

# *Helicobacter pylori* IgG Antibodies in Aqueous Humor and Serum of Subjects With Primary Open Angle and Pseudo-exfoliation Glaucoma in a South Indian Population

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**Purpose:** A prospective, nonrandomized, comparative study was carried out to investigate levels of anti-*Helicobacter pylori*-specific IgG antibodies in the aqueous humor and serum of patients with primary open angle glaucoma (POAG), exfoliation syndrome [pseudo-exfoliation glaucoma (PXFG)], and with normotensive cataract patients, who served as controls.

**Methods:** Aqueous humor was aspirated at the beginning of glaucoma surgery from 50 eyes of 50 patients with POAG, with PXFG and at the beginning of phacoemulsification cataract surgery from controls. Serum samples were obtained. Anti-*H. pylori* IgG concentration in the aqueous humor and serum was measured by means of enzyme linked immunosorbent assay.

**Results:** Serum analysis of anti-*H. pylori* IgG antibodies revealed statistically significant difference between POAG and PXFG ( $52.26 \pm 52.51$  vs.  $25.22 \pm 35.27$ ,  $P = 0.01$ ). Also, the difference between POAG and controls was statistically significant ( $54.05 \pm 55.04$  vs.  $33.83 \pm 41.73$ ,  $P = 0.04$ ). However, on comparing PXFG with the control group, the difference was statistically insignificant ( $P = 0.12$ ). The mean concentration of anti-*H. pylori* IgG antibodies in aqueous humor of patients in POAG and controls were not statistically different ( $3.93 \pm 5.14$  vs.  $2.65 \pm 2.87$ , respectively,  $P = 0.73$ ). The mean concentration of anti-*H. pylori* IgG antibodies in aqueous humor of patients in PXFG and controls were not statistically different ( $8.87 \pm 30.25$  vs.  $2.65 \pm 2.87$ , respectively,  $P = 0.83$ ). There was also no statistical difference of IgG levels between POAG and PXFG ( $3.93 \pm 5.14$  vs.  $8.87 \pm 30.25$ , respectively,  $P = 0.87$ ).

**Conclusions:** The levels of anti-*H. pylori* IgG titers in sera of individuals with POAG were significantly higher compared with

PXFG and control groups. We support the hypothesis of the role of anti-*H. pylori* antibodies in causative mechanism for POAG. We could not find a significant link between the anti-*H. pylori* IgG antibodies and the PXFG.

**Key Words:** primary open angle glaucoma, pseudo-exfoliation glaucoma, *helicobacter pylori*

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*Helicobacter pylori* has been causally implicated in the genesis of gastric ulceration and gastric carcinoma.<sup>1,2</sup> Researchers have found a relatively high prevalence of *H. pylori* infection, approaching 85%, in individuals suffering from gastritis, duodenal ulceration, and gastric carcinoma in one South Indian population.<sup>3</sup> Primary open angle glaucoma (POAG) and pseudo-exfoliation glaucoma (PXFG) are leading causes of blindness in South India.<sup>4,5</sup>

Recent evidence suggests a pathogenetic association between POAG and endothelin dependent vascular dysregulation and impaired ocular blood flow.<sup>6–8</sup> The concept of immune system facilitating the development of glaucomatous optic neuropathy in some susceptible individuals has gained more credence with evidence accumulating for the causative role of autoantibodies in a number of peripheral neuropathies, for example, Guillain-Barre syndrome.<sup>9</sup> The possibility of an infectious pathogenetic mechanism in PXFG was suggested in one Norwegian study, where the prevalence of PXFG was significantly more common in spouses of patients with the disease.<sup>10</sup>

Kountouras et al<sup>11</sup> have established a higher prevalence of *H. pylori* infection in the sera of patients with POAG and PXFG compared with age-matched control participants with anemia, in a Greek population. In another study by the same investigators,<sup>12</sup> it was concluded that a one week long course of omeprazole, claritromycin, and amoxicillin could improve glaucoma parameters in the subgroup of patients in whom *H. pylori* eradication was successful, suggesting a possible causal link between *H. pylori* and glaucoma. In a recent study, they concluded that *H. pylori*-specific IgG antibody levels were significantly increased in both the aqueous humor

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and serum of patients with POAG and PXFG.<sup>13</sup> There have also been suggestions to the contrary that there is no role for *H. pylori* in pathogenesis of glaucoma. Galloway et al<sup>14</sup> found no association between exposure to *H. pylori* infection and open angle glaucoma in their study conducted in a Canadian population.

