Prevalence of Positive QuantiFERON-TB Gold In-Tube Test in Uveitis and its Clinical Implications in a Country Nonendemic for Tuberculosis

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• PURPOSE: To report on the prevalence and clinical implications of positive QuantiFERON-Gold (QFT-G) test results in the diagnostic evaluation of a large cohort of consecutive patients with uveitis in the Netherlands.

• DESIGN: Retrospective cross-sectional study.

• METHODS: This study included 710 consecutive patients who all underwent evaluation for uveitis including QFT-G testing. The ocular features, comorbidity, and abnormalities in diagnostic imaging and laboratory tests were registered for QFT-G–positive patients with uveitis.

• RESULTS: Of all patients, 13% (92/710) were positive for QFT-G. Previously treated tuberculosis (TB) was documented in 2 patients. Of all 92 QFT-G–positive patients, culture-proven active TB was observed in 1 case. The proportion of patients with uveitis of unknown etiology was higher in QFT-G–positive than in the QFT-G–negative patients (54/92, 59% vs 238/618, 39%; P = .0004). The uveitis features of QFT-G–positive patients were mainly nonspecific. Of all QFT-G–positive patients with uveitis, 17 patients had chest imaging changes suggesting either TB or sarcoidosis. Twenty-nine QFT-G–positive patients with otherwise unexplained uveitis completed antituberculous therapy (29/710; 4% of all included patients) with beneficial effect in most cases.

• CONCLUSION: The QFT-G tested positive in 13% of patients with uveitis in the Netherlands, whereas only sporadic patients had a documented previous or active TB infection. The proportion of patients with unexplained uveitis was higher in QFT-G–positive patients. Though the association between uveitis and a positive QFT-G test might be coincidental, the majority of treated QFT-G–positive patients with otherwise unexplained severe uveitis cause had a beneficial response to antituberculous therapy. (Am J Ophthalmol 2019;■:■–■. © 2019 Elsevier Inc. All rights reserved.)

U VEITIS MAY COMPLICATE AN ACTIVE TUBERCU-losis (TB) infection, but uveitis has often been reported to develop in patients with latent TB infections. The link between a latent TB infection and the development of uveitis was initially based on multiple case reports and a beneficial response of uveitis activity to antituberculous treatment (ATT) in a proportion of QuantiFERON-GOLD (QFT-G)–positive patients (Cellestis Limited, Carnegie, Victoria, Australia) with otherwise unexplained uveitis.[1–8] Two recent prospective studies demonstrate an excess of idiopathic uveitis in the QFT-G–positive but otherwise healthy population, which favors a genuine link between uveitis and latent TB.[9,10]

The pathogenesis of uveitis in the setting of TB infection is not yet entirely understood. Active infection as well as immune-mediated reactions in the absence of replicating bacteria have both been suggested to play a role.[1,9,10] Broncheoalveolar studies in a cohort of 109 patients with the positive tuberculin skin test and uveitis of undetermined cause have not demonstrated any active TB infection.[11] In contrast, cultures positive for *Mycobacterium tuberculosis* were documented from lymph nodes detected on chest imaging in some QFT-G–positive patients with uveitis (but without any systemic complaints).[12] Polymerase chain reaction (PCR) studies in intraocular fluid samples of patients with (presumed) TB-related uveitis was only occasionally positive for M tuberculosis.[13]

Patients with uveitis who are otherwise healthy and who test positive on an interferon gamma release assay cause a diagnostic and therapeutic dilemma. Uveitis in these patients might be related to their TB infection but could also be coincidental. The ocular characteristics previously related to latent TB-associated uveitis are serpiginous-like choroiditis, multifocal choroiditis, and retinal occlusive vasculitis.[1,4,14–18]

Most studies on uveitis in QFT-G–positive patients have included predominantly patients who have signs that are suggestive for TB-associated uveitis. The purpose of our study is to determine the prevalence of positive QFT-G

testing in a large number of consecutive patients with uveitis in a nonendemic country and to report on the ocular and systemic features of patients with positive QFT-G tests.

