%) based on PCR results. Supplemental Table 9 (available at [AJO.com](http://ajophth.com)) describes these 26 cases in relation to pretest and posttest diagnoses, immune status, empiric therapy, and change in therapy. Four were immunocompetent; two suspected of toxoplasmosis and one of panuveitis were confirmed to have HSV 2-related necrotizing herpetic retinopathy; one suspected of herpetic retinopathy had CMVR. Twenty-two cases were immunocompromised. Five suspected of toxoplasmosis had CMVR ($n = 2$), VZV ($n = 2$), or syphilis ($n = 1$). Ten cases suspected of viral chorioretinitis had VZV instead of CMVR ($n = 3$), CMV instead of herpetic retinopathy ($n = 5$), or toxoplasmosis ($n = 2$). Three cases with nonspecific pretest diagnoses were confirmed by PCR as having CMV. Serologic analysis detected three cases of syphilis with pretest diagnoses of panuveitis ($n = 2$) or endogenous endophthalmitis ($n = 1$). Change in therapy led to resolution in 25 of 26 cases; the cause of the remaining case was not determined.

DISCUSSION

POLYMERASE CHAIN REACTION TESTING OF OCULAR FLUID is recognized as an adjunct in the diagnosis and treatment of infectious posterior uveitis. Its usefulness can be judged in a variety of ways. The clinical sensitivity and specificity of a testing strategy, rather than the nominal sensitivity of the test itself, depends on prevalence of disease in the tested population and sample acquisition and transportation, among other factors. The study was performed in a tertiary referral center with an open-access emergency room and a large number of immunocompromised patients. A microbiology laboratory to handle specimens and the necessary equipment for obtaining samples were readily available. We found

excellent specificity and good sensitivity in a population of patients similar to those who may be considered for testing in other centers.

Strengths of this study include a large number of cases with a wide variety of pathologic characteristics and etiologic agents enabling calculation of the relative risks for clinical characteristics that indicate that testing is likely to be positive, including retinal vascular inflammation, extensive retinitis, optic nerve involvement, and immunocompromised state. Most of those patients in whom the initial therapy was changed after PCR testing were immunocompromised (85%). Testing early after presentation barely missed statistical significance as a predictor of PCR positivity in this series, but has been reported to be more likely to yield a positive result in viral uveitis¹¹, similar to viral meningitis in which PCR results are more likely to be positive within two weeks of the onset of symptoms.¹² Our study did not include the precise date of onset of symptoms, which may be more predictive of obtaining positive PCR results than the date of presentation. Rothova and associates also identified extensive retinitis as a predictor of positive diagnostic testing.¹³ Otherwise, there is little information predictive of which patients are most favorable to undergo testing by PCR.

This study also supports the use of aqueous humor for testing. Three-quarters of the specimens were aqueous humor, which can be acquired more readily and more cheaply than vitreous humor, and in this series, actually was more likely to demonstrate positive results, although not significantly so. The number of cases with both aqueous and vitreous sampled was too small to draw any conclusions other than that aqueous seems to be an adequate substrate for testing, as previously reported by others.^{11,14}

Diagnosis of toxoplasmosis raises some special issues. Montoya and associates stated a preference for vitreous testing in toxoplasmic chorioretinitis because of the large size of the organism.¹⁵ The diagnostic yield for PCR for toxoplasmic chorioretinitis in this series was comparable with that for viral retinitis (12 of 18 cases, or 67%) and is higher than the nine (36%) of 25 cases reported by De Groot-Mijnes and associates or by Fardeau and associates for 34 patients with a final diagnosis of toxoplasmic chorioretinitis, of whom 79% had positive antibodies and only 27% demonstrated positive PCR results.^{11,16} Immune status may influence results; Fardeau and associates concluded that large lesions in immunocompromised individuals were more likely to have positive results.¹⁶ Similarly, Labalette and associates reported a yield of 60% from PCR testing in elderly patients with lesions of toxoplasmic chorioretinitis larger than 3 disc diameters vs only three (25%) of 12 in those with smaller lesions.¹⁷ In the series of Groot-Mijnes and associates, results for intraocular antibody production were positive in 92% of patients, and, in contrast to viral retinitis, delayed testing by more than three weeks after onset of symptoms was more likely to lead to positive PCR results for toxoplasmosis.¹¹ Antibody determination was advocated to complement PCR, especially in the diagnosis of toxoplasmosis. The same research group later compared PCR and antibody determinations in 27 immunocompromised patients; PCR was more likely to be positive in viral disease and antibodies were more likely to be positive in toxoplasmosis.¹⁸ In extensive, diffuse toxoplasmic chorioretinitis mimicking acute retinal necrosis, all testing, whether by PCR or antibodies or culture, is likely to demonstrate

positive results.¹⁹ The current results indicate that PCR is a valid technique in atypical toxoplasmosis that cannot be diagnosed with certainty on clinical examination.

