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The Association between QuantiFERON-TB Gold Test and Clinical Manifestations of Uveitis in the United States

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Abstract

Purpose: To report the prevalence of QuantiFERON-TB Gold (QFT-G) positivity among uveitis patients compared to general population and to evaluate the differences in clinical features of uveitis.

Design: Retrospective cohort study.

- **Setting:** Institutional.
- **Patient Population:** 418 consecutive new uveitis patients, regardless of clinical suspicion, were tested for QFT-G.
- **Observation Procedures:** Demographics, TB risk factors, clinical characteristics of uveitis were collected.
- **Main Outcome Measures**: The frequency of QFT-G positivity among uveitis patients and characteristic clinical features among QFT-G positive patients.

Results: QFT-G positivity was found in 60/418 patients with uveitis (14.4%, 95% CI: 11.18 – 18.14) higher than the general US population (5%, 95% CI: 4.2 – 5.8, p<.001). Age, gender and residence were similar between QFT-G positive and negative groups. Uveitis patients with positive QFT-G were more likely to be foreign born or have a recent travel history (OR:5.84; 95% CI: 2.83 – 12.05; p<.001). QFT-G positive patients were more likely to present with granulomatous uveitis (OR 2.90; 95%CI 1.36 – 6.21; p=.006). No significant association was found with specific clinical features such as choroiditis, retinal vasculitis, occlusive vasculitis, and serpiginoid choroiditis (p>.05 for each). Prevalence of TB-uveitis based on treatment response was 1.19%.

Conclusions: Our study demonstrates significantly higher prevalence of QFT-G positivity among uveitis patients compared to average US population. Characteristic signs of TB uveitis

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reported in endemic countries were not seen in this cohort. Implications of higher prevalence of QFT-G positivity among uveitis patients require further investigation.

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This study suggests that the prevalence of latent tuberculosis in uveitis population from a tertiary center is significantly higher than in general population in the United States (14.4% vs 5%, p<.001). Having been born or traveled outside the United States or having granulomatous uveitis was significantly associated with a positive QuantiFERON-TB Gold test.

INTRODUCTION

Tuberculosis (TB) remains a major global health concern and confers significant mortality and morbidity in both developed and developing countries.[1] According to The World Health Organization, one-third of the world's population is infected with TB, a chronic systemic infectious disease caused by *Mycobacterium tuberculosis.*[1] About 90% of the cases are classified as latent TB infection (LTBI).[2] LTBI is defined as the state of persistent immune response to stimulation by Mycobacterium tuberculosis antigens without evidence of clinically manifest active TB.[2]

TB is thought to affect the lungs in 80% of patients, with the remaining 20% being affected in other organs.[3] Ocular involvement in patients with systemic TB is quite variable between studies depending on the criteria used for the diagnosis and the population sampled and may be seen in up to 18% of cases.[3–5] Prevalence of ocular TB as an etiology of uveitis varies from 0.5% in USA up to 11% in endemic areas.[6–8] Diagnostic criteria for TB-uveitis as defined by the Collaborative Ocular TB Study Group (COTS) are: any clinical sign of intraocular inflammation and/or scleritis in the setting of no evidence of other uveitic entities, plus, demonstration of mycobacteria or its genome either in ocular fluids or other organs, or a corroborative test result such as positive tuberculin skin test (TST) or interferon gamma release assay (IGRA).[9] Identification of mycobacteria is not always possible and is complicated by low sensitivity in ocular culture or PCR assay due to the low bacterial load.[10] As such, clinicians make the diagnosis of probable ocular TB based on positive ancillary testing (TST, IGRA, chest imaging) combined with characteristic clinical phenotypes. For example, serpiginous choroiditis, choroidal granulomas, and retinal vasculitis have been reported as classical features of ocular TB.[7,8,11,12]

QuantiFERON-TB Gold (QFT-G) test (Cellestis Inc., Carnegie, Victoria, Australia), is a newer diagnostic test for TB infection that measures the release of interferon-gamma after stimulation in vitro by *M. tuberculosis* antigens using ELISA. The reported sensitivity of QFT-G varies from 62% to 95% (pooled value 80%) and specificity varies from 92% to 100% (pooled value 98%).[13]

