SCIENTIFIC REPORT

Inflammatory ocular hypertension syndrome (IOHS) in patients with syphilitic uveitis

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Aim: To determine the prevalence and clinical characteristics of the inflammatory ocular hypertension syndrome (IOHS) in patients with uveitis and serological evidence of syphilis.

Methods: A retrospective, observational case review of 39 consecutive patients with uveitis and serological evidence of syphilis was carried out between January 1977 and December 2001. Other causes of uveitis were excluded. The prevalence and clinical characteristics of IOHS among patients with uveitis and serological evidence of syphilis were documented. IOHS was defined as an increase in intraocular pressure (IOP) of more than 21 mm Hg that began at the onset of acute, recurrent, or chronic anterior chamber inflammation and reversed promptly with appropriate anti-inflammatory or antimicrobial treatment.

Results: Of the 39 patients with uveitis and serological evidence of syphilis, eight eyes from seven patients (18%) presented with IOHS, a significantly higher prevalence than in the uveitis population at large (2.3%; $p<0.001$). Best-corrected visual acuity varied from 20/20 to 20/200, with a median of 20/40, and three of the eight eyes (37.5%) had granulomatous features, including large keratic precipitates and, in two eyes, Koeppe nodules. Intraocular pressure varied from 23 to 51 mm Hg, with a mean of 36 and a median of 34. One patient had bilateral IOHS.

Conclusions: Syphilitic uveitis should be included in the differential diagnosis of IOHS along with more commonly recognised causes.

Although uveitis is most typically associated with acutely decreased intraocular pressure (IOP), because inflammation of the ciliary body causes decreased aqueous humour production, raised IOP can also occur.[1–4] Mechanisms of acutely raised IOP in patients with uveitis are multiple but can include pupillary seclusion with iris bombé producing angle closure, peripheral anterior synechiae formation limiting outflow, anterior displacement of the iris root in the setting of exudative detachment of the ciliary body, and direct inflammation of the trabecular meshwork that can lead to a phenomenon previously described as the inflammatory ocular hypertension syndrome (IOHS).[3] This is defined as an acute and transient increase in intraocular pressure in the setting of acute or recurrent inflammation, which responds readily to anti-inflammatory or antimicrobial therapy, or both. Well known causes of IOHS include herpetic anterior uveitis[5 6] and the Posner-Schlossman syndrome.[7] Other less common causes include sarcoid uveitis,[8 9] toxoplasmic retinochoroiditis,[10 11] listeria endophthalmitis,[12] and cytomegalovirus infection.[13] Although secondary glaucoma has been well described in patients with longstanding uveitis due to syphilis,[4 14] we are unaware of any previous reports describing the occurrence of the IOHS in patients with uveitis and serological evidence of syphilis. We describe the prevalence and clinical characteristics of IOHS in a cohort of patients with uveitis and positive syphilis serology seen over a 25 year period at the Francis I Proctor Foundation.

METHODS

Institutional review board/ethics committee approval was obtained for collection and review of patient data from a database containing the clinical findings of all patients seen in the uveitis clinic at the Francis I Proctor Foundation of the University of California at San Francisco between January 1977 and December 2001. We reviewed the records of consecutive patients at their initial presentation with acute, recurrent, or chronic uveitis, positive syphilis serology, and no other identified causes. Demographic, clinical, and laboratory data were analysed for all patients. Clinical presentation of the patient's anterior uveitis was characterised as either mild (trace to 1+ cells), moderate (2+ cells), or severe (3–4+ cells). The clinical presentation was identified as acute if the symptoms began for the first time within the previous three months, chronic if they had been present continuously for more than three months, and recurrent if they had onset again after a symptom-free interval of more than three months. Patients with uveitis, serological evidence of syphilis, and no other identifiable cause for their inflammation were included in the study. Inflammatory ocular hypertension syndrome was defined as a raised IOP of more than 21 mm Hg that began at the onset of anterior chamber inflammation documented initially at our institution or at the referring centre before the initiation of anti-inflammatory treatment, and the increase in IOP must have reversed readily with appropriate anti-inflammatory or antimicrobial therapy or both.[3]

Patients with concurrent vesicular or follicular conjunctivitis, evidence of previous or active herpetic keratitis, decreased corneal sensation, or patchy or sectoral iris atrophy were presumed to have herpetic anterior uveitis and were excluded from the review. Patients with markedly narrowed angles or angles with extensive peripheral anterior synechiae formation or iris seclusion were also excluded in all groups, thereby excluding other possible causes of uveitic glaucoma.

