Original Article

Clinical spectrum, diagnostic criteria, and polymerase chain reaction of aqueous humor in viral and toxoplasma detection in Fuchs' uveitis syndrome

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Aim: The aim of this study is to describe the clinical features and diagnostic criteria of Fuchs' uveitis (FU) and to determine whether it has an association with virus and toxoplasma in the aqueous humor during cataract surgery. **Setting and Design**: This is a prospective, case–control study. **Materials and Methods**: Patients with FU ($n = 25$), anterior uveitis ($n = 15$), and no uveitis (normal) ($n = 50$) were included based on predefined inclusion and exclusion criteria for all three groups. Polymerase chain reaction (PCR) of aqueous humor and serum for rubella, herpes simplex virus (HSV), cytomegalovirus (CMV), varicella-zoster virus (VZV), and toxoplasma was done using conventional uniplex PCR. **Statistical Analysis**: It was done using SPSS software using Chi-square test for categorical variables, and $P < 0.05$ was considered statistically significant. **Results**: Ninety patients were enrolled in the study in three groups, comparable for age, gender, and laterality of ocular involvement. All patients had diffuse keratic precipitates in FU group ($P = 0001$) with none having posterior synechiae ($P = 0.046$) which was statistically significant when compared to anterior uveitis patients. Iris nodules were noted in one case in both groups. Serum and aqueous PCR was negative for detection of VZV, CMV, toxoplasma, and rubella in all groups. PCR for HSV was positive in one patient in "normal" group but was not statistically significant. **Conclusion:** Our study shows that diagnosis of FU is mainly clinical. There appears to be no role of aqueous humor testing for viruses by PCR to aid in etiological diagnosis.

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Fuchs' uveitis (FU) is a chronic nongranulomatous idiopathic, unilateral, or bilateral low-grade anterior uveitis characterized by iris heterochromia. The uveitis is typically noted in the lighter-colored eye of a young adult with minimal ocular symptoms and no related systemic disease.[1] Historically, Aristotle described the condition as "heteroglaucos." Ernst Fuchs expanded the work of Weill and produced a landmark paper of 38 cases describing etiology, pathology, and clinical signs of the entity.[1] FU accounts for 2–11% of all cases of anterior uveitis.[2] The International Uveitis Study Group (1984) attributes a 3.2% incidence in uveitic population.[3] The clinical signs common to this entity are heterochromia of iris, keratic precipitates (KPs) (stellate), nodules on the iris, absence of posterior synechiae, minimal aqueous flare, and iris vascular abnormalities.[4-7] Cataract, glaucoma, and sparse vitreous opacities are common complications.[6]

The pathophysiology of FU has remained an enigma till date. Hereditary causes, sympathetic nerve dysfunction, infections, and autoimmunity have been studied as causative factors.[8] Recently, rubella virus has been studied for possible association based on the presence of virus-specific intraocular antibodies and persistence of the virus intraocularly.[9,10] Earlier studies have shown association of FU with toxoplasmosis, varicella-zoster virus (VZV), and herpes simplex virus (HSV).[11,12] However, the criteria of FU were not specified in these studies. Furthermore, laboratory methods such as polymerase chain reaction (PCR) have been used widely for viral nucleic acid (DNA/RNA) detection in aqueous humor in FU. The pathognomonic clinical features are often overlooked in a busy outpatient setting, even in the presence of classical findings, as the presence of one of the findings (such as large KPs or vitreous opacities) may mislead the clinician to diagnose this as idiopathic anterior uveitis or granulomatous intermediate uveitis. Patients often present with decreased vision due to cataract, and although the results of cataract surgery have excellent prognosis in FU, these patients are warned about guarded prognosis generally associated with uveitic cataracts. Patient may be unnecessarily subjected to multiple serological and other laboratory tests whereas the diagnosis needs to be purely clinical.

In this study, we have described the characteristic clinical features in FU and compared them with two other cohort

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groups: Anterior uveitis and normal patient groups, all of whom subsequently underwent cataract surgery. We have also attempted to detect rubella, HSV, cytomegalovirus (CMV), VZV, and toxoplasma nucleic acid in aqueous humor and serum of the three groups. The purpose of the study is to describe classic clinical features and clinical diagnostic criteria and to determine whether PCR testing of aqueous humor can help establish the etiological diagnosis by showing an association with rubella, HSV, CMV, VZV, and toxoplasma at the time of cataract surgery.

Materials and Methods

This is a prospective, nonrandomized cohort study at a tertiary eye care center in Southern India and included patients of Indian origin referred to the institute from all over the country. The study was approved by the institutional review board and Institutional Ethics Committee. Written informed consent was taken from all patients.

The patients included in the study were from three groups. (a) Normal group (nonuveitic eyes): This included patients with no other ocular disease who were scheduled to undergo routine cataract surgery. They served as controls for both the clinical features and for PCR for various viral antigens from aqueous humor. (b) Uveitic eyes (non-FU): This included patients who were diagnosed as idiopathic anterior uveitis and were scheduled to undergo routine cataract surgery. They served as controls for PCR for various viral antigens from aqueous humor. (c) Study group (FU): This included patients who fulfilled the diagnostic criteria for FU and were scheduled to undergo cataract surgery.