The prevalence of *H. pylori* infection may vary in the general population and may be dependent upon cultural, socioeconomic, and geographic differences. We, therefore, performed a prospective case control analysis investigating prevalence of exposure to *H. pylori* in subjects with POAG and exfoliation glaucoma in a South Indian population.

## SUBJECTS AND METHODS

### Participants

This study was performed on 150 subjects at Aravind Eye Hospital, Madurai, India. Consecutive 50 subjects who had POAG and 50 with PXFG each requiring glaucoma surgery because of inadequate control of their intraocular pressure or because of progressive disc and visual field damage were selected. Fifty patients undergoing cataract surgery for senile cataract were selected as controls. All 3 groups of subjects were natives from within a 200 km radius around Madurai, Tamil Nadu in South India. Subjects in all the 3 groups were matched for sex. Subjects were enrolled consecutively between July 2004 and April 2005.

The inclusion criteria for entry into this study consisted of POAG subjects who entered in the present study and had a history of intraocular pressure more than 22 mm Hg or greater, typical glaucomatous optic nerve head changes (eg, thinning or notching in the inferior or superior temporal areas of optic nerve head, or total glaucomatous cupping), and typical visual field loss (eg, a paracentral, arcuate or seidel's scotoma, or a nasal step). PXFG subjects had to have an exfoliation material deposited on the cornea, lens, and/or pupil margins in addition to the criteria for the eyes with POAG.

Eyes with ophthalmic conditions other than glaucoma (eg, uveitis, current conjunctivitis, and progressive retinal diseases), a myopic refractive error exceeding -8.00 diopters, and previous ophthalmic surgery were excluded.

Subjects were also excluded if they had taken H-2 receptor antagonists, proton pump inhibitors, antibiotics, bismuth compounds, or nonsteroidal anti-inflammatory drugs (excluding low doses of aspirin, ie, 80 mg 2 to 3 times weekly) in the preceding 4 weeks. Subjects were excluded if they had undergone previous gastric surgery, were on anticoagulant therapy; were alcohol abusers; had allergy to penicillin and macrolides, had evidence on the basis of their clinical history, medical records, and clinical examination of gastric cancer or other neoplasia or had severe cardiac, pulmonary, liver, or kidney disorders.

Institutional Review Board approval was obtained. All subjects gave both verbal and written informed consent for participating in this study. All subjects underwent detailed ocular examination with slit lamp

biomicroscopy. Intraocular pressure was measured using calibrated Goldman applanation tonometer. Stereoscopic evaluation of the vertical cup disc ratio was performed in all cases.

All subjects were given tobramycin, 0.3%, 4 times daily to the operated eye 3 days before surgery. Cyclopentolate, 1%, and phenylephrine, 2.5%, eye drops were used for mydriasis 4 times 1 hour before the start of surgery. All eyes underwent a modified Van Lint akinesia and retrobulbar injection using both 2% lidocaine hydrochloride and 0.75% bupivacaine hydrochloride. Aqueous humor was obtained before creating the sclera flap in glaucoma surgery and before fashioning a corneoscleral tunnel in the phacoemulsification group. Sixty micro liters of aqueous humor using a 30-gauge needle on tuberculin syringe was aspirated through clear cornea. The sample was stored in a freezer at -20°C, and was transferred when the enzyme-linked immunosorbent assay (ELISA) was to be carried out (within 20 to 25 d).