The gold standard used in this study was the final clinical diagnosis after consideration of all data, including the PCR results and response to treatment. The patient population examined in this study may differ from that encountered by other clinicians and institutions, which also may have different criteria for which patients merit testing. Positive and negative predictive values are heavily dependent on the prevalence of disease; therefore, these numbers will vary with the clinical setting. In some patients, diagnostic vitrectomy will remain the most appropriate diagnostic strategy because it allows access to greater quantities of intraocular fluid and to tissue specimens for cytologic analysis, flow cytometry, and retinochoroidal biopsy.⁹

Four patients had more than one herpes-class virus detected on PCR testing. This may be interpreted as a byproduct of the high sensitivity of the PCR technique. However, it is not unreasonable to assume that certain viruses in dormant states can be liberated in an inflamed eye, causing DNA to be detected on PCR testing, making more than one true positive result both possible and clinically relevant because CMV requires different antiviral therapy than VZV or HSV. Sugita and associates found high levels of EBV DNA by RT-PCR in four eyes with confirmed VZV infection.²⁰ Our dual-positive cases were not a significant factor in analysis because only four (3%) of 133 patients had more than one infectious agent detected. Use of RT-PCR with a cut-off level for numbers of copies considered positive as used here also should reduce the number of false-positive results.²⁰ More problematic is the number of false-negative results leading to a negative predictive value of only 67.9%, in contrast to the positive predictive value of 98.7%. Positive PCR results from intraocular fluid therefore clearly are relevant to confirmation of a final clinical diagnosis, but negative results cannot exclude infectious disease. Consideration of the factors identified here as increasing the odds of positive PCR results should improve case selection and reduce the number of false-negative results.

An assumption is made that more rapid diagnosis and differentiation between various causes is beneficial to ultimate visual outcomes; however, this was not evaluated in this series. Conventional management with sequential empiric therapies until a clinical response is obtained may not be inferior to earlier, more precise diagnosis and treatment. Similarly, the cost utility of PCR testing is unclear. Serologic testing for syphilis efficiently diagnosed 10 cases of syphilitic chorioretinitis in this series; waiting 24 hours for results of syphilis serologic analysis before testing by PCR would have been cost effective for those patients, but would have led to a delay in reaching a definitive diagnosis for others.

In summary, PCR testing of aqueous humor can be a safe, easily performed first-line diagnostic procedure that is useful as an adjunct to careful history and clinical examination. In most cases, vitreous sampling was not required, and PCR reaction alone without antibody testing resulted in a large percentage of confirmed diagnoses. Our data suggest that patients with viral retinitis or chorioretinitis that is atypical in appearance at presentation, especially with visible retinal vascular lesions, extensive retinitis, optic nerve involvement, or

immunocompromised state, may benefit from adjunctive anterior chamber PCR testing, especially if the testing is carried out relatively early in the disease course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Biography

Thomas Harper, MD, completed medical school at the University of Louisville School of Medicine in Louisville, Kentucky. He completed his ophthalmology residency and vitreoretinal surgery fellowship at the Bascom Palmer Eye Institute in Miami, Florida. Currently, Dr Harper is a Chief Resident 2008 to 2009.

TABLE 1

Characteristics of Patients Undergoing Diagnostic Testing of Intraocular Fluid Specimens with Polymerase Chain Reaction for Possible Infectious Uveitis Affecting the Posterior Segment

No. of Patients	133
Gender	
Male	75 (56%)
Female	58 (44%)
Race	
White	45 (34%)
Black	43 (32%)
Hispanic	44 (33%)
Other	1 (1%)
Mean age (yrs)	47 ± 21
Age range	1 month to 89 years
Immune status	
HIV positive	61 (46%)
HIV negative	54 (41%)
Other immunocompromised state	18 (14%)
Follow-up (mos)	
1	109 (82%)
6	72 (54%)
Mean visual acuity in the study eye, logMAR (SD)	
Baseline	1.5 (1.1)
1 mo	1.3 (1.1)
6 mos	1.3 (1.2)

HIV = human immunodeficiency virus; logMAR = logarithm of the minimum angle of resolution; mos = months; SD = standard deviation; yrs = years.