So far, limited data are available on the prevalence of LTBI (based on QFT-G positivity) in the general uveitis population, especially in areas of low TB burden. Routine screening for TB for all patients with uveitis is not recommended unless there are risk factors such as previous TB exposure, residence in an endemic area or known classic presenting features such as Eales disease, choroidal tuberculoma, and serpiginoid tuberculous choroiditis. More

recently, TB testing is being performed prior to initiation of tumor necrosis factor α inhibitors due to the risk of TB reactivation.[14,15] In endemic areas the reported prevalence of LTBI among uveitis patients varies from 7% to 61%.[16–19] The aim of this study was to evaluate the association of positive QFT-G testing in a uveitis population, thereby reporting on the prevalence of LTBI in a tertiary uveitis referral clinic in a non-endemic region; and to compare the phenotypic differences in the group of patients with positive QFT-G as compared to the group with negative QFT-G test.

PATIENTS AND METHODS

A review of all new uveitis patients seen under institutional review board-approved clinical research protocol at the National Eye Institute from 2013– 2019 was performed. The study adhered to the tenets of the Declaration of Helsinki. All patients seen in the uveitis clinic, provided written informed consent and underwent a comprehensive eye examination and a standardized panel of laboratory testing for infectious and inflammatory causes of uveitis regardless of clinical suspicion for any particular etiology. The laboratory panel included complete blood count, chemistry, urinalysis, screening for syphilis, HIV, hepatitis, tuberculosis (QFT-G assay), sarcoidosis (Angiotensin-converting enzyme, lysozyme), autoantibodies, HLA panel and others. All patients with positive QFT-G received chest X-ray and were evaluated by infectious disease specialists. Chest computerized tomography was performed as needed based on recommendations of infectious diseases service. LTBI is defined as positive QFT-G in the absence of evidence for active systemic TB. QFT-G test was classified positive according to the manufacturer's instructions (values ≥0.35 IU/mL). Clinical diagnosis and characteristics of uveitis were determined through a query of the electronic medical record followed by individual medical record review for confirmation. Patient demographics such as gender, race, age at presentation, presence of known TB risk factors, and laterality was compared across QFT-G positive and negative cohorts. Uveitis was classified according to anatomic localization, as recommended by the Standardization of Uveitis Nomenclature Working Group.[20] The presence of retinal vasculitis was confirmed by fluorescein angiography.

Our study did not recruit healthy controls to assess prevalence of QFT-G positivity among general population. Therefore, the prevalence of latent TB in the uveitis cohort was compared to the prevalence in general population using publicly available data on QFT-G testing among general US population.[21]

Data analyses were done by using SPSS v.17.0 statistical software for Windows (SPSS Inc., Chicago, IL). Multivariable logistic regression model was used to analyze the association between clinical factors and the QFT-G positivity and to estimate the odds ratios of each outcome measure with a 95% confidence interval adjusted for age, gender and race. A two-tailed p value of <.05 was considered significant.

RESULTS

Four hundred and forty nine consecutive patients were seen and tested for QFT-G. Of these 449 patients the presence of uveitis was confirmed in 418 patients. None of the

patients had a known diagnosis of active TB prior to the onset of their uveitis. Demographic characteristics of the 418 uveitis patients based on their QFT-G test results are shown in the Table. QFT-G was positive in 60 patients yielding a prevalence of 14.4% (95% CI: 11.18 – 18.14) which was significantly higher than the LTBI rate in general US population 5% (95% CI: 4.2 – 5.8, p<.001).[21] Nine of these 60 patients (15%) tested positive prior to being referred to our clinic. All 9 of these patients retested positive as part of this study. Geographically, 89.5% of the patients resided in the Washington DC metro area including neighboring states of Maryland and Virginia. There was no statistically significant difference among QFT-G positive and negative patients in terms of residence (p=.43).

QFT-G positive patients were more likely to be older than QFT-G negative counterparts (OR: 1.02; 95% CI: 1.00–1.04; p=.02), but no significant gender difference was observed (Table). Patients with positive QFT-G test were more likely to be of Asian race than White non-Hispanic ethnicity (OR: 5.15; 95% CI: 2.24–11.84; p<.001, Table). Among different race/ethnicities, the prevalence of QFT-G positivity was 8.7% among non-Hispanic Whites, 13.4% in Blacks, 18.2% in Hispanics, and 31.9% in Asians.