METHODS

• PARTICIPANTS: Participants were adult patients with uveitis who underwent a diagnostic evaluation at the Erasmus University Medical Center in Rotterdam, The Netherlands, between January 2011 and July 2017. The medical ethical committee of Erasmus University Medical Center approved this retrospective cross-sectional study.

• ASSESSMENT OF CLINICAL CHARACTERISTICS: Anatomical classification of uveitis was performed according to the Standardization of Uveitis Nomenclature Working Group.[19] The diagnostic evaluation of uveitis patients includes erythrocyte sedimentation rate, C-reactive protein, a complete blood cell count, serum angiotensin-converting enzyme (ACE; cut-off 68 U/mL), and syphilis serology. In patients with anterior uveitis and panuveitis, human leukocyte antigen B27 was determined.

The QFT-G was introduced in the standard evaluation for uveitis in 2010 in our center (regardless of anatomic localization of uveitis and irrespective of a suspicion of TB-associated uveitis). QFT-G was considered positive according to the manufacturer's instructions ($\geq$0.35 IU/mL).

The cause of uveitis was determined after the relevant diagnostic tests were performed and subsequently patients with uveitis were classified according to their QFT-G test result. Patients with uveitis of unknown cause despite the diagnostic evaluation but who had positive QFT-G test results were still classified as uveitis of unknown cause and separately indicated. Medical records of QFT-G–positive patients with uveitis were further investigated for systemic and ocular characteristics.

• ASSESSMENT OF CLINICAL CHARACTERISTICS IN QFT-G–POSITIVE PATIENTS: A definitive diagnosis of TB-associated uveitis was made in patients with active systemic TB proven by a positive microbiology test anywhere in the body and without any other explanation of uveitis.[13,14,19,20] After exclusion of other causes of uveitis, presumed active TB was diagnosed in 4 patients without positive culture and/or PCR sequencing, but with positive QFT-G test and clinical features typical of active TB disease (ie, constitutional symptoms, such as fevers, night sweats, and weight loss, as well as pulmonary and extrapulmonary signs suggesting active TB).[20] Previous TB was defined as a history of documented treatment for TB. In our uveitis population, latent TB was considered in patients with positive QFT-G tests who were otherwise healthy and who did not exhibit signs of active TB.

A definitive diagnosis of sarcoidosis was considered in biopsy-confirmed cases in which other granulomatous diseases were excluded. Presumed sarcoidosis was considered in patients with chest imaging consistent with the diagnosis of sarcoidosis.

Serpiginous-like choroiditis was defined as patients with multiple serpiginous-like chorioretinal lesions not located adjacent to the optic disc.[21–23]

Results of ACE and soluble interleukin-2 receptor (sIL-2R), if available, were also registered. Systemic comorbidities and outcomes of tissue biopsy specimens (whenever performed) were noted.[24]

Chest imaging was reviewed for all QFT-G–positive patients by 2 pulmonologists. This included 75 chest radiographs, 35 computed tomography scans, and 10 somatostatin receptor scintigraphy scans. Five of the computed tomography scans of the chest (14%) were combined with fluor-18-deoxyglucose (FDG) positron emission tomography (PET) scanning.

Chest imaging findings consistent with the diagnosis of sarcoidosis were defined as symmetrical bilateral hilar and subcarinal lymph node enlargement and/or interstitial lung patterns (eg, micronodules with a typical perilymphatic distribution and upper lobe predominance).[25,26] Findings suggestive of active TB were defined as parenchymal infiltrates (typically apical and posterior segments of the upper lobes or superior segments of the lower lobes) with or without cavitary lesions or unilateral hilar and/or mediastinal lymphadenopathy. Findings suggestive of healed TB were fibrotic scars, nodules with calcification, and pleural thickening (with or without calcification).[19,25]