In addition, we drew 3 mL venous blood from each subject on the same day of surgery. We centrifuged samples at 3000 g for 10 minutes to obtain serum, and then aliquoted and stored the serum at -20°C in the laboratory freezer until assay (within 20 to 25 d).

### Anti-*H. pylori* IgG Analysis

Commercially available ELISA (IBL, Germany) was used. The ELISA test were carried out in duplicates. The recommended cutoff limit for *H. pylori* detection was 8 U/mL. Levels above this were defined as positive.

For aqueous analysis, we determined our own cutoff value by the method as follows. The mean of corrected optical density (OD) values of the aqueous humor samples (based on negative ELISA assay in serum) was calculated and added to 3 times the SD.<sup>15</sup> Those aqueous humor samples with OD greater than the mean of negative aqueous humor samples plus 3 SDs were considered to be positive, whereas those with OD less than the mean of negative aqueous humor samples plus 3 SDs were considered negative. According to this method, cutoff value of 7.1 U/mL was established. Subjects with a value less than 7.1 U/mL were considered *H. pylori*-negative.

### Statistical Analysis

Mann-Whitney *U* test was used to compare mean values and  $\chi^2$  test was used to compare the categorical variables. Univariate odds ratios (ORs) were calculated for the association between risk factors and glaucoma groups. These analyses were performed using the statistical package STATA 8.1 (College Station, TX).

## RESULTS

The demographic data is described in Table 1. There is no statistically significant difference in sex between the groups. However, the control group is statistically younger than both the glaucoma and pseudo-exfoliation groups.

**TABLE 1.** The Demographic Distribution of the Study Population

Characteristic	Group A (n = 50) POAG	Group B (n = 50) PXFG	Group C (n = 50) Control
Age (y), mean*	63.7	67.0	59.3
Range (y)	(40-81)	(36-85)	(38-84)
Sex (M:F)†	31:19	33:17	31:19

\*Statistically significant difference in mean age was found among groups by Kruskal Wallis Test ( $P$  value < 0.001).

†Statistically significant association was not found between sex and groups by Pearson  $\chi^2$  ( $P$  value 0.892).

Clinical data is found in Table 2. Using Mann-Whitney test mean logMAR visual acuity revealed statistical differences between control group and those with POAG ( $P = 0.02$ ). This difference was because of comparatively denser cataracts among control groups. However, this finding would have had no effect on our study outcome. There was no statistical difference among POAG and PXFG, and PXFG and controls.

Mean intraocular pressure between POAG was  $20.3 \pm 8.28$  mm Hg, PXFG group was  $24.40 \pm 11.87$  mm Hg, and control group was  $15.0 \pm 3.43$  mm Hg. Mann-Whitney  $U$  test revealed significant statistical difference between POAG and controls ( $P = 0.02$ ). However, there was no statistical difference among PXFG and controls, and PXFG and POAG.

Mean vertical cupping in POAG and PXFG was statistically more compared with control group ( $0.82 \pm 0.10$  vs.  $0.48 \pm 0.22$ ; Mann-Whitney  $U$  test  $P = 0.02$  and  $0.79 \pm 0.15$  vs.  $0.48 \pm 0.22$ , Mann-Whitney  $U$  test;  $P = 0.08$ , respectively) (Table 2). Difference of vertical cupping between POAG and PXFG was statistically insignificant ( $P = 0.27$ ).

Serum analysis of anti-*H. pylori* IgG antibodies revealed that the POAG group ( $52.26 \pm 52.51$ ) had significantly higher titers (Mann-Whitney  $U$  test;  $P = 0.01$ ) than the PXFG group ( $25.22 \pm 35.27$ ). The differences between POAG and control groups were significant ( $54.05 \pm 55.04$  vs.  $33.83 \pm 41.73$ , Mann-Whitney  $U$  test;  $P = 0.04$ ). There was no significant difference when the control and PXFG groups were compared (Mann-Whitney  $U$  test;  $P = 0.12$ ).