Of the patients who tested QFT-G positive, 44 (73.3%) were either foreign born or had a recent history of travel outside the United States. Birth or travel history was recorded in the charts of 215 of the 358 QFT-G negative patients. Of these 215 patients, 70 (32.6%) were either foreign born or had a recent history of travel outside the United States which was significantly lower than in QFT-G positive group (OR: 5.84; 95% CI: 2.83–12.05; p<.001, Table). Among patients who were U.S. born and had no recent history of foreign travel the prevalence of QFT-G positivity was 9.9%, while it was 38.6% among patients who were foreign born or had a recent foreign travel history.

In the subgroup of 275 patients with available birth/travel history, Asian race had an OR of 2.06 (95% CI: 0.77–5.51, p=0.15) compared to white non-Hispanic persons in the multivariable regression model.

There was no significant difference between patients with or without QFT-G positivity in terms of laterality and anatomic location of uveitis (Table). In multivariable regression analyses, even when adjusted for age, gender and race/ethnicity, clinical appearance suggestive of granulomatous uveitis was more likely to be present in QFT-G positive group (21.7% vs 8.4%; OR:2.90; 95% CI: 1.36–6.21, p=.006) while no significant difference was observed in other characteristics such as choroiditis, retinal vasculitis, occlusive vasculitis, and serpiginous choroiditis between groups (Table). No significant relationship was found between QFT-G test values and these clinical phenotypes (p>.05 for all). Although uveitis with idiopathic etiology was more common in QFT-G positive patients compared to QFT-G negative patients (68.3% vs 58.7%), the difference was not statistically significant (Table).

Since prednisone or other immunosuppressive therapy may affect QFT-G test results, we looked at systemic treatment at the time of testing. The use of any systemic prednisone and/or other immunosuppressive therapy was 10% in the QFT-G positive group and 22.3% in the QFT-G negative group (p=.03). The rate of prednisone use was not significantly different (6.7% vs 15.4%, respectively; p=.07). Among patients who tested positive for

QFT-G, none of them were on tumor necrosis factor (TNF) inhibitors at the time of testing. Among patients who tested negative for QFT-G, 14 (3.9%) of them were on TNF inhibitors at the time of testing.

Out of 60 QFT-G positive patients, 33 had sufficient follow-up at our center to determine outcomes of LTBI treatment. Only one of the 60 patients was considered to have active TB based on identifiable mycobacteria genome (PCR) in the eye and clinical and radiographic evidence of multiple TB lesions in other organs. Of the 33 patients who received anti-TB treatment (ATT), 32 patients completed treatment for LTBI. Among these 32 patients, 19 received monotherapy and 13 received multidrug (3 −4 drugs) therapy based on infectious disease recommendations and risk factors as recommended by their infectious disease specialist. Twenty seven of the 32 patients (84.4%) required additional anti-inflammatory treatment (steroids, antimetabolites or biologics) for control of their intraocular inflammation despite appropriate course of TB treatment. In the remaining 5 patients, inflammation resolved with ATT alone without requiring immunosuppression. These 5 patients meet the criteria for being categorized as TB-uveitis based on COTS criteria resulting in a prevalence of TB-uveitis of 1.19% among uveitis patients in this tertiary center study. Out of 5 patients who did not require additional immunomodulatory treatment after TB therapy, 2 had posterior uveitis with choroidal granuloma, 2 had granulomatous panuveitis (with retinal vasculitis in one of them) and 1 with non-granulomatous panuveitis with retinal vasculitis. Mean QFT-G value was 6.01 ± 4.54 IU/ml (range: 1.74– 11.63) in patients that required only anti-TB treatment and 5.11 ± 5.15 IU/ml (range: 0.35– 18.6) among patients that required additional anti-inflammatory treatment (p=.44).

DISCUSSION

Our study shows that, in a nonendemic area in the US, LTBI based on positive QFT-G was significantly higher than the LTBI rate in general US population (14.4% vs 5%, p<.001).[21] Specifically, LTBI rate is only 2.8% in US born individuals and 15.9% among foreign born individuals.[21] Our cohort had higher LTBI rates overall; 38.6% among foreign born uveitis patients and 9.9% among US born uveitis patients. We found that Asian race and international travel/foreign birth history were associated with increased odds of testing positive for QFT-G among uveitis patients (Table).