All patients with (presumed) active TB were given ATT as well as all QFT-G–positive patients with severe, sight threatening uveitis in whom no other cause of uveitis could be established. ATT consisted of 3 drugs for patients with severe uveitis and a positive QFT-G test and no systemic localization of TB infection: isoniazid, rifampicin, and pyrazinamide for 2 months, followed by isoniazid and rifampicin for an additional 4 months. Patients with uveitis and evidence of active TB disease elsewhere also received ethambutol until isoniazid sensitivity was proven, according to national guidelines. In addition, QFT-G–positive patients (with established diagnoses other than TB) in anticipation of steroid-sparing agents also underwent ATT consisting of only rifampicin and isoniazid for 4 months to prevent reactivation of latent TB according to national guidelines.[27]

The threshold for the definition of a TB-endemic country was defined as an incidence of >50 cases per 100,000 population, according to the Dutch Guideline definition for TB risk groups.[28,29]

• STATISTICAL ANALYSIS: The mean, standard deviation, and range are reported for continuous measures. For categorical measures, percentages are reported, and the comparisons are performed using either the χ^2 or Fisher exact

TABLE 1. General Characteristics of Uveitis Patients

	Total (N = 710)	Positive QFT-G Test (n = 92)	Negative QFT-G Test (n = 618)
Race, n (%)			
Nonwhite	237 (33)	58 (63)	179 (29)
White	473 (67)	34 (37)	439 (71)
Gender, n (%)			
Male	258 (36)	41 (45)	217 (35)
Female	452 (64)	51 (55)	401 (65)
Anatomic localization, n (%)			
Anterior	186 (26)	19 (21)	167 (27)
Intermediate	62 (9)	3 (3)	59 (10)
Posterior	193 (27)	25 (27)	168 (27)
Panuveitis	231 (33)	40 (43)	191 (31)
Scleritis	38 (5)	5 (5)	33 (5)
Associated systemic disease (noninfectious), n (%)	251 (36)	19 (21)	232 (38)
Sarcoidosis (biopsy proven)	75 (30)	1 (5)	74 (32)
Sarcoidosis (presumed)	37 (15)	6 (32)	31 (13)
Infection, n (%)	71 (9)	7 (8)[a]	64 (10)
Clinical entity, n (%)	96 (14)	12 (13)	84 (14)
Masquerade syndrome[b]	30 (31)	6 (50)	24 (29)
Unknown cause, n (%)	292 (41)	54 (59)[b]	238 (39)[c]

QTF-G = QuantiFERON-TB Gold; TB = tuberculosis.

[a]Including presumed active tuberculosis (n = 4), active tuberculosis (n = 1), and toxoplasmosis (n = 2).

[b]Including vitreoretinal lymphoma (n = 6), retinal vascular occlusions (n = 4), drusen (n = 2),degenerative vitreous floaters (n = 2), macular dystrophy (n = 3), myopic degeneration (n = 2), retinitis pigmentosa (n = 2), Coats' disease (n = 1), ocular ischemic syndrome (n = 1), hypertensive retinopathy (n = 1), chronic serous chorioretinopathy (n = 1), idiopathic intracranial hypertension (n = 1), retinal macroaneurysm (n = 1), optic neuritis (n = 1), idiopathic macular telangiectasia (n = 1), and optic atrophy (n = 1).

[c]The proportion of uveitis with unknown etiology was higher in QFT-G–positive than in QFT-G–negative patients (54/92 [59%] vs 238/618 [39%]; P = .0004).

tests. All P values were 2-tailed, and statistical significance was set at P < .05.

RESULTS

THE GENERAL CHARACTERISTICS OF OUR UVEITIS POPULA-tion according to their QFT-G test results are shown in Table 1. The population consisted mostly of white patients (67%) with a slight female predominance (64%). Ninety-two patients of 710 (13%) tested positive for QFT-G. QFT-G–positive patients were more often of nonwhite origin (58/92; 63%) compared with QFT-G–negative patients (179/618 [29%]; P = .0001) but did not differ in gender (P = .08).