Patients without any ocular disease such as corneal dystrophies, corneal ectasias, glaucoma, raised intraocular pressure, hypotony, ocular ischemic syndrome, neovascularization of iris, angle or retina, any choroidal or retinal pathology: Healed toxoplasma scars, diabetic retinopathy, macular edema, and age-related macular degeneration who were scheduled to undergo cataract surgery were included in the normal (nonuveitic) group. On the other hand, patients who were diagnosed as anterior uveitis of either idiopathic or autoimmune etiology and who did not have any evidence of postcataract or posttraumatic uveitis, intermediate, posterior or panuveitis, active keratitis (keratouveitis) or conjunctivitis, and primary or secondary glaucoma were included in the idiopathic anterior uveitis group. The study group which included patients of FU was diagnosed based on the presence of a combination of clinical signs based on criteria described by Kimura *et al*., in which two of the three major criteria with or without the presence of minor criteria were required for diagnosis. The major criteria included the presence of (i) diffuse KPs (stellate or nonstellate), (ii) mild anterior chamber reaction defined as up to 2+ cells and flare, (iii) absence of posterior synechiae, and (iv) absence of ciliary congestion or red eye. The minor criteria for diagnosis included (i) heterochromia of the iris with/without iris depigmentary changes, (ii) presence of multiple nodules on iris, (iii) presence of vitreous opacities, and (iv) unilateral or bilateral involvement (one eye only was enrolled). Patients with the presence of any other active or quiescent ocular inflammatory disease: Keratitis or conjunctivitis and presence of retinochoroidal scars were excluded from the study.

The study enrolled 25 patients with FU, 15 patients with non-FU anterior uveitis, and fifty age- and gender-matched controls were included in the study. The sample size was calculated to give 80% power to the study with an alpha error of 0.05. The required minimum number of patients of FU and anterior uveitis was 18 and 15 in each group, respectively. The control was taken in 1:2. All patients underwent complete ophthalmological evaluation, which included history taking, high contrast, visual acuities (uncorrected and best-corrected) recorded on Early Treatment of Diabetic Retinopathy Study chart, slit lamp biomicroscopy, including documentation of KPs, grading of anterior chamber cells, and flare and cataract grading, and indirect ophthalmoscopy for retinal evaluation. All slit lamp and indirect ophthalmoscopy examinations were done by two senior ophthalmologists. Goldmann applanation tonometry was done in all cases. All patients underwent cataract surgery (either standard phacoemulsification or small-incision cataract surgery) with placement of posterior chamber intraocular lens under peribulbar or topical anesthesia in a standard fashion. Postoperatively, the patients followed up on the 1st postoperative day, 1-week, 1-month, and 3 months.

10 cc peripheral venous blood was collected and centrifuged to separate the serum. Intraoperatively, before any other procedure just before cataract surgery, a sterile 26-gauge needle mounted on a tuberculin syringe was used to perform a paracentesis, and 0.2 ml of aqueous humor was collected. The fluid was then transferred to a sterile eppendorf and transported to the microbiology laboratory for analysis. Both serum and aqueous were processed for conventional uniplex PCR for detection of DNA of HSV-1, VZV, CMV, and toxoplasma and RNA of rubella virus.[13-16] All PCRs were carried out in a thermocycler (minicycler – PTC-150, MJ research INC, MA, USA). The products of amplification were electrophoretically resolved on 1.5% agarose gel and visualized for analysis after being stained with ethidium bromide.

The data were analyzed using IBM SPSS Statistics for Windows, Version 20.0. (Armonk, NY: IBM Corp). Categorical data of the three groups were analyzed using Chi-square test. Fisher's *t*-test was used for analysis of nonparametric data. A two-tailed $P < 0.05$ was taken to be statistically significant.

Results

A total of ninety patients were included in the study - 25 patients of FU, 15 of anterior uveitis (non-FU), and fifty of controls (normal). The baseline characteristics of the three groups were comparable in age, gender, and laterality of ocular involvement [Table 1].

The clinical features are shown in Table 2. The common signs were medium-sized KPs, anterior chamber reaction, and cataract. KPs were seen in all (100%) FU patients while none had posterior synechiae ($P = 0.046$), which is statistically significant. In comparison, in the uveitis group, 7 (46.7%) patients had KPs and 5 (15.5%) had posterior synechiae. Fisher's exact test comparing the presence of KPs between FU and anterior uveitis group showed a *P* value of 0.0001, which was statistically significant. However, anterior chamber reaction (>3 cells) was seen in only 10 (6.2%) patients of FU. Iris nodules were seen in one case each in uveitic and FU groups. None of the FU cases demonstrated posterior segment reaction though visualization

was difficult in 15 cases due to advanced cataract, in which case the findings were confirmed postoperatively.