The prevalence of IGRA positivity among Navy recruits entering boot camp at a training command center in Illinois, USA was 1.8%.[22] During 2004–2013, the annual percentage of service members in the U.S. Armed Forces diagnosed with LTBI was 0.9% in 2011 and 1.6% in 2006 (overall 1.3%).[23] The rate of LTBI was lowest in individuals with White non-Hispanic ethnicity and highest in Asian/Pacific Islanders (0.8% vs 4%).[23]

In our cohort, the highest prevalence of QFT-G positivity was among Asians (31.9%) followed by Hispanic ethnicity (18.2%). This finding is consistent with previous reports, including the multinational COTS-1 study.[9] This can be explained by the fact that India and China comprise 38% of the world’s TB infections.[24] However, even though Asian ethnicity was overrepresented in our cohort at 11.2% (Asian Americans constitute only 5.8% of the

entire US population) the rate of QFT positivity among Asian uveitis patients in this cohort was still higher (31.9%) than in general Asian American population(17.5%).[21,25]

Previous studies reporting QFT-G positivity rates among uveitis patients in non-endemic areas are highly variable (13%−67%) and selectively tested patients with ocular manifestations suggestive of TB resulting in higher rates of QFT-G positivity.[14,26–32] Most recently, Groen-Hakan et al.[14] reported the prevalence of QFT-G positivity among uveitis patients in the Netherlands regardless of risk factors. They reported a higher prevalence of QFT-G positivity at 13% compared to general population; and a higher proportion of non-Caucasians and idiopathic uveitis among QFT-G positive patients. In a similarly designed study from Thailand, a highly endemic area for TB, Pathanapitoon et al.[33] reported QFT-G positivity at 36% among consecutive new uveitis patients while in healthy Thai population the QFT-G positivity was reported to be 17%. None of their uveitis patients were identified with active systemic TB. Although the designs of these studies are similar, the study cohorts are ethnically different than ours. Additionally, we were able to identify several clinically relevant risk factors in our study using a multivariable logistic regression (Table).

The large multinational COTS study showed regional differences in the prevalence and nomenclature used for ocular TB as well as management with ATT, which impacts treatment and visual outcomes.[34,35] In prior literature, the presence of choroidal granulomas, occlusive retinal vasculitis, and multifocal or serpiginous choroiditis have been more strongly associated with TB.[9,30–33,36,37] We noted that the clinical presentation of granulomatous uveitis was significantly higher in QFT-G positive patients however, serpiginoid choroiditis and occlusive vasculitis were observed at low rates in our cohort as well as in the Dutch cohort, while in the cohort from Thailand occlusive retinal vasculitis was significantly higher in QFT-G positive uveitis patients suggesting that areas of low endemicity may have different clinical characteristics.

One of the criteria for diagnosing a patient with TB-uveitis in the setting of a positive QFT-G is the response to ATT.[9] In a French cohort, of the 25 patients who received ATT,15 patients (60%) had resolution of intraocular inflammation with successful corticosteroid taper. Median QFT-G test value was significantly higher in the group with successful therapeutic response compared to the group with treatment failure (7.67 IU/mL vs. 1.22 IU/mL, P = .026).[26] In our study, no significant difference was found in QFT-G test values between patients who required immunomodulatory treatment in addition to ATT and who did not (p=.44).

Attempts to infer a causal relationship based on therapeutic response has been complicated by concomitant use of steroids in most ATT regimens. In our cohort, 84.4% of patients who were fully treated with ATT needed additional immunomodulatory treatment for ocular inflammation despite appropriate TB treatment, thus not fulfilling the criteria for ocular TB. This brings us to the fundamental question of whether these QFT-G positive patients truly had TB-uveitis or whether *M. tuberculosis* could be acting as an adjuvant as described in experimental autoimmune uveitis mice models.[38] The strong adjuvant effect of *Mycobacterium* is used for cancer immunotherapy and intravesical Bacillus-Calmette–Guérin (BCG) administration has been used in the treatment of non-invasive bladder

