Retinal Nerve Fiber Layer Defect and Cerebral Small Vessel Disease

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PURPOSE. To determine whether retinal nerve fiber layer defect (RNFLD) is associated with cerebral small vessel diseases (SVDs) and to identify risk factors for RNFLD.

METHODS. A total of 4421 Korean subjects who underwent health checkups including brain magnetic resonance imaging (MRI) and fundus photography between January 2008 and October 2009 were included in this study. Co-morbid systemic diseases including hypertension, diabetes mellitus, and stroke or ocular diseases were evaluated using detailed questionnaires and medical records. Two experienced ophthalmologists assessed RNFLD on fundus photographs, according to the definition that describes the condition as marked thinning or absence of retinal nerve fiber layer bundles.

RESULTS. RNFLD was detected in 238 of 4395 eligible subjects, and the estimated prevalence was 5.4%. Multivariate regression analysis results showed the prevalence of RNFLD to be significantly higher in hypertensive subjects (odds ratio [OR], 1.73; 95% confidence interval [CI], 1.28–2.34), in those with cerebral SVD based on MRI (OR, 1.58; 95% CI, 1.17–2.12), and in male (OR, 1.47; 95% CI, 1.10–1.96) and older subjects (OR, 1.02; 95% CI, 1.00–1.03). Among the cases of cerebral SVD, white matter lesions (WMLs) were associated with RNFLD, whereas lacunar infarctions were not significantly associated with it.

CONCLUSIONS. The results indicate that RNFLD may be related to the presence of cerebral SVD, particularly WMLs. Furthermore, being older and male and having hypertension increase the risk of RNFLD.

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Cerebral small-vessel disease (SVD) is an important cause of stroke and vascular dementia.1,2 Disease of the small perforating arteries in the brain can present as lacunar infarcts (LIs) or diffuse white matter lesions (WMLs), which are observed radiologically as a low signal on brain computed tomography (CT) imaging and a high signal on T2-weighted magnetic resonance imaging (MRI).

The results of some recent studies suggest that silent cerebral infarcts (SCIs) induced by SVD are associated with the prevalence and progression of normal-tension glaucoma (NTG).3–7 Elevated intraocular pressure (IOP) is relevant to the pathogenesis and treatment of glaucoma, but factors other than IOP also have been suggested based on the evidence that cerebrovascular diseases, myocardial ischemia, and migraine tend to occur more frequently in patients with NTG.8–10

As NTG is generally asymptomatic in its early stages, many efforts have been made to detect glaucomatous changes of the optic disc shape and retinal nerve fiber layer (RNFL) by examining fundus photographs.11–15 Retinal nerve fiber layer defect (RNFLD), induced by ganglion cell death and axonal loss, is among the characteristic features of glaucoma.14 Because it can precede detectable optic disc changes and visual field losses,15 it is routinely assessed in screening for glaucoma and particularly NTG. Despite the potential importance of the RNFLD, little attention has been paid thus far to its possible relationship to cerebral SVD. Therefore, in the present study, we used MRI to determine whether RNFLD is related to the presence of cerebral SVD and also identified other risk factors for RNFLD.

MATERIALS AND METHODS

Subjects

This retrospective study entailed a review of the records of consecutive patients who underwent health checkups including brain MRI and fundus photography at the Healthcare Gangnam Center of Seoul National University Hospital from January 2008 through October 2009. A total of 4421 subjects, all Korean, were included in the study.

All subjects underwent brain MRI and fundus photography as part of a routine medical checkup. Their medical records and interview questionnaires obtained from the Healthcare system were used to screen for the presence of systemic diseases such as hypertension, diabetes mellitus, and stroke. Subjects having a systolic blood pressure above 140 mm Hg or a diastolic blood pressure above 90 mm Hg or taking antihypertensive drugs were considered to have systemic hypertension. Subjects with an 8-hour fasting glucose greater than or equal to 126 mg/dL or who were taking antihyperglycemic medications were defined as having diabetes. Stroke was defined as a new focal neurologic deficit of vascular origin lasting at least 24 hours. Previous ocular diseases such as glaucoma were also taken into consideration. Subjects with a history or evidence of symptomatic stroke and those whose fundus photographs did not allow for a confident evaluation of RNFLD were excluded from the study. Institutional Review Board approval was obtained from the Seoul National University Hospital Clinical Research Institute, and the study was conducted in accordance with all Declaration of Helsinki specifications.