The mean level of anti-*H. pylori* IgG positivity in the sera of subjects tested in POAG group (70.0%) compared with PXFG (44.0%) was significant ( $P = 0.009$ ). There was also a significantly higher level in the controls than PXFG group (66.0% and 44.0%, respectively,  $P = 0.027$ ). There was no significant difference between the POAG and controls groups ( $P = 0.67$ ).

The mean concentrations of anti-*H. pylori* IgG antibodies in aqueous humor of subjects in the POAG and control groups were not statistically different ( $3.93 \pm 5.14$  vs.  $2.65 \pm 2.87$ , respectively; Mann-Whitney  $U$  test;  $P = 0.73$ ). Similarly, the mean concentrations of anti-*H. pylori* IgG antibodies in aqueous humor of

**TABLE 2.** Clinical Data and Levels of *H. pylori* IgG Antibodies in Serum and in Aqueous Humor

Characteristic	Group A (n = 50) POAG	Group B (n = 50) PXFG	Group C (n = 50) Control	Odds Ratio (95% CI)		P		
				A vs. B	A vs. C	A vs. B	A vs. C	B vs. C
Mean visual acuity (± SE)	0.77 ± 0.70	0.90 ± 0.77	1.11 ± 0.82	—	—	0.31	0.02	0.14
Intraocular pressure (± SE)	20.34 ± 8.28	24.40 ± 11.87	15.00 ± 3.43	—	—	0.30	0.02	0.14
Mean vertical cupping (± SE)	0.82 ± 0.10	0.79 ± 0.15	0.48 ± 0.22	—	—	0.27	0.02	0.08
Anti- <i>H. pylori</i> IgG, serum U/mL	54.05 ± 55.04	25.22 ± 35.27	33.83 ± 41.73	—	—	0.001	0.04	0.12
Anti- <i>H. pylori</i> IgG, aqueous U/mL	3.93 ± 5.14	8.87 ± 30.25	2.65 ± 2.87	—	—	0.87	0.73	0.83
<i>H. pylori</i> -positive cases in aqueous humor (Anti- <i>H. pylori</i> IgG)	4 (8.0%)	5 (10.0%)	2 (4.0%)	1.28 (0.32-5.1)	2.07 (0.36-12.13)	> 0.99	0.68	0.44
ELISA-positive cases in serum	35 (70.0%)	22 (44.0%)	33 (66.0%)	0.33 (0.14-0.79)	1.2 (0.52-2.80)	0.009	0.67	0.027

SE indicates standard error.

Group A is POAG, Group B is PXFG, and Groups C is controls.

subjects in PXFG and controls were not statistically different ( $8.87 \pm 30.25$  vs.  $2.65 \pm 2.87$ , respectively, Mann-Whitney *U* test;  $P = 0.83$ ). There was no statistical difference of IgG levels between POAG and PXFG (Mann-Whitney *U* test;  $P = 0.87$ ).

The OR for association of *H. pylori*-positive cases in the aqueous humor (anti-*H. pylori* IgG aqueous OD  $> 0.71$ ) between 2 glaucoma groups was 1.28 [0.95% confidence interval (CI): 0.32 to 5.1]. The OR of POAG subjects compared with controls was 2.07 (0.95% CI: 0.36 to 12.13). The equivalent OR of PXFG compared with controls was 2.67 (0.95% CI: 0.48 to 14.74) (Table 2).

The power of this study to determine a 25% difference between the 2 glaucoma groups was  $< 80\%$  (power of the study: 75.5%).