cancer by the stimulation immune system, especially cell-mediated immunity.[39] Anterior uveitis, chorioretinitis, panuveitis, and autoimmune retinopathy have been reported after the administration intravesical BCG[40–44] Garip et al.[40] reported bilateral granulomatous anterior uveitis after intravesical BCG administration which responded to steroid therapy alone. They reported strong proliferation and secretion of proinflammatory cytokines after in vitro stimulation of patient's peripheral blood mononuclear cells with several retinal autoantigens. They also reported several homologies on the level of amino acid sequence between BCG proteins and retinal autoantigens which suggest a potential cross reaction of immune response targeting the eye. Panuveitis is also reported after TST in the absence of TB.[45] Altogether, previously published literature and our results suggest that uveitis can be caused by intraocular TB infection or potentially be a result of immune stimulation without intraocular infection. The relationship between ocular inflammation and positive QFT-G is yet unclear, especially in low endemic areas, which necessitates further studies.

As with every retrospective study, the results of our study should be interpreted with caution. Because of the tertiary nature of our clinic, it is likely that more complicated cases are included in this cohort leading to a selection bias. Moreover, we did not routinely attempt isolation of *M. tuberculosis* from ocular fluids or tissue. Our study was also limited by missing data, heterogeneity in ATT and corticosteroid regimens, lack of information on travel and birth history in some of the QFT-G negative patients and lack of a control group with ocular diseases other than uveitis. Lack of detailed travel history such as timing, duration, and location of travel might have influenced our results. We also noted that patients with a negative QFT-G were more likely to have been on immunosuppressives at the time of testing which may have led to underestimation of the overall prevalence of latent TB among uveitis patients. It is possible that this may have also caused missed risk factors beyond those that were identified (such as place of birth or race/ethnicity). However, the strength of our study lies in the fact that all patients were tested for TB in a systematic way regardless of clinical suspicion at presentation.

In summary, this study includes a large uveitis cohort from a non-endemic area and shows significantly higher prevalence of LTBI among systematically screened uveitis patients. Our data illustrates that predictive clinical features of ocular TB seen in endemic countries such as serpiginoid choroiditis, retinal vasculitis are not present in low endemic regions and that most patients with positive QFT-G required immunosuppressive therapy despite appropriate ATT. The relationship between positive QuantiFERON and ocular inflammation and the implications of higher prevalence of LTBI among uveitis patients require further investigation.