All patients with the IOHS underwent a chest *x* ray, purified protein derivative (PPD) skin test with placement of controls, and serum angiotensin converting enzyme (ACE) testing. All patients with positive syphilis serology were subsequently started on intravenous penicillin for intraocular involvement. Differences in proportions among those with and without the IOHS were compared using a χ^2 or Fisher's exact test statistic. The Student test statistic was used for comparison of the means of the age of onset. Probability (p) values <0.05 were considered statistically significant.

Abbreviations: FTA-ABS, fluorescent treponomal antibody absorbed; IOHS, inflammatory ocular hypertension syndrome; IOP, intraocular pressure; RPR, rapid plasma reagin; VDRL, Venereal Disease Research Laboratory

Table 1 Inflammatory ocular hypertension syndrome in patients with uveitis and positive syphilis serology

Case/age/sex/race	Visual acuity	Eye involved	Clinical features of the uveitis	IOP (mm Hg)	Serology
1/55/M/latino	OD 20/50 OS 20/20	OD	Mild, chronic, anterior, granulomatous uveitis with large keratic precipitates and scattered posterior synechiae	OD: 51	+FTA-ABS +RPR
2/58/F/black	OD 20/200 OS 20/20	OD	Severe acute, anterior non-granulomatous uveitis	OD: 31	+FTA-ABS +VDRL
3/40/M/black	OD 20/20 OS 20/20	OD	Mild, acute, anterior, granulomatous uveitis with large keratic precipitates and scattered Koeppe nodules	OD: 30	+FTA-ABS +RPR
4/79/M/white	OD 20/70 OS 20/100	Both	OD: Moderate, acute, anterior non-granulomatous uveitis OS: Mild, acute, anterior, non-granulomatous uveitis with scattered posterior synechiae	OD: 50 OS: 34	+FTA-ABS
5/42/M/Indian	OD 20/20 OS 20/80	OS	Mild, recurrent, anterior, non-granulomatous uveitis.	OS: 34	+FTA-ABS
6/61/M/Japanese	OD 20/200 OS 20/20	OD	Mild, recurrent, anterior non-granulomatous uveitis. Cataract OD	OD: 34	+FTA-ABS
7/45/F/white	OD 20/25 OS 20/25	OS	Moderate, acute, anterior granulomatous uveitis with large keratic precipitates and scattered Koeppe nodules	OS: 23	+FTA-ABS

F, female; FTA-ABS, fluorescent treponomal antibody absorbed; M, male; OD, right eye; OS, left eye; RPR, rapid plasma reagin; VDRL, Venereal Disease Research Laboratory.

RESULTS

Eight eyes in seven of the 39 consecutive patients (18.0%) with uveitis and serological evidence of syphilis had a raised IOP of more than 21 mm Hg at the onset of inflammation which reversed readily with appropriate anti-inflammatory or anti-microbial therapy (table 1). This was significantly higher than the proportion of patients with the IOHS from any cause in the uveitis population at large (61 of 2706, 2.3%; $p<0.001$). Among the 39 patients with positive syphilis serology, the age of onset of those with the IOHS tended to be older than in those without the IOHS, although the sample sizes were small and the difference failed to achieve statistical significance ($p<0.14$) (table 2). Race and sex did not appear to differ significantly between the two groups ($p<1$). We had the following reasons for believing that all the patients had syphilitic uveitis: first, all the patients had positive FTA-ABS; second, 43% had either a positive RPR or a positive VRDL (more than the 8% reported by Barile and Flynn[15] in their patients with syphilitic uveitis); third, tests for other causes of uveitis were negative; and fourth, none of our patients had clinical evidence of herpetic anterior uveitis. While the diagnosis of the Posner–Schlossman syndrome could not be excluded with absolute certainty in the three patients with unilateral non-granulomatous anterior uveitis, this diagnosis would be considered extremely atypical in the four patients with either bilateral or granulomatous anterior inflammation.