PCR for HSV Type 1 showed negative values in all FU, except one sample in normal group tested. PCR for VZV, CMV, rubella virus, and toxoplasma was negative for all three groups [Table 3]. Using Chi-square test, *P* value was found to be 0.42 for PCR reaction (Chi-square of 4.948 with 5 degrees of freedom). This finding was not statistically significant.

Discussion

The diagnosis of FU is primarily clinical, unfortunately often missed by ophthalmologists. As a result, patients are subjected to unnecessary investigations and chronic immunosuppressive therapy with no response. The incidence of misdiagnosis may be as high as 92%.[17] In our study, the major signs of diffuse KPs and absent posterior synechiae were present in 100% cases. These findings combined with 40% showing anterior chamber reaction make diagnosis of FU easy to establish. All patients in our series had cataract by default as it was our inclusion criterion. If the diagnostic signs of FU are compared with those in anterior uveitis, we find that only 46.7% cases had KPs while posterior synechiae were seen in 33.3%. Therefore, the constellation of clinical signs of a young patient with anterior uveitis, without red eye, with KPs, and no posterior synechiae should be pathognomonic for diagnosis of FU. These findings reinforce that FU is a clinical and not a laboratory diagnosis. This entity should be kept first on the differential list so that FU is not missed in the clinics.

The etiopathogenesis of FU has been speculative. Earlier literature pointed to the idiopathic nature of the disease.[2,8] However, recent reports have proposed an infectious etiology. Association of rubella virus with FU has been strongly proposed by various study groups.[9,10,18] In some studies, PCR of aqueous fluid was positive for rubella virus ranging from 14% to 18%.[9,19,20] The Goldmann-Witmer index (GWI) for intraocular antibody synthesis and PCR has been used to substantiate this association, and the results improved to 91.67% in study by Quentin *et al*.[9] In our study, PCR was used as it has high sensitivity and specificity.[15] However, results were negative in all samples. Hence, our study reinforces that use of PCR in establishing the viral etiology in the diagnosis of FU is unlikely to yield additional benefit as the results are often negative.

Ocular toxoplasmosis has been studied as an etiology of FU.[11,17] However, these case reports were retrospective with preexisting toxoplasma lesions in the posterior segment. Our analysis of aqueous humor and serum with nested PCR[16] was negative in all samples. Nested PCR is highly sensitive and specific when tested for the B1 toxoplasma gene[16] as was done in our study. None of our FU patients had ocular lesions suggestive of previous toxoplasmosis.

Few case reports in literature have also linked FU with HSV.[12,18] However, positive PCR for HSV in this disease was in only a single case report.[12] In our study, only one case of normal group was positive for HSV on PCR.

We also did PCR for CMV and VZV to determine any association with the disease but found none.

This is a prospective study to investigate the correlation of various clinical signs of uveitis to establish a diagnosis of FU. Moreover, the study also determines the low utility of testing presence of viral and toxoplasma antigens in FU. The disease seems to be driven predominantly by antigen-antibody reaction in the later stages, rather than the presence of live viral antigen in the ocular fluids. The present study has certain limitations. The sensitivity and specificity of PCR are not 100%, and combining with GWI could have yielded more specific results. At the time of initiating this study, we did not have ability to perform GWI. However, an adequate sample size and proper cohort matching give scientific credence to our findings.

Table 1: Demographic data of three groups

	Number of males	Number of females	Age: Mean±SD
Overall	48	42	45.17±14.01
Fuchs	12	13	44.9±14.08
Anterior uveitis	8	7	45.06±12.19
Normal eye	28	22	45.17±14.08

SD: Standard deviation

Table 2: Clinical features of Fuchs uveitis and anterior uveitis cases

Clinical sign	Fuchs (*n*)	Anterior uveitis (*n*)	*P*
Keratic precipitates	25	7	0.0001
Iris heterochromia	0	0	1.00
Iris nodule	1	1	1.00
Anterior chamber reaction	10	7	0.748
Posterior synechiae	0	5	0.0046
Cataract	25	15	1.00
Glaucoma	0	0	1.00
Posterior chamber findings	0	0	1.00
Hypopyon	0	4	0.000

n: Number of patients

Table 3: Polymerase chain reaction analysis of aqueous humor for herpes simplex virus, varicella-zoster virus, cytomegalovirus, adenovirus, and toxoplasma

	HSV Type 1	VZV	Cytomegalovirus	Adenovirus	Toxoplasma
Normal (*n*=50)	0	0	0	0	0
Fuchs uveitis (*n*=25)	0	0	0	0	0
Anterior uveitis (*n*=15)	1	0	0	0	0

HSV: Herpes simplex virus, VZV: Varicella-zoster virus

Conclusion

This study concludes that a clinical diagnosis is most necessary in cases of FU. This can decrease time loss and financial burden of expensive serological tests or PCR in such patients. This also helps in prognosticating the disease, as FU is relatively benign with no adverse effects reported despite chronic inflammation, and has the best prognosis for vision after cataract surgery.[21]

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Conflicts of interest

There are no conflicts of interest.

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