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References

1. Dye C, Scheele S, Dolin P, Pathania V, Raviglione MC. Consensus statement. Global burden of tuberculosis: estimated incidence, prevalence, and mortality by country. WHO Global Surveillance and Monitoring Project. JAMA. 1999;282(7):677–686. [PubMed: 10517722]
2. Bloom BR, Atun R, Cohen T, et al. Tuberculosis. In: Holmes KK, Bertozzi S, Bloom BR, Jha P, eds. Major infectious diseases. 3rd edition. Washington (DC): The International Bank for Reconstruction and Development / The World Bank; 2017 11 3 Chapter 11.
3. Albert DM, Raven ML. Ocular tuberculosis. Microbiol Spectr. 2016;4(6).
4. Bouza E, Merino P, Muñoz P, Sanchez-Carrillo C, Yáñez J, Cortés C. Ocular tuberculosis. A prospective study in a general hospital. Medicine (Baltimore). 1997;76(1):53–61. [PubMed: 9064488]
5. Babu RB, Sudharshan S, Kumarasamy N, Therese L, Biswas J. Ocular tuberculosis in acquired immunodeficiency syndrome. Am J Ophthalmol. 2006;142(3):413–418. [PubMed: 16935585]
6. Shakarchi FI. Ocular tuberculosis: current perspectives. Clin Ophthalmol. 2015;9:2223–2227. [PubMed: 26648690]
7. Malalis JF, Goldstein DA. Advances in tuberculosis-associated uveitis. Int Ophthalmol Clin. 2015;55(2):37–46.
8. Abu El-Asrar AM, Abouammoh M, Al-Mezaine HS. Tuberculous uveitis. Middle East Afr J Ophthalmol. 2009;16(4):188–201. [PubMed: 20404986]
9. Agrawal R, Gunasekeran DV, Grant R, et al. Clinical features and outcomes of patients with tubercular uveitis treated with antitubercular therapy in the Collaborative Ocular TuberculosisStudy (COTS)-1. JAMA Ophthalmol. 2017;135(12):1318–1327. [PubMed: 29075752]
10. Yeh S, Sen HN, Colyer M, Zapor M, Wroblewski K. Update on ocular tuberculosis. Curr Opin Ophthalmol. 2012;23(6):551–556. [PubMed: 23047173]
11. Gupta A, Sharma A, Bansal R, Sharma K. Classification of intraocular tuberculosis. Ocul Immunol Inflamm. 2015;23(1):7–13. [PubMed: 25314361]
12. Krassas N, Wells J, Bell C, Woodhead M, Jones N. Presumed tuberculosis-associated uveitis: rising incidence and widening criteria for diagnosis in a non-endemic area. Eye (Lond). 2018;32(1):87–92. [PubMed: 28776591]
13. Mori T Usefulness of interferon-gamma release assays for diagnosing TB infection and problems with these assays. J Infect Chemother. 2009;15(3):143–155. [PubMed: 19554399]
14. Groen-Hakan F, van Laar JAM, Bakker M, van Hagen PM, Hardjosantoso H, Rothova A. Prevalence Of Positive Quantiferon-Tb Gold In-Tube Test In Uveitis And Its Clinical Implications In A Country Non-Endemic For Tuberculosis. Am J Ophthalmol 2020;211:151–158. [PubMed: 31734135]
15. Jabs DA, Busingye J. Approach to the diagnosis of the uveitides. Am J Ophthalmol. 2013;156(2):228–236. [PubMed: 23668682]
16. La Distia Nora R, Sitompul R, Bakker M, et al. Tuberculosis and other causes of uveitis in Indonesia. Eye (Lond). 2018;32(3):546–554. [PubMed: 29099497]
17. Yeo TK, Ho SL, Lim WK, Teoh SC. Causes of visual loss associated with uveitis in a Singapore tertiary eye center. Ocul Immunol Inflamm. 2013;21(4):264–269. [PubMed: 23617254]
18. Win MZ, Win T, Myint S, Shwe T, Sandar H. Epidemiology of uveitis in a tertiary eye center in Myanmar. Ocul Immunol Inflamm. 2017;25(sup1):S69–S74. [PubMed: 26967588]
19. Al Dhahri H, Al Rubaie K, Hemachandran S, et al. Patterns of uveitis in a university-based tertiary referral center in Riyadh, Saudi Arabia. Ocul Immunol Inflamm. 2015;23(4):311–319. [PubMed: 25058456]
20. Jabs DA, Nussenblatt RB, Rosenbaum JT; Standardization of uveitis nomenclature (SUN) Working Group. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. Am J Ophthalmol. 2005;140(3):509–516. [PubMed: 16196117]
21. Miramontes R, Hill AN, Yelk Woodruff RS, et al. Tuberculosis infection in the United States: Prevalence estimates from the National Health and Nutrition Examination Survey, 2011–2012. PLoS One. 2015;10(11):e0140881. [PubMed: 26536035]

