Investigation of the Association between Helicobacter pylori Infection and Normal Tension Glaucoma

Joon Mo Kim, Seok Hwan Kim, Ki Ho Park, So Young Han, and Hyyoung Sub Shim

PURPOSE. To investigate whether Helicobacter pylori infection is associated with normal tension glaucoma (NTG).

METHODS. One hundred consecutive NTG patients (group 1) from an outpatient glaucoma clinic were enrolled. Medical records of the 88 control participants (control 1) of the outpatient clinic, and 104 NTG patients (group 2) and 1116 healthy controls (control 2) (1220 subjects in total) from a primary health care center were reviewed retrospectively to compare the results. Serum samples from all subjects were analyzed for the presence of H. pylori-specific immunoglobulin G antibodies using ELISA. The distributions of serologic H. pylori test results of the NTG patients and control subjects were compared, and possible associations between clinical phenotypes and positive serologic results were assessed. Bilaterality of NTG patients was also analyzed.

RESULTS. NTG patients had significantly more positive serologic results than did the healthy controls. There were significant differences between group 1 and control 1 patients (P = 0.020; odds ratio [OR], 2.05), group 1 and control 2 patients (P = 0.016; OR, 1.73), and group 2 and control 2 patients (P = 0.008; OR, 1.83). However, no significant association was found between clinical characteristics and a positive serologic result for H. pylori in NTG patients.

CONCLUSIONS. This study suggests that H. pylori infection may be associated with an increased risk for NTG. H. pylori may play a role in the development or progression of NTG as a secondary aggravating factor because of the coexistence of other main causes or it may be the primary cause. (Invest Ophthalmol Vis Sci. 2011;52:665–668) DOI:10.1167/iovs.10-6096

Helicobacter pylori is a common bacterium; approximately 50% of the world’s population has been estimated to be infected. H. pylori is a spiral Gram-negative bacteria that is associated with various upper gastrointestinal diseases.1,2 Although its main reservoir is the stomach, H. pylori may induce a strong systemic host immune response and the release of various vasoactive and proinflammatory substances.3–5 Moreover, H. pylori may be associated with the arteriosclerosis-induced increase in platelet activation and aggregation.6–7 Thus, it is plausible that H. pylori contributes to the development of diseases in extragastrointestinal areas. Indeed, H. pylori infection has been implicated in ischemic heart disease, cerebrovascular disease, Raynaud’s phenomenon, and migraine.6,8–11

Kountouras et al.12 reported the first link between H. pylori infection and primary open-angle glaucoma (POAG) and pseudoexfoliation glaucoma (PXG) in the Greek population. These authors suggested that H. pylori infection may influence the pathophysiology of glaucoma by causing the release of various proinflammatory and vasoactive substances and by influencing the apoptotic process. However, other studies13,14 have failed to confirm this association. Whether exposure to this bacterial agent promotes the initiation and progression of glaucoma is thus still controversial.7,15–17 Recent studies have suggested that H. pylori may be related to Posner-Schlossman syndrome.18

Normal-tension glaucoma (NTG) involves progressive glaucomatous optic neuropathy and corresponding visual field defects but intraocular pressure (IOP) in the normal range. Moreover, because the IOP remains normal, mechanisms involving ocular blood flow or an autoimmune reaction are believed to play a role in the pathogenesis of NTG.19,20 Previous studies15–17 support hypotheses that vasoactive substances, platelet function alterations, and molecular mimicry affect the pathogenesis of NTG. Therefore, we considered it likely that H. pylori infection may be associated with the pathogenesis of NTG rather than the pathogeneses of POAG or PXG, in which a high IOP is recognized as a major pathogenic factor. H. pylori infection and NTG are common diseases in Koreans, a genetically homogenous population group. Thus, we investigated whether H. pylori infection is associated with NTG in the Korean population.

MATERIALS AND METHODS

Participants

The study population was composed of 100 consecutive NTG patients (group 1), 88 control participants (control 1), 104 NTG patients (group 2), and 1116 healthy controls (control 2). Group 1 was from an outpatient glaucoma clinic of Kangbuk Samsung Hospital consecutively from July 2004 to April 2005. In control 1, control participants, consisted of all subjects who underwent H. pylori serologic testing in the outpatient ophthalmology clinic during the same study period as group 1. All participants in control 1 underwent eyelid examinations for occlusalplastic symptoms or cataract assessment at the same clinic. Subjects with glaucoma, previous ocular surgery, and serious external or retinal disease were excluded from control 1. Eighty-eight subjects were enrolled in this study after application of the exclusion criteria. Group 2 and control 2 were recruited from a primary health care center (KangNam Health Care Center) during routine health checkups from October 2003 to April 2005. All subjects were of Korean ethnicity. All subjects in group 2 and all controls visited the center voluntarily. Confirmative diagnoses of NTG were made by a glaucoma specialist in the glaucoma clinic. Patients were diagnosed using the following criteria: typical glaucomatous optic neuropathy including
controls. No visual field testing was performed on patients who were found to have NTG during a routine health checkup. NS, not significant.