The proportion of uveitis with unknown etiology was higher in QFT-G–positive than in QFT-G–negative patients (54/92 [59%] vs 238/618 [39%]; P = .0004). Anatomic classification of uveitis was similar in QFT-G–positive and QFT-G–negative patients, but panuveitis was more common in QFT-G–positive patients (40/92 [43%] vs 191/618 [31%]; P = .02).

Overall, 38% of QFT-G–positive patients were born outside the Netherlands in a TB-endemic country (Table 2). Age did not correlate with the QFT-G levels (Spearman ρ correlation coefficient −0.134, P = .203). The median QFT-G value of QFT-G–positive patients was 3.45 U/mL (interquartile range [IQR] 9.8) and was different in QFT-G–positive patients with a known cause of uveitis when compared with the remainder of QFT-G–positive patients with uveitis (0.8 U/mL [IQR 8.5] vs 6.8 U/mL [IQR 11.5]; P = .06).

The characteristics of patients with QFT-G–positive uveitis are shown in Table 2. Documented previous TB was observed in 2 patients who received full ATT before developing uveitis (1 patient had human leukocyte antigen B27–associated uveitis and 1 patient had uveitis of unknown cause). Active TB was diagnosed in 1 patient and presumed active TB was diagnosed in 4 patients. The etiology of uveitis, other than (presumed) TB or sarcoidosis, was established in 26 of 92 (28%) of QFT-G–positive patients; no cause was identified in 54

TABLE 2. Characteristics of Patients with Uveitis Positive in QuantiFERON-TB Gold Test

	Positive QFT-G Test			
	Total (N = 92)	Uveitis of Unknown Origin (n = 54)	(Presumed) TB or Sarcoidosis (n = 12)[a]	Uveitis with an Established Cause Other than TB or Sarcoidosis (n = 26)[b]
Mean age at uveitis onset, years (±SD)	46.1 (±15.5)	45.8 (±15.2)	48.2 (±17.3)	45.9 (±15.2)
Race, n (%)				
Nonwhite	57 (62)	35 (65)	8 (67)	14 (54)
White	35 (38)	19 (35)	4 (33)	12 (46)
Gender, n (%)				
Male	41 (45)	21 (39)	3 (25)	17 (65)
Female	51 (55)	33 (61)	9 (75)	9 (35)
Laterality, n (%)				
Unilateral	37 (40)	22 (41)	4 (33)	11 (42)
Bilateral	55 (60)	32 (59)	8 (67)	15 (58)
Anatomic localization, n (%)				
Anterior	19 (21)	11 (20)	4 (33)	4 (15)
Intermediate	3 (3)	2 (4)	1 (8)	0
Posterior	25 (27)	13 (24)	1 (8)	11 (42)
Panuveitis	40 (43)	23 (43)	6 (50)	11 (42)
Scleritis	5 (5)	5 (9)	0	0
Specific ocular manifestations, n (%)				
Occlusive vasculitis	7 (8)	6 (11)	0	1 (4)[c]
Serpiginous-like choroiditis	5 (5)	4 (7)	1 (8)	0
Serpiginous choroiditis	2 (2)	2 (4)	0	0
Born outside the Netherlands,[d] n (%)	55 (60)	36 (67)	4 (33)	15 (58)
In TB-endemic country	35 (38)	25 (46)	1 (8)	9 (35)
In country nonendemic for TB	20 (22)	11 (20)	3 (25)	6 (23)
Born in the Netherlands,[d] n (%)	34 (37)	17 (31)	6 (50)	11 (42)
Stay >6 months in TB-endemic area	4 (12)	4 (24)	0	0
QFT-G value >5.0,[e] n (%)	39 (45)	25 (46)	6 (50)	8 (31)
Median QFT-G value, U/mL (IQR)	3.45 (9.8)	4.2 (10.7)	4.6 (9.0)	0.8 (8.5)

IQR = interquartile range; QFT-G = QuantiFERON-TB Gold; SD = standard deviation; TB = tuberculosis.