## DISCUSSION

Multiple factors result in impairment of aqueous outflow through trabecular meshwork in POAG with consequent increase in intraocular pressure. Additionally, little is known about the exact factors that trigger the onset of PXFG.<sup>16</sup> Recently, evidence to suggest pathogenic association between POAG, endothelin dependent vascular dysregulation, and impaired ocular blood flow has been reported.<sup>6-8</sup>

In some subjects with glaucoma, an autoimmune mechanism has been postulated to play a significant role in glaucomatous optic nerve damage.<sup>17,18</sup> Autoimmune injury to optic nerve may occur directly by autoantibodies or indirectly by way of a mimicked autoimmune response to a sensitizing antigen, which in turn damages retinal ganglion cells.<sup>18-21</sup> The evidence that autoantibodies to proteins in retina and/or optic nerve may contribute to glaucomatous optic neuropathy is consistent with findings in the general medical literature. There are suggestions for a causative role for autoantibodies in peripheral neuropathies, including myasthenia gravis, Guillain-Barre syndrome, and multiple sclerosis; where autoantibodies to specific neural targets have been found to impair native neural function.<sup>21</sup>

*H. pylori* is a spiral gram-negative bacterium, colonizing the gastric mucosa<sup>22</sup> and implicated in gastritis, duodenal ulceration, and gastric carcinoma.<sup>1,2</sup>

*H. pylori* has also been thought to be associated with immunoneurologic conditions like Gullain-Barre syndrome and Sjorgen syndrome.<sup>21</sup> *H. pylori* antibodies are known to cross-react with ciliary body epithelial antigens and *H. pylori* induces apoptosis in gastric mucosa by enhancing both expression of the cell death receptor Fas and sensitivity to Fas-mediated apoptosis.<sup>23-26</sup> Human trabecular meshwork cells can be stimulated to undergo apoptosis via the Fas/FasL pathway.<sup>27</sup>

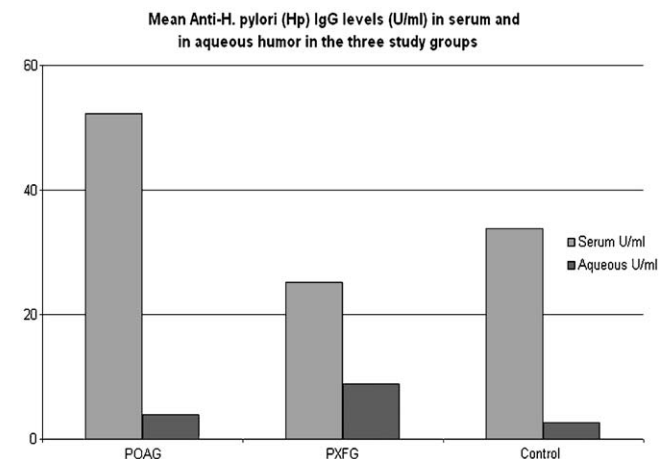
Vacuolating cytotoxin (VacA) has been reported to form anion selective, low conductance, voltage dependent channels in planar membranes. The formation of low-conductance VacA pores in the cell membrane results in a change in ion permeability. In addition, sequence homo-

logy between VacA and the human ( $\text{Na}^+ + \text{K}^+$ )-ATPase A subunit has been reported. Concerning the association between serum and cerebrospinal fluid antibodies, every subject with positive cerebrospinal fluid anti-recombinant-VacA (anti-r-VacA) IgG has been shown to have positive serum antibodies to *H. pylori*, and few subjects with serum anti-r-VacA IgG have showed delayed F wave latencies.<sup>9</sup>

It is possible that the increased titer of anti-*H. pylori* IgG antibodies in aqueous humor and serum samples of POAG and PXFG subjects offer indirect evidence for the role of this agent in a cascade of events resulting in the damage caused by glaucomatous optic neuropathy in some individuals (Fig. 1).<sup>11</sup>

In our study, the level of anti-*H. pylori* IgG titers in the sera of individuals with POAG was significantly higher compared with individuals belonging to pseudo-exfoliation and control groups. However, aqueous anti-*H. pylori* IgG titers failed to show any statistical difference among the 3 groups.