χ² test.
† Independent t-test.

rim thinning or notching in the inferior or superior temporal area of the optic nerve head or total glaucomatous cupping; corresponding typical visual field loss including paracentral or arcuate scotoma or a nasal step, diurnal IOP persistently <21 mm Hg (without medication), open anterior chamber angle by gonioscopy, and no other known secondary cause of glaucomatous optic neuropathy. IOP was measured using a Goldmann applanation tonometer, and visual fields were evaluated using the 30–2 program of a visual field analyzer (Humphrey Visual Field Analyzer model 640; Zeiss Inc., San Leandro, CA). The first two perimetric results obtained in each case were excluded to avoid learning effects, and the next two perimetric results were used as baseline values. Mean deviation (MD) and pattern SD (PSD) values were obtained by averaging baseline perimetric values. Age- and sex-matched consecutive control subjects were recruited during the same period at the same center. These subjects had a best-corrected visual acuity >20/25, an IOP <21 mm Hg by noncontact tonometer, and no findings suspicious of glaucoma in the disc or retinal nerve fiber layer in digital fundus photographs. No visual field testing was performed on controls.

Study Design
This study included 100 consecutive cases of NTG seen at a glaucoma outpatient clinic from July 2004 through April 2005. Medical records, including demographic features and serologic test results, of the 104 NTG patients and 88 control participants in the outpatient clinic and of the 1116 healthy controls (1220 subjects in total) from a primary health care center were reviewed retrospectively. This study was approved by the Institutional Review Board and adhered to the principles of the Helsinki Declaration, and group 1 participants were enrolled after they gave informed consent. The distributions of serologic H. pylori test results and demographic features such as the age, sex, and IOPs of the NTG patients and control subjects were compared. Associations between clinical characteristics (sex, age at diagnosis, baseline IOP, laterality, cup-to-disc ratio, MD, and PSD) of the NTG patients and serologic results were also assessed. In subjects with bilateral NTG, the more advanced eye was used in the analyses. Bilaterality of NTG patients was also analyzed. Statistical analysis was performed using χ² analysis, logistic regression analysis, or the independent t-test, as appropriate. P <0.05 was considered statistically significant, and statistical analyses were performed using PASW 17.0 (SPSS, Chicago, IL).

Serologic Analysis
Serologic tests were performed for all subjects. Serologic analyses were performed for primary health care center subjects as part of the routine health checkup with their consent. Peripheral venous blood was drawn from each subject, and the levels of IgG antibody against H. pylori were analyzed quantitatively using an enzyme-linked immunosorbent assay (Genedia H. pylori ELISA; Green Cross Medical Science Corp., Seoul, South Korea). The manufacturer-recommended cutoff limit of 15 U/mL for H. pylori positivity was used. Sera of all subjects were tested in the same laboratory.

RESULTS
No age or sex differences were observed between the NTG patients and the controls (Table 1). NTG patients had higher IOPs than did the controls (P <0.001), and a positive serologic result for H. pylori was found to be significantly associated with risk for NTG (group 1: 72% vs. 28%; P = 0.018; 95% confidence interval [CI], 1.10–2.72; group 2: 73.1% vs. 59.8%; P = 0.008; odds ratio [OR], 1.83; 95% CI, 1.17–2.86; Table 2). However, no significant association was found between clinical characteristics (sex, age at diagnosis, baseline IOP, bilaterality, MD, or PSD) and serologic results in NTG patients (Table 3).

Group 1 patients showed more severe and bilateral involvement than did group 2 patients (P <0.001). In total, 138 of 204 patients had bilateral NTG. However, there was no statistically significant difference in H. pylori positivity between patients with unilateral NTG and those with bilateral NTG (P = 0.800).

DISCUSSION
In this study, we found that H. pylori infection was associated with risk for NTG. More NTG patients were positive for H. pylori than were control group patients. Outpatient clinic NTG patients had more severe bilateral involvement than did routine health checkup NTG patients, possibly because routine health checkups in Korea are designed to detect early-stage disease; therefore, most patients had early glaucoma and had only been affected by the disease for a short time. In contrast, university hospitals in Korea care for patients with more advanced disease. Nevertheless, the finding that bilaterality and severity were not significantly different between these two groups suggests that although H. pylori infection may lead to the development of glaucoma, it does not affect its progression. Consideration of the similar levels of H. pylori positivity between bilateral and unilateral NTG and the systemic nature of H. pylori infection led us to postulate that infection or the presence of antibodies against H. pylori may