TABLE 2

Clinical Diagnosis before Testing Intraocular Fluid with Polymerase Chain Reaction in Patients with Possible Infectious Uveitis Affecting the Posterior Segment

Diagnosis	No.	%
Necrotizing herpetic retinitis	45	34
Toxoplasmosis	23	17
Panuveitis/chorioretinitis	23	17
Cytomegalovirus retinitis	21	16
Endophthalmitis	11	8
Vasculitis	6	5
Other ^a	4	3

^aIncludes one retrolenticular mass, one vitreous hemorrhage in an immunocompromised patient, one case suspicious for ocular lymphoma, and one retinal detachment in an immunocompromised patient.

TABLE 3

Anatomic Location of Inflammation before Diagnostic Testing of Intraocular Fluid with Polymerase Chain Reaction

Distribution	No. of Cases (% of Total), n = 133
Unilateral ^a	90 (68%)
Right eye	56 (62%)
Left eye	34 (38%)
Bilateral	43 (32%)
Anterior chamber inflammation in the sampled eye	94 (71%)
Vitreous inflammation	95 (71%)
Retinal or choroidal inflammation	125 (94%)

^a In the unilateral cases, there were more right eyes than left eyes ($P = .026$, Chi-square test).

Clinical Sensitivity and Specificity of Polymerase Chain Reaction in Aqueous and Vitreous Specimens from Patients with Possible Infectious Uveitis Affecting the Posterior Segment

TABLE 4

Sampling Site	No. of Patients	No. (%) True Positive Results	No. (%) False-Positive Results	No. (%) True Negative Results	No. (%) False-Negative Results	Sensitivity/Specificity
Aqueous ^a	101	62 (61%)	0	25 (25%)	14 (14%)	82%/100%
Vitreous ^b	32	14 (44%)	1 (3%)	13 (41%)	4 (13%)	78%/93%
Total	133	76 (57%)	1 (1%)	38 (29%)	18 (14%)	81%/97%

^aSix of these patients also had a vitreous sample not included in this Table. Four showed negative results from both sites; one had positive herpes simplex virus 2 results from aqueous but negative results from vitreous; and one had positive toxoplasmosis results from aqueous and equivocal results from vitreous.

^bFour of these patients also had an aqueous sample not included in this Table. One had negative results from both sites; one had positive Epstein-Barr virus results from both sites; one had positive cytomegalovirus results from the vitreous, but cytomegalovirus was not tested from the aqueous; and one had positive Epstein-Barr virus results from the vitreous and negative results from aqueous.

TABLE 5

Number of Polymerase Chain Reaction Tests and Positive Results for Each Infectious Agent

Infectious Agent	No. of Tests Performed	No. (%) Positive Results
Herpes simplex virus 1	120 ^a	4 (3%)
Herpes simplex virus 2		12 (10%)
Varicella zoster virus	115	25 (22%)
Cytomegalovirus	108	24 (22%)
Epstein-Barr virus	23	3 (13%)
Toxoplasmosis	66	12 (18%)
Human T-cell lymphotropic virus 1	1	1 (100%)
All	433	81 (18.7%) ^b

^aBoth herpes simplex virus 1 and 2 are amplified from the same polymerase chain reaction.

^bEighty-one positive results (rather than 77 as in Tables 4 and 6) are recorded because four patients had two positive test results: one necrotizing herpetic retinitis patient had positive herpes simplex virus 1 and 2 results; one patient had positive results for both herpes simplex virus 1 and cytomegalovirus; one cytomegalovirus patient was positive for cytomegalovirus and herpes simplex virus 2; and one patient with infectious chorioretinitis of uncertain cause was positive for varicella zoster virus and Epstein-Barr virus.

TABLE 6
Number of Patients with Possible Infectious Uveitis and Positive Polymerase Chain Reaction Results for Each Pretest Diagnosis

Pretest Diagnosis (No.)	HSV1	HSV2	VZV	CMV	TOXO	EBV	HTLV	Patients (%) with at Least One Positive PCR Result
Necrotizing herpetic retinitis (45) ^a	4	8 ^c	18	7 ^c	1			36 (80%)
CMVR (21) ^a		1 ^c	2	11	2	1		16 (76%)
Toxoplasmosis (23) ^a		2	3	1	7			13 (57%)
Chorioretinitis NOS (1) ^a			1			1 ^c		1 (100%)
Subtotal (90)	4	11 ^c	24	19 ^c	10	2 ^c		66 (73%)
Panuveitis/chorioretinitis (22) ^b		1		3	2		1	7 (32%)
Endophthalmitis (11) ^b				1				1 (9%)
Vasculitis (6) ^b			1			1		2 (33%)
Other (4) ^b				1				1 (25%)
Subtotal (43)	0	1	1	5	2	1	1	11 (26%)
Total (133)	4	12	25	24	12	3	1	77 (58%)