[a]Includes 1 patient with active TB. The patient with active TB-associated uveitis presented at 26 years of age with tuberculous psoas abscess (proven by cultures and polymerase chain reaction study) and uveitis for which he received full anti-TB treatment. Chest imaging during this period showed bilateral hilar lymphadenopathy. Four and a half years after the onset, he developed a recurrence of his uveitis and an abnormal mucosal lesion in his nose. A biopsy specimen was obtained, and it showed noncaseating granulomatous inflammation consistent with the diagnosis of sarcoidosis while polymerase chain reaction sequencing for Mycobacterium spp and cultures remained negative. Subsequent evaluation by a pulmonologist confirmed also pulmonary involvement with symmetrical hilar and mediastinal lymphadenopathy seen on a computed tomography scan of the chest. A biopsy specimen of the pulmonary lymph nodes showed granulomatous inflammation without any evidence of M tuberculosis (negative culture and polymerase chain reaction sequencing). The soluble interleukin-2 receptor level was 8258 pg/mL.

[b]This group consisted of Behçet disease (n = 4), human leukocyte antigen B27–associated uveitis (n = 4), Vogt-Koyanagi-Harada syndrome (n = 3), toxoplasmosis (n = 2), birdshot chorioretinopathy (n = 2), sympathetic ophthalmia (n = 1), lens-induced uveitis (n = 1), acute zonal occult outer retinopathy (n = 1), multiple sclerosis–associated uveitis (n = 1), and masquerade syndrome (n = 7).

[c]This one patient had occlusive vasculitis because of Behçet disease.

[d]Unknown place of birth in 3/92 (3%) of patients and unknown if the patient stayed in an TB endemic in 7/92 (8%).

[e]Exact values were not available in 10 patients.

patients and the remaining 12 patients were diagnosed with (presumed) TB or sarcoidosis (Table 2). The ocular features of QFT-G–positive patients with uveitis of undetermined cause (n = 54) were generally nonspecific. Serpiginous-like lesions were seen in 4 of 54 [7%] and occlusive vasculitis in 6 of 54 [11%], of which 3 were men between 30 and 45 years of age. Patients with serpiginous-like lesions and/or occlusive vasculitis had similar QFT-G levels compared with the remaining QFT-G–positive patients (≥5.0 IU/mL in 6/13 [46%] vs 33/79 [42%]; P = .77).

ATT was initiated in 36 QFT-G–positive patients with severe uveitis of unknown origin. Of these, 7 did not complete ATT because of side effects resulting in 29 of 36

TABLE 3. Chest Imaging and Laboratory Results in Patients with Uveitis Positive in QuantiFERON-TB Gold Test

	Total (N = 92)	Positive QFT-G Test		
		Uveitis of Unknown Origin (n = 54)	(Presumed) TB or Sarcoidosis (n = 12)	Uveitis with an Established Cause Other than TB or Sarcoidosis (n = 26)
Total imaging available, n (%)	78 (85)	50 (93)v	12 (100)	16 (62)
Total chest imaging consistent with sarcoidosis and/or TB[a]	17 (22)	5 (10)	12 (100)	0
Tissue biopsy available, n (%)	9 (10)[b]	4 (7)	4 (33)	1 (4)
Consistent with TB	0	0	0	0
Consistent with sarcoidosis	1 (100)	0	1 (33)[c]	0
ACE available, n (%)	73 (79)	43 (80)	12 (100)	18 (69)
ACE ≥68 U/L	14 (19)	7 (16)	6 (50)	1 (6)
sIL-2R available, n (%)	43 (47)	29 (54)	9 (75)	5 (19)
sIL-2R ≥4000 pg/mL	21 (49)	10 (34)	9 (100)	2 (40)

ACE = angiotensin-converting enzyme; QFT-G = QuantiFERON-TB Gold; sIL-2R = soluble interleukin-2 receptor; TB = tuberculosis.

[a]Of these, 11 were detected by positron emission tomography/computed tomography scan, 1 by somatostatin receptor scintigraphy scan, 3 with both radiography and positron emission tomography/computed tomography scan of the chest, and 2 by both positron emission tomography/computed tomography scan of the chest and somatostatin receptor scintigraphy scan.