Table 1. Clinical Characteristics of NTG Patients and Healthy Controls

<table>
<thead>
<tr>
<th></th>
<th>NTG Group 1</th>
<th>Control 1</th>
<th>NTG Group 2</th>
<th>Control 2</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects, n</td>
<td>100</td>
<td>88</td>
<td>104</td>
<td>1116</td>
<td>NS†</td>
</tr>
<tr>
<td>Male-female ratio</td>
<td>74:26</td>
<td>59:19</td>
<td>64:40</td>
<td>591:525</td>
<td>NS†</td>
</tr>
<tr>
<td>Age, y</td>
<td>55.6 ± 13.3</td>
<td>49.8 ± 15.5</td>
<td>53.4 ± 8.1</td>
<td>51.9 ± 9.5</td>
<td>NS†</td>
</tr>
<tr>
<td>IOP, mm Hg</td>
<td>15.24 ± 2.59</td>
<td>14.2 ± 2.65</td>
<td>14.9 ± 2.9</td>
<td>13.5 ± 2.6</td>
<td>P &lt; 0.001†</td>
</tr>
</tbody>
</table>

Group 1 included patients with glaucoma detected in a glaucoma outpatient clinic. Group 2 included patients who were found to have NTG during a routine health checkup. NS, not significant.

Table 2. Distribution of Serologic H. pylori Results in NTG Patients and Healthy Controls

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Control 1</th>
<th>Group 2</th>
<th>Control 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>H. pylori positive, n (%)</td>
<td>72 (72)</td>
<td>49 (55.7)</td>
<td>76 (73.1)</td>
<td>667 (59.8)</td>
</tr>
<tr>
<td>H. pylori negative, n (%)</td>
<td>28 (28)</td>
<td>39 (44.3)</td>
<td>28 (26.9)</td>
<td>449 (40.2)</td>
</tr>
<tr>
<td>Total, n</td>
<td>100</td>
<td>88</td>
<td>104</td>
<td>1116</td>
</tr>
</tbody>
</table>

Statistically significant differences between group 1 and control 1 (P = 0.020; OR, 2.05; 95% CI, 1.12–3.75), group 1 and control 2 (P = 0.016; OR, 1.75; 95% CI, 1.10–2.72), and group 2 and control 2 (P = 0.008; OR, 1.83; 95% CI, 1.17–2.86; logistic regression analysis).
aggregate glaucoma rather than cause direct damage leading to its development. This hypothesis states that *H. pylori* infection may be a secondary aggravating factor rather than a main cause of NTG, though verification of this hypothesis may be difficult because histologic proof is required.

Kountouras et al. were the first investigators to report an association between *H. pylori* and glaucoma, and they subsequently reported that *H. pylori* IgG antibody levels were elevated in the aqueous humor and sera of POAG and PXG patients. In addition, they showed that *H. pylori* eradication therapy had a positive influence on visual field parameters and IOP in POAG patients. In addition, another study based on serologic testing showed a possible relationship between *H. pylori* infection and POAG. However, a study by Galloway et al. in a Canadian population demonstrated that *H. pylori* infection is not associated with POAG, PXG, NTG, or ocular hypertension. Although there is a possibility of an association between POAG and NTG, we postulated in this study that *H. pylori* infection might be associated with NTG based on the notion that the non-IOP component may play a more important role in the pathophysiology of NTG than in POAG or PXG. Thus, we undertook this retrospective case-controlled study in a large population.

Some limitations in the study by Galloway et al. should be noted. Their NTG group was composed of only 19 patients; thus, the statistical power of the study was limited. In addition, the study might have been limited by a selection artifact, because the prevalence of *H. pylori* infection among the controls was 20%, which was markedly lower than the 50% value reported for Canadians 60 to 70 years of age in another study. In contrast, the prevalence of *H. pylori* infection in the control group of the present study was 59.8%, which is similar to that reported for the adult Korean population in Seoul. In Korea, 56.0% of 15,916 population-based subjects were positive for anti-*H. pylori* IgG infection in 2005, and the seroprevalence of asymptomatic healthy subjects was significantly decreased compared with that in 1998 (59.6% vs. 66.9%).