22. Lempp JM, Zajdowicz MJ, Hankinson AL, et al. Assessment of the QuantiFERON-TB Gold In-Tube test for the detection of Mycobacterium tuberculosis infection in United States Navy recruits. PLoS One. 2017;12(5):e0177752. [PubMed: 28545136]
23. Armed Forces Health Surveillance Center (AFHSC). Brief report: number of tuberculosis tests and diagnoses of latent tuberculosis infection in active component service members, U.S. Armed Forces, January 2004–December 2014. MSMR. 2014;21(12):8–10.
24. Sulis G, Roggi A, Matteelli A, Raviglione MC. Tuberculosis: epidemiology and control. Mediterr J Hematol Infect Dis. 2014;6(1):e2014070. [PubMed: 25408856]
25. Hoeffel EM, Rastogi S, Kim MO, Shahid H. The Asian Population: 2010. 2010 Census Briefs;Issued March 2012.
26. Gineys R, Bodaghi B, Carcelain G, et al. QuantiFERON-TB gold cut-off value: implications for the management of tuberculosis-related ocular inflammation. Am J Ophthalmol. 2011;152(3):433–440.e1. [PubMed: 21652022]
27. Itty S, Bakri SJ, Pulido JS, et al. Initial results of QuantiFERON-TB Gold testing in patients with uveitis. Eye (Lond). 2009;23(4):904–909. [PubMed: 18451874]
28. Kurup SK, Buggage RR, Clarke GL, Ursea R, Lim WK, Nussenblatt RB. Gamma interferon assay as an alternative to PPD skin testing in selected patients with granulomatous intraocular inflammatory disease. Can J Ophthalmol. 2006;41(6):737–740. [PubMed: 17224956]
29. Mackensen F, Becker MD, Wiehler U, Max R, Dalpke A, Zimmermann S. QuantiFERON TB-Gold--a new test strengthening long-suspected tuberculous involvement in serpiginous-like choroiditis. Am J Ophthalmol. 2008;146(5):761–766. [PubMed: 18718569]
30. Lee C, Agrawal R, Pavesio C. Ocular tuberculosis--A clinical conundrum. Ocul Immunol Inflamm. 2016;24(2):237–242. [PubMed: 26110355]
31. Sudheer B, Lalitha P, Kumar AL, Rathinam S. Polymerase chain reaction and its correlation with clinical features and treatment response in tubercular uveitis. Ocul Immunol Inflamm. 2018;26(6):845–852. [PubMed: 28665743]
32. Ahn SJ, Kim KE, Woo SJ, Park KH. The usefulness of interferon-gamma release assay for diagnosis of tuberculosis-related uveitis in Korea. Korean J Ophthalmol. 2014;28(3):226–233. [PubMed: 24882956]
33. Pathanapitoon K, Kunavisarut P, Sirirungsi W, Rothova A. Looking for Ocular Tuberculosis: Prevalence and Clinical Manifestations of Patients with Uveitis and Positive QuantiFERON ®-TB Gold Test. Ocul Immunol Inflamm. 2018;26(6):819–826. [PubMed: 27849401]
34. Agrawal R, Agarwal A, Jabs DA, et al. Standardization of Nomenclature for Ocular Tuberculosis - Results of Collaborative Ocular Tuberculosis Study (COTS) Workshop. Ocul Immunol Inflamm. 2019;1–11. Online ahead of print.
35. Agrawal R, Gunasekeran DV, Raje D, et al. Global Variations and Challenges With Tubercular Uveitis in the Collaborative Ocular Tuberculosis Study. Invest Ophthalmol Vis Sci. 2018;59(10):4162–4171. [PubMed: 30120485]
36. La Distia Nora R, van Velthoven ME, Ten Dam-van Loon NH, et al. Clinical manifestations of patients with intraocular inflammation and positive QuantiFERON-TB gold in-tube test in a country nonendemic for tuberculosis. Am J Ophthalmol. 2014;157(4):754–761. [PubMed: 24262781]
37. Ng KK, Nisbet M, Damato EM, Sims JL. Presumed tuberculous uveitis in non endemic country for tuberculosis: case series from a New Zealand tertiary uveitis clinic. Clin Experiment Ophthalmol. 2017;45(4):357–365. [PubMed: 27896896]
38. Caspi RR, Roberge FG, Chan CC, et al. A new model of autoimmune disease. Experimental autoimmune uveoretinitis induced in mice with two different retinal antigens. J Immunol. 1988;140(5):1490–1495. [PubMed: 3346541]
39. Fuge O, Vasdev N, Allchorne P, Green JS. Immunotherapy for bladder cancer. Res Rep Urol. 2015;7:65–79. [PubMed: 26000263]
40. Garip A, Diedrichs-Möhring M, Thurau SR, Deeg CA, Wildner G. Uveitis in a patient treated with Bacille-Calmette-Guérin: possible antigenic mimicry of mycobacterial and retinal antigens. Ophthalmology. 2009;116:2457–62.e1–2. [PubMed: 19815288]