Table 2 The entire cohort of patients with uveitis and serological evidence of syphilis

	IOHS	Without IOHS	p Value
Mean age (years)	53	40.5	<0.14
Sex			
Female	2 (28.6%)	16 (50%)	<1
Male	5 (71.4%)	16 (50%)	
Anterior pattern			
Granulomatous	2 (28.6%)	12 (37.5%)	<1
Non-granulomatous	5 (71.4%)	20 (62.5%)	
Location			
Anterior	7 (100%)	6 (18.8%)	<0.01
Diffuse	0	21 (65.6%)	
Posterior	0	4 (12.5%)	
Intermediate	0	1 (3.1%)	
Race			
Black	2 (28.6%)	11 (34.4%)	<1
White	2 (28.6%)	17 (53.1%)	<1
Hispanic	1 (14.3%)	1 (3.1%)	<1
Other	2 (28.6%)	3 (9.4%)	<1

IOHS, inflammatory ocular hypertension syndrome.

Vision at presentation varied from 20/20 to 20/200, with a median of 20/40. Three of eight eyes (37.5%) with IOHS had inferiorly distributed large, or ''granulomatous'', keratic precipitates, and two of these three eyes also had Koeppe nodules. The mean and median intraocular pressures of the eight eyes with IOHS were 36 mm Hg and 34 mm Hg, respectively (range 23 to 51). One patient had IOHS bilaterally. In each case, the IOP improved with topical corticosteroids and eventually returned to normal off all medication as the inflammation subsided. IOP lowering agents were used transiently in selected patients while the inflammation was being controlled, in order to shorten the duration of extreme elevations in pressure. Subsequent attempts to contact the patients for further follow up were unsuccessful and we were unable to determine the precise duration of inflammation in our retrospective review.

DISCUSSION

The annual incidence of primary and secondary syphilis in immunocompetent individuals declined steadily in the 1990s, only to experience a resurgence in the past few years.[16] Known as the ''great imitator'', syphilis may produce a variety of ocular complications, including interstitial keratitis, vitritis, vasculitis, retinitis, neuroretinitis, and serous retinal detachments.[15 17–19] The reported prevalence of uveitis and serological evidence of syphilis has varied from study to study. Tamesis and Foster,[18] for example, reported a prevalence of 2.5% in their clinic in Boston, whereas Henderly and colleagues[19] reported a prevalence at their tertiary referral centre of 0.8%. Barile and Flynn found that 8% of their 552 patients in New York had reactive treponemal antibody assays.[15]

Over a span of 25 years, 39 of the 2706 patients (1.4%) seen in the uveitis clinic at the Francis I Proctor Foundation had uveitis in the setting of positive syphilis serology and the absence of evidence of other causes for their inflammation. Of these 39 patients, eight eyes from seven patients (18.0%) developed a rise in IOP at the onset of acute or recurrent inflammation which responded readily to appropriate anti-inflammatory and antimicrobial therapy. Patients with uveitis and positive syphilis serology were thus nearly eight times more likely to develop the IOHS than patients in the uveitis population at large (2.3%).

Given that the IOP rose and decreased acutely and in parallel with the anterior chamber inflammation, we classified these patients as having IOHS, as defined by Koh and Barton.[3] This is in contrast to other causes of IOP elevation in patients with

uveitis, such as long term corticosteroid use or chronic damage to the trabecular meshwork, with or without the formation of anterior synechiae.[2] Mechanisms evoked to explain the IOHS have included clogging of the trabecular meshwork with inflammatory debris and a prostaglandin mediated increase in vascular permeability causing increased aqueous humour production.[2] Interestingly, the vast majority of causes of the IOHS are infectious in nature.[5 6 10–13]

There have been many reports of an association between various aetiologies of uveitis and glaucoma but not of a transient rise in IOP that responds quickly to topical anti-inflammatory therapy.[4 14 20] Panek *et al*[4] reported that the prevalence of a secondary rise in IOP was 12% in patients with acute uveitis. Merayo-Lloves *et al*[14] reported a 9.6% prevalence of secondary glaucoma with acute, recurrent, and chronic uveitis. The fact that the IOHS was not differentiated from uveitic glaucoma as a whole in these studies may explain why we report a prevalence of 2.3% in comparison to their higher percentages. While syphilis is well recognised to produce elevations in IOP in the setting of longstanding or chronic uveitis,[14] no one to our knowledge has described syphilis as a cause of an acute rise in IOP of the sort classically associated with herpetic anterior uveitis,[5 6 13] the Posner–Schlossman syndrome,[7] sarcoid uveitis,[8 9] or toxoplasmic retinochoroiditis.[10 11] The findings in our patients suggest that syphilitic uveitis should be included as a possible cause of IOHS, and that acute elevations of IOP in the absence of angle closure in patients with uveitis may provide a valuable clue to the diagnosis in such cases.

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