Magnetic Resonance Imaging

MRI scans were conducted with 1.5-T superconducting magnets (Magnetom Espree; Siemens, Munich, Germany). The slice thickness was 5...
mm with an interslice gap of 20%. Cerebral SVD, including LI and WML, were defined as follows: LIs were considered present if focal hyperintensities 3 mm in size or larger were visible on T2-weighted images of the brain stem, basal ganglia, internal capsule, thalamus, or deep cerebral white matter. Infarcts greater in size than 20 mm were defined as chronic infarctions and were not included in the LIs. WMLs were defined as regions of hyperintensity on proton density and T2-weighted images, without prominent hypointensity on T1-weighted scans. The white matter lesions were rated visually by degree on axial FLAIR (fluid-attenuated inversion recovery) images using the Fazekas scale: grade 1, punctate; grade 2, early confluent; or grade 3, confluent. One experienced neuroradiologist who was blinded to all subjects’ fundus photography results reviewed the MR images. To evaluate the reproducibility of MRI readings, 50 randomly selected MRI images were evaluated by two examiners, and interobserver agreement in the reproducibility of MRI readings, 50 randomly selected MRI images were evaluated by two examiners, and interobserver agreement in

### Fundus Photography

A fundus photograph using a 45° digital nonmydriatic fundus camera (model EOS D60; Canon Inc., Utsunomiya, Japan) was obtained for each subject. Two experienced ophthalmologists (MK and JWK), who were masked to the subject’s identity and MRI results, evaluated the color photographs to detect any RNFLD or other optic disc or retinal abnormalities. Any disagreements were resolved via discussion and, if necessary, an additional grader (KHP) was consulted. Localized RNFLD was defined as a wedge-shaped, not a spindlelike defect, running toward or touching the optic disc border for not more than 60° of the circumference of the optic disc. Its depth was graded on a scale of 0 to 3 based on the difference in the RNFL visibility in the area of the localized RNFL defect compared with the neighboring sectors. This grading was a subjective one, ranging from 0, for abundant nerve fiber bundles visible, to 2, for no nerve fiber bundle visible. Grade 1 and 2 RNFLDs were used for analysis. Diffuse atrophy of RNFL was defined as a diffuse thinning or absence of RNFL of grade D1 (less brightness, fine striated texture and distinct large but still blurred small vessels), and larger than 60° from the optic disc. RNFLD-like normal variants or optic nerve diseases, such as a split RNFL or nonspecific spindlelike defects, were regarded as non-RNFLD. Glaucomatous optic disc changes were defined as follows: (1) a vertical cup-to-disc ratio of the optic nerve head of ≥0.7; (2) neuroretinal rim notching, thinning, or excavation; (3) an interocular difference in vertical cup-to-disc ratio ≥0.2.

### Statistical Analyses

To compare the clinical variables between the groups with and without RNFLD, Student’s t-test and Pearson’s χ² test were conducted. Univariate and multivariate logistic regression analyses, using odds ratio (OR) calculations and estimations of the 95% confidence intervals (CI), were performed to determine risk factors for the presence of RNFLD (SPSS ver. 12; SPSS Inc, Chicago, IL) was used for statistical analyses. P < 0.05 were regarded as statistically significant.

### Results

A total of 4421 Korean patients were included in the study. Among them, 22 were excluded due to poor image quality on the fundus photographs, caused by cataracts, media opacity, or small pupil, and 4 subjects were excluded because of history or evidence of symptomatic stroke. The mean age of the remaining 4395 subjects was 53.5 ± 9.4 (SD) years; 2709 (61.6%) were men, and 1686 (38.5%) were women.

RNFLD was detected in 5.4% of the included subjects. The results of the comparison of demographic parameters between the RNFLD and non-RNFLD groups are shown in Table 1. Glaucomatous optic disc changes were found in 35.7% of the RNFLD group and 5.4% of the non-RNFLD group. Most of the neuropotential rim changes of optic disc in the non-RNFLD group were increased cup-to-disc ratio, which is often seen in physiologic large cup.

Cerebral SVD, including LIs and WMLs, was detected in 1077 (24.5%) subjects. There was excellent interobserver agreement in assessing the presence of cerebral SVD in MRI images (κ = 0.911). The detection rate of cerebral SVD was significantly higher in the RNFLD group than in the non-RNFLD group (37.8% vs. 23.7%; P < 0.001). Cerebral SVD was divided into three subgroups: solitary lacunar infarction (SLI), solitary white matter lesions (SWMLs), and both lacunar infarction and white matter lesions (LI_WML). The prevalence of SWML and LI_WML were significantly higher in the RNFLD group (P < 0.001), whereas SLI did not differ significantly between the RNFLD group and the non-RNFLD group (P = 0.287; Table 1).

Table 2 shows the anatomic locations of cerebral SVD in patients with RNFLD and without RNFD. The most common location was periventricular area, followed by the frontal lobe.