[b]Including biopsy of hilar lymph nodes (n = 5), histologic examination of enucleated eye (n = 2), lymph node located in the neck (n = 1), and skin biopsy (n = 1).

[c]This patient was diagnosed with sarcoidosis by biopsy of hilar lymph nodes which showed granulomatous inflammation, negative polymerase chain reaction sequencing for *Mycobacterium tuberculosis* spp, negative tuberculosis culture, and negative auramine stains. The biopsy specimen obtained from the patient with active TB who was later diagnosed with sarcoidosis was not taken into account in this table, as histologic evidence of sarcoidosis was gained after treatment for TB.

patients who completed ATT (81% of all with intention to treat; 29/54 [54%] of all QFT-G–positive patients with uveitis of unknown etiology).

Of 29 fully treated patients,16 (55%) were without uveitis activity at the time of ATT completion and 20 (69%) were quiet at 1 year of follow-up. However, 12 (41%) needed systemic immunomodulatory drugs and/or periocular corticosteroid injections during ATT because of their ongoing uveitis activity. Of nontreated QFT-G–positive patients with uveitis of unknown origin, 13 (100%) patients (followed for ≥1 year after QFT-G testing) were without inflammatory activity at 1 year of follow-up and 7 (58%) patients (followed for ≥18 months after QFT-G testing) were without inflammatory activity at 18 months of follow-up. Nevertheless, 5 (42%) patients needed systemic immunomodulatory drugs and/or periocular corticosteroid injections in this period because of their ongoing uveitis activity.

Abnormal radiologic features suggesting the diagnosis of sarcoidosis and/or TB were observed in 17 of 66 (26%) of QFT-G–positive patients with an undetermined cause of uveitis (Table 3). Four patients had a biopsy specimen obtained from their enlarged hilar lymph nodes, but none of the tests performed was positive for M tuberculosis (negative PCR for M tuberculosis spp and negative cultures and/or stains). FDG accumulation was observed in the mediastinal or hilar lymph nodes in all 5 performed

FDG-PET/computed tomography scans. Of these, 3 fulfilled the criteria for the diagnosis of sarcoidosis and 1 had intraocular lymphoma. The remaining patient was diagnosed with presumed active TB and showed nonspecific intrathoracic and intraabdominal generalized lymphadenopathy. The QFT-G level in this patient was 15.18 IU/mL and the sIL-2R level was elevated (6200 pg/mL). A biopsy specimen of the pulmonary lymph nodes was obtained, and the specimen revealed an absence of granulomatous inflammation and negative results for M tuberculosis.

Serum ACE was elevated in 14 of 73 (19%) patients and sIL-2R was elevated in 21 of 43 [49%] of QFT-G–positive patients. Serum ACE and QFT-G test levels were associated with each other (Spearman ρ correlation coefficient 0.294; P = .004, 2-sided); sIL-2R and QFT-G test levels were not (Spearman ρ correlation coefficient 0.091; P = .39).

DISCUSSION

THIS RETROSPECTIVE STUDY REVEALED POSITIVE QFT-G test results in 13% of a large Dutch uveitis cohort, of which only few had (presumed) active TB. An excess

of unexplained uveitis was observed in QFT-G–positive patients, suggesting an association between latent TB infection and uveitis at least in a part of QFT-G–positive patients.

Only 1 patient in the QFT-G–positive group had concurrent culture-proven TB, which is similar to other studies from non–TB-endemic countries.[30] In 54 of 92 (59%) of QFT-G–positive patients, no cause for uveitis could be identified and therefore their uveitis could be related to a previous TB infection.