41. Wertheim M, Astbury N. Bilateral uveitis after intravesical BCG immunotherapy for bladder carcinoma. Br J Ophthalmol. 2002;86(6):706. [PubMed: 12034701]
42. Guex-Crosier Y, Chamot L, Zografos L. Chorioretinitis induced by intravesical Bacillus Calmette-Guérin (BCG) instillations for urinary bladder carcinoma. Klin Monbl Augenheilkd. 2003;220(3):193–195. [PubMed: 12664378]
43. Uppal GS, Shah AN, Tossounis CM, Tappin MJ. Bilateral panuveitis following intravesical BCG immunotherapy for bladder carcinoma. Ocul Immunol Inflamm. 2010;18(4):292–296. [PubMed: 20662661]
44. Sharan S, Thirkill CE, Grigg JR. Autoimmune retinopathy associated with intravesical BCG therapy. Br J Ophthalmol. 2005;89(7):927–928. [PubMed: 15965187]
45. Burgoyne CF, Verstraeten TC, Friberg TR. Tuberculin skin-test-induced uveitis in the absence of tuberculosis. Graefes Arch Clin Exp Ophthalmol. 1991;229(3):232–236. [PubMed: 1869057]

HIGHLIGHTS

- Latent tuberculosis is more common in uveitis population than in general population
- Granulomatous uveitis is associated with positive QuantiFERON-TB Gold test.
- Being born/travel outside the US is associated with positive QuantiFERON test.
- Additional immunomodulatory treatment is needed despite TB treatment in most cases.

Table.

Comparison of demographic and clinical characteristics between QFT-G positive and negative patients

	Total (N=418)		QFT-G positive (N=60)		QFT-G negative (N=358)		OR	95% CI	P value
Median age in years (range)	45 (9–92)		50 (22–85)		44 (9–92)		1.02	1.00–1.04	.02
	N	**% [a]**	**N**	**% [a]**	**N**	**% [a]**			
Gender									
Male [b]	169	40.4	27	45	142	39.7			
Female	249	59.6	33	55	216	60.3	0.76	0.43–1.36	.36
Race/Ethnicity									
White (non-Hispanic) [b]	161	38.5	14	23.3	147	41.1			
Black	157	37.6	21	35	136	38	1.64	0.80–3.39	.18
Asian	47	11.2	15	25	32	8.9	5.15	2.24–11.84	<.001
White (Hispanic)	33	7.9	6	10	27	7.5	2.84	0.98–8.29	.06
Other	20	4.8	4	6.7	16	4.5	3.07	0.88–10.67	.08
Foreign Birth/Recent Travel [c]									
No [b]	161	58.5 [c]	16	26.7	145	67.4 [c]			
Yes	114	41.5 [c]	44	73.3	70	32.6 [c]	5.84	2.83–12.05	<.001
Laterality									
Unilateral [b]	168	40.2	24	40	144	40.2			
Bilateral	250	59.8	36	60	214	59.8	1.07	0.60–1.91	.82
Anatomic Location									
Anterior [b]	92	22	19	31.7	73	20.4			
Intermediate or anterior/ intermediate	86	20.6	7	11.7	79	22.1	0.46	0.18–1.21	.12
Posterior	127	30.4	15	25	112	31.3	0.67	0.31–1.47	.32
Pan	113	27	19	31.7	94	26.3	0.79	0.38–1.65	.53
Idiopathic Etiology									
No [b]	167	40	19	31.7	148	41.3			
Yes	251	60	41	68.3	210	58.7	1.39	0.76–2.54	.29
Uveitis characteristics [d]									
Granulomatous	43	10.3	13	21.7	30	8.4	2.90	1.36–6.21	.006
Choroiditis	80	19.1	9	15	71	19.8	0.86	0.39–1.87	.70
Retinal vasculitis	115	27.5	12	20	103	28.8	0.65	0.32–1.30	.22
Occlusive vasculitis	25	6	5	8.3	20	5.6	1.48	0.51–4.29	.48
Serpiginous choroiditis	10	2.4	2	3.3	8	2.2	2.57	0.47–14.20	.280

QFT-G, Quantiferon-TB Gold test. OR, odds ratio.

[a] % within columns.

[b] Reference category for multivariable logistic regression analyses.

[c] Travel and birth history data were available in all QFT-G positive patients but in 215 patients who were QFT-G negative. Percentages and OR were calculated for patients with available data.

[d] Uveitis characteristics typically associated with TB-uveitis are listed. These characteristics are not mutually exclusive.