CMV = cytomegalovirus; CMVR = cytomegalovirus retinitis; EBV = Epstein-Barr virus; HSV = herpes simplex virus; HTLV = human T-cell lymphotropic virus 1; NOS = not otherwise specified; PCR = polymerase chain reaction; TOXO = toxoplasmosis; VZV = varicella zoster virus.

^aPositive PCR results would be expected based on pretest diagnosis.

^bNegative PCR results would be expected based on pretest diagnosis.

^cDenotes that one of the positive results was considered a false positive, because four patients had positive results for two organisms. The pathogen consistent with the final diagnosis was considered to be the true positive result. One patient with infectious chorioretinitis of uncertain origin was considered to have false-positive results for two organisms, VZV and EBV, because no satisfactory diagnosis was ever reached.

Number of Patients with Positive Polymerase Chain Reaction Results in Cases with Final Clinical Diagnosis of Posterior Segment Infectious Uveitis

TABLE 7

Posttest Diagnosis (No.)	HSV1	HSV2	VZV	CMV	TOXO	EBV	HTLV	Patients (%) with Positive PCR Results ^a	
Necrotizing herpetic retinitis (43) ^b	4	11 ^c	24	1 ^c				38 (88%)	
CMVR (28)		1 ^c		23				23 (82%)	
Toxoplasmosis (18)					12			12 (67%)	
EBV chorioretinitis (2)						2		2 (100%)	
Chorioretinitis of unknown cause (3)			1 ^c			1 ^c		1 (33%)	
HTLV-1 uveitis (1)							1	1 (100%)	
Total (95)	4	12 ^c	25 ^c	24 ^c	12	3 ^c	1	77 (81%)	

CMV = cytomegalovirus; CMVR = cytomegalovirus retinitis; EBV = Epstein-Barr virus; HSV = herpes simplex virus; HTLV = human T-cell lymphotropic virus 1; NOS = not otherwise specified; PCR = polymerase chain reaction; TOXO = toxoplasmosis; VZV = varicella zoster virus.

^a Positive PCR results are greater than total number of patients because four patients had positive results for two organisms.

^b Four of these patients had clinical findings of progressive outer retinal necrosis and positive VZV PCR results.

^c Denotes that a positive result was considered a false positive in the four patients who had positive results for two organisms (one patient with chorioretinitis of uncertain cause had false-positive results for two organisms, VZV and EBV).

TABLE 8

Relative Risk Ratio of Positive Polymerase Chain Reaction Results According to Pretest Clinical Findings in Patients with Possible Posterior Segment Infectious Uveitis

Sign	Detectable PCR Results When Sign Present, % (n/N)	Detectable PCR Results When Sign Absent, % (n/N)	Relative Risk of Positive PCR Results When Sign Present (95% CI)	P value
Posterior synechiae	45% (9/20)	60% (68/113)	0.75 (0.45 to 1.24)	.31 ^a
Hypopyon	14% (1/7)	60% (76/126)	0.24 (0.82 to 0.99)	.041 ^b
Anterior chamber inflammation	57% (54/94)	59% (23/39)	0.97 (0.71 to 1.33)	1.00 ^a
Visible retinal vascular lesions	74% (57/77)	36% (20/56)	2.07 (1.42 to 3.02)	< .001 ^a
Optic nerve involvement	78% (28/36)	51% (49/97)	1.54 (1.18 to 2.00)	.008 ^a
Immunocompromised (n = 79, 61 HIV+)	66% (52/79)	46% (25/54)	1.42 (1.02 to 1.97)	.039 ^a
Sampling within one week of presentation	62% (66/106)	41% (11/27)	1.53 (0.95 to 2.47)	.071 ^a
Extensive retinitis ^c	76% (40/53)	46% (37/80)	1.63 (1.23 to 2.16)	.002 ^a

CI = confidence interval; HIV = human immunodeficiency virus; PCR = polymerase chain reaction.

^a Chi-square test.

^b Fisher exact test.

^c Lesions present in both the periphery and the posterior pole.