No pathophysiologic link between *H. pylori* infection and NTG has been identified. If *H. pylori* can live in the trabecular meshwork, decreased outflow facility induced by inflammation may cause ocular hypertension and glaucoma. Some studies collected aqueous humor from anterior chamber to analyze the correlations. In one study *H. pylori* was detected at significantly higher levels in the POAG group. Another study showed significantly higher levels of *H. pylori* IgG antibody in the PXE group than in the POAG group. Deshpande et al. reported both POAG and PXE groups showed significant high levels of antibody though it was higher in the POAG group than in the PXE group. However, this mechanism is not expected in NTG patients. In NTG patients, *H. pylori* infection may lead to optic disc damage by decreasing ocular blood flow, secreting toxic materials, and causing antibody-induced apoptosis attributed to inflammation in the retrobulbar area. Although this hypothesis can be proved with invasive retrobulbar tissue biopsies, these are difficult to perform in practice. Several other possible hypotheses for the association between *H. pylori* infection and NPG have been suggested, such as the release of proinflammatory and vasoactive substances, platelet activation and aggregation, induction of increased levels of tissue factor-like procoagulants, development of cross-mimicry between endothelial and *H. pylori* antigens, and production of reactive oxygen species. It is also intriguing that *H. pylori* infection has been reported to be associated with diverse nondigestive diseases, such as cerebrovascular disease, ischemic heart disease, and migraine, all of which are associated with NTG. Thus, the pathophysiologic role of *H. pylori* infection in NTG requires further clarification. Endoscopic biopsy remains the gold standard for diagnosing *H. pylori* infection. However, this technique is complicated, requires special skills, is time consuming, and thus is inappropriate for screening large populations. In addition, it does not reveal the presence of a previous infection. The urea breath test is a possible alternative means of detecting *H. pylori* infection and is a reliable and noninvasive method. However, it is expensive, time consuming, produces a radioactive product, and detects only current infections and thus is not appropriate for large populations. The presence of IgG antibodies against *H. pylori* can be determined by standardized ELISA testing, which is inexpensive and rapid, and ELISA can detect exposure to *H. pylori* regardless of treatment. Moreover, ELISA is generally viewed to have high sensitivity and specificity (beyond 90%), despite the fact that some authors have reported suboptimal accuracies for ELISA. The present study had several limitations. First, we assessed the nature of the association between NTG and *H. pylori* infection by cross-sectional analysis, which could not determine the temporal relation between the two. Thus, we could not establish whether *H. pylori* infection is a risk factor for NTG development or progression. However, it has been reported that the prevalence of *H. pylori* infection increases with age from childhood, whereas NTG usually develops in those older than 50 years of age, which provides strong indirect evidence that *H. pylori* infection precedes NTG development. It is also possible that *H. pylori* infection and NTG have a common predisposing factor. Second, because of the retro-

### Table 3. Associations between Clinical Characteristics and *H. pylori* Serologic Results for NTG Patients

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male-female ratio</td>
<td>54.18</td>
<td>46.30</td>
<td>20.8</td>
<td>18.10</td>
<td>NS†</td>
</tr>
<tr>
<td>Bilaterality, %</td>
<td>88.9</td>
<td>19.7</td>
<td>78.6</td>
<td>32.1</td>
<td>NS†</td>
</tr>
<tr>
<td>IOP, mm Hg</td>
<td>15.54 ± 2.9</td>
<td>14.8 ± 3.2</td>
<td>16.4 ± 2.29</td>
<td>15.6 ± 2.3</td>
<td>NS‡</td>
</tr>
<tr>
<td>MD, dB‡</td>
<td>−10.49 ± 7.35</td>
<td>−3.00 ± 3.53</td>
<td>−9.63 ± 8.72</td>
<td>−3.75 ± 4.26</td>
<td>NS‡</td>
</tr>
<tr>
<td>PSD, dB‡</td>
<td>6.48 ± 4.05</td>
<td>5.11 ± 4.37</td>
<td>6.07 ± 4.44</td>
<td>5.05 ± 3.70</td>
<td>NS‡</td>
</tr>
</tbody>
</table>

NS, not significant; CDR, cup-to-disc ratio; MD, mean deviation; PSD, pattern standard deviation.

* Independent * test.
† Chi-square test.
‡ Baseline value of the Humphrey Visual Field Analyzer 30–2 program.
spective nature of our study (group 2 and control patients), we cannot exclude the possible effects of selection artifacts. However, we recruited consecutive patients (group 1) to minimize selection artifacts. Prospective validation of our results may be necessary. Third, it is also possible that members of the control group will eventually develop NTG because the average age of this group was approximately 50 years. In addition, the control group may contain early-stage glaucoma patients with small optic discs because we did not perform standard perimetry for the control group. However, we took retinal nerve fiber layer images to minimize that possibility.

In conclusion, we showed that *H. pylori* infection may be associated with the risk for NTG development in the Korean population. Clinicians who care for patients with *H. pylori* infection should also consider that *H. pylori* can cause not only digestive illness but also eye disease. *H. pylori* may play a role in the development or progression of NTG as a secondary aggravating factor because of the coexistence of other primary causes or it may be the primary cause, although the exact pathophysiology is still unclear. Moreover, based on our results, we were not able to determine whether the association is attributed to the actions of *H. pylori* itself or to the antibodies produced against it by the host. To elucidate the precise role of *H. pylori* in the development of NTG, further studies are required.

**References**