A positive QFT-G test indicates a true infection with M tuberculosis but cannot distinguish between active and latent TB infections. The laboratory discrimination between these 2 conditions is currently not feasible. Therefore, the mere presence of a positive QFT-G test is not enough evidence for causation. Especially in endemic countries, the prevalence of positive QFT-G is high and the association with uveitis can be coincidental. Also in countries that are nonendemic for TB, a high prevalence ($\leq$23%) of QFT-G positivity in the uveitis population was observed; howevern these studies included predominantly patients with clinical suspicion of ocular TB.[12,31–34] Nonetheless, a disproportionally high prevalence of QFT-G–positive uveitis patients was observed in the present series, even higher than reported in Dutch high-risk groups (0.01% in high-risk groups, eg, TB contacts).[35,36]

The pathogenesis of uveitis in the setting of latent TB infection is not yet entirely understood. Active TB infection affecting the eye was repeatedly suggested, which is supported by previous studies that demonstrated positive M tuberculosis cultures in lymph nodes of QFT-G–positive patients with uveitis without any other symptoms, suggesting active extraocular TB. However, cultures and/or PCR on ocular fluid samples remain negative in most cases and Mycobacteria are typically difficult to find by histologic examination, reflecting that ocular TB represents a paucibacillary inflammation.[37] Therefore, the diagnosis of presumed ocular TB was proposed in the presence of ocular findings suggestive of tuberculosis (ie, choroidal granuloma, broad-based posterior synechiae, retinal vasculitis with or without choroiditis, or serpiginous-like choroiditis) combined with evidence of replicating bacilli elsewhere in the body.[38] However, most of our QFT-G–positive patients did not fulfill these clinical ocular criteria, which might be explained by inclusion bias of previous studies. Our study encompassed all consecutive patients with uveitis, which might explain a relative lack of ocular signs typical for presumed TB. This phenomenon was also noted in prospective studies from endemic countries.[9,10] An alternative theory about the pathogenesis in TB-associated uveitis is an immune reaction to TB antigens and subsequent cross-reaction with ocular antigens causing autoimmunity, though the evidence of such process is lacking.[39]

Chest imaging suggesting the diagnosis of TB and/or sarcoidosis in was noted in 17 (18%) of QFT-G–positive patients, but our results do not provide information about the infectious or noninfectious causes of these abnormalities. The presence of pulmonary changes suggesting sarcoidosis might be explained by the fact that sarcoidosis can be triggered by persistent presentation of poorly degradable antigens, including M tuberculosis, and the subsequent host response to it.[40–43]

A positive QFT-G test in a patient with uveitis does not confirm that uveitis is of TB origin. Hence, a response to ATT might aid in the diagnosis of TB-associated uveitis.[38] However, ATT represents a lengthy treatment and might be associated with adverse effects. In our institution, all patients with active extraocular TB receive ATT and we recommend ATT to all QFT-G–positive patients with severe and sight-threatening uveitis. In the remaining cases with uveitis not responding to local treatment, a shared decision with the patient regarding ATT is taken. Herein, the ophthalmologist explains the possible (but not certain) relationship of uveitis and TB, informs the patient about the potential cure of uveitis with ATT, and discusses the possible adverse effects. The patient decides whether he or she will undergo the treatment. In consequence, the exact efficacy of ATT treatment in our study cannot be reliably evaluated: only patients with severe uveitis received ATT, and the numbers of QFT-G–positive patients treated with ATT were limited. In consequence, QFT-G–positive patients who did not receive ATT had milder uveitis, which might explain their beneficial outcomes. Our study is limited by the retrospective collection of data and the variable length of follow-up. As in all retrospective studies, the heterogeneity of investigations was documented and there were no systematic indications for performing computed tomography scans and biopsy procedures. The strength of our study lies in the large cohort of consecutive patients with uveitis tested by QFT-G, without a selection of patients with clinical suspicion of ocular TB. The results of QFT-G testing are also relevant for further management of patients with uveitis who require systemic immunosuppressive treatment regimens, such as biologic drugs.

In conclusion, the major findings of this study include the high prevalence of 13% of positive QFT-G tests in a Dutch uveitis population and an excess of unexplained uveitis in QFT-G–positive patients. We conclude that QFT-G testing is useful in the evaluation for uveitis in nonendemic countries because the QFT-G–positive patients with uveitis of otherwise unexplained origin might benefit from ATT, especially those with severe and sight-threatening uveitis.

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