In the previous studies, Kountouras and colleagues have postulated a possible role of *H. pylori* in pathobiology of POAG and PXFG.<sup>11,12</sup> They have concluded that *H. pylori*-specific antibody levels are significantly increased in both aqueous humor and serum of subjects with POAG and PXFG.<sup>13</sup> Moreover, the level of titers of anti-*H. pylori* antibody in these subjects might reflect the severity of glaucomatous damage. They document that it would be reasonable to expect a difference in the level of *H. pylori*-specific antibodies among glaucoma groups, because PXFG has been proposed to possess a different pathogenic background from that suspected in POAG. They documented that in PXFG subjects there is a significant degree of impairment in blood aqueous humor barrier, which would potentially influence the level of *H. pylori* antibodies present in aqueous humor. This concept seemed to extend to POAG subjects and is supported by the strong correlation observed between



**FIGURE 1.** The mean anti-*H. pylori* IgG levels (units/mL) in serum and aqueous humor in the 3 study groups (POAG and PXFG and the controls were cataract subjects).

aqueous and serum IgG levels in both types of glaucoma subjects in their study. They also hypothesized that *H. pylori* antibodies may circulate in bloodstream and enter the aqueous circulation via blood aqueous humor barrier; in aqueous humor, they may reach significant level sufficient to impact the development and progression of glaucoma.<sup>13</sup>

We have postulated a possible role for anti-*H. pylori* antibodies in the pathophysiology of POAG. We could not find significant link between anti-*H. pylori* IgG antibodies in sera of patients with PEFG. Our results could be because of the different pathogenic mechanisms underlying these glaucoma groups. Exfoliation glaucoma is a form of open angle glaucoma secondary to blockade of trabecular meshwork by exfoliation material and the release of pigments or both leading to high intraocular pressure and subsequent glaucomatous optic nerve head damage.<sup>28</sup> PXFG is less likely to be directly related to serum anti-*H. pylori* status of these individuals. Our study was not designed to verify the hypothesis of disturbed blood aqueous humor barrier proposed by Kountouras et al.<sup>13</sup>

Although we have studied a much larger population compared with Kountouras et al,<sup>13</sup> one limitation of our study was that subjects were not age-matched, as the mean age of individuals undergoing cataract surgery only was comparatively almost a decade less than the individuals in POAG and PXFG groups. Another limitation is that our population is fairly homogenous and in the South Indian population, the infection rate of *H. pylori* is 83.3%,<sup>29</sup> requiring a very large population to be screened to prove the statistical difference in *H. pylori* infection among subjects with glaucoma and general population.

Infection rate of *H. pylori* in the South Indian population is observed to be high, 83.3%<sup>29</sup> as compared with 37%<sup>30</sup> reported for the developed world. The prevalence of POAG in several populations studied in South India<sup>4,5,31</sup> is not different from that in the white population studies reported from the West.<sup>32-34</sup> The low prevalence of POAG despite a high prevalence of *H. pylori* infection in the general population of South India questions any direct role for *H. pylori* in pathogenesis of POAG.

Gill et al<sup>35</sup> studied IgG and IgA anti-*H. pylori* antibodies in various age subgroups in North Indian population without upper gastrointestinal symptoms. They reported prevalence of *H. pylori* infection in 22%, 56%, and 87% in 0 to 4, 5 to 9, and 10 to 19-year age groups, respectively, and it remained almost constant up to the fifth decade and significant fall of IgG and IgA prevalence was observed from the fifth to the seventh decades. Definite POAG was reported to be present in 3.8% of those aged 40 years or more by the Aravind comprehensive eye survey<sup>5</sup> In contrast, prevalence of POAG increases with age<sup>5,32,36</sup> and a decreasing rate of *H. pylori* infection with age<sup>35</sup> seems to suggest causes other than mere *H. pylori* infection in POAG pathogenesis. It is, however, also possible that auto immune injury

to the optic nerve from *H. pylori* antibodies is initiated in the early years of life and manifests in the later decades of life, which could partly explain the increasing POAG prevalence with increasing age, although evidence of *H. pylori* infection progressively declines with aging.

In conclusion, we hypothesize a possible role for *H. pylori* infection in causative mechanism of POAG. However, further studies in other populations are required to substantiate the role of *H. pylori* infection in pathogenesis of POAG.

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