### Risk Factors for RNFLD

Risk factors for RNFLD are summarized in Tables 3 and 4. Certain variables were subjected to univariate analysis: age, sex, diagnosis of hypertension, and diabetes mellitus; MRI findings such as cerebral SVDs, brain atrophy, aneurysm, cerebral vascular stenosis, pineal cysts, suprasellar mass lesions; and fundus abnormalities including drusen, epiretinal membrane (ERM), and diabetic retinopathy (DMR). In univariate regression analysis, older age, male sex, hypertension, diabetes mellitus, cerebral SVD, and vascular stenosis were associated significantly with the presence of RNFLD (Table 3). Multivariate logistic regression analysis results showed that having hypertension (OR 1.73; 95% CI, 1.28–2.34; P < 0.001) and cerebral SVD (OR 1.58; 95% CI, 1.17–2.12; P = 0.003) and being male (OR 1.47; 95% CI, 1.10–1.96; P = 0.011) and older (OR 1.02; 95% CI, 1.00–1.03; P = 0.034) increased the risk for RNFLD (Table 4, Figs. 1, 2). The subgroups of cerebral SVD—SWMLs and LI_WMLs—remained significant risk factors for RNFLD (OR, 1.54; 95% CI 1.12–2.10; P = 0.007 and OR, 2.66;
TABLE 3. Distribution of Cerebral Small Vessel Disease by Anatomic Location

<table>
<thead>
<tr>
<th>SVD Location</th>
<th>RNFLD Group with Cerebral SVD (n = 90)</th>
<th>Non-RNFLD Group with Cerebral SVD (n = 987)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Periventricular area</td>
<td>31 (34.4)</td>
<td>262 (26.5)</td>
</tr>
<tr>
<td>Frontal lobes</td>
<td>22 (24.4)</td>
<td>238 (24.1)</td>
</tr>
<tr>
<td>Parietal lobes</td>
<td>17 (18.9)</td>
<td>191 (19.4)</td>
</tr>
<tr>
<td>Temporal lobes</td>
<td>5 (5.5)</td>
<td>39 (4.0)</td>
</tr>
<tr>
<td>Occipital lobes</td>
<td>2 (2.2)</td>
<td>18 (1.8)</td>
</tr>
<tr>
<td>Basal ganglia</td>
<td>9 (10.0)</td>
<td>106 (10.7)</td>
</tr>
<tr>
<td>Centrum semiovale</td>
<td>6 (6.7)</td>
<td>55 (5.6)</td>
</tr>
<tr>
<td>Pons</td>
<td>2 (2.2)</td>
<td>27 (2.7)</td>
</tr>
<tr>
<td>Midbrain</td>
<td>1 (1.1)</td>
<td>2 (0.2)</td>
</tr>
<tr>
<td>Thalamus</td>
<td>4 (4.4)</td>
<td>32 (3.2)</td>
</tr>
<tr>
<td>Corona radiate</td>
<td>1 (1.1)</td>
<td>4 (0.4)</td>
</tr>
<tr>
<td>Cerebellar area</td>
<td>1 (1.1)</td>
<td>9 (0.9)</td>
</tr>
<tr>
<td>External capsule</td>
<td>6 (6.7)</td>
<td>18 (1.8)</td>
</tr>
<tr>
<td>Internal capsule</td>
<td>1 (1.1)</td>
<td>4 (0.4)</td>
</tr>
<tr>
<td>Caudate nucleus</td>
<td>0 (0)</td>
<td>10 (1.0)</td>
</tr>
</tbody>
</table>

Data are the number (%). A patient having more than one SVD lesion in the same location was counted as having only one SVD at that location. A patient with more than one location of SVD was double counted. 95% CI 1.28–5.55; P = 0.009, respectively) whereas SLI was not associated with RNFLD (Table 4).

DISCUSSION

Several studies have been conducted that focused on the association between cerebral SVD and NTG. However, most of the studies were conducted in NTG patients, and there has been little information presented thus far regarding the association between RNFLD and the presence of cerebral SVD in a large population. The results of the present study demonstrate an association between RNFLD and cerebral SVD in a large population. To the best of our knowledge, this study is the first to report an association between cerebral SVD and NTG. However, most of the previous studies focused on the association between RNFLD and NTG. Therefore, RNFLD has been encountered more frequently than ever before. For that reason, we assessed RNFLD in the present study, even though RNFLD does not always equate to a diagnosis of glaucoma.

Although subjects with RNFLD cannot simply be considered as glaucoma patients, RNFLD is considered to be a pathologic condition. Jonas and Schiro reported that localized RNFLD was very rarely observed in normal eyes and it almost always indicated an optic nerve abnormality. Furthermore, many studies have shown a high detection rate of glaucoma in subjects referred to the glaucoma clinic from health-screening centers. Kim et al. reported that 28% of Korean subjects who were referred to the glaucoma clinic after a health-screening examination using nonmydriatic fundus photography had definite visual field defects. Other subjects without visual field defects also showed higher pattern standard deviation values on the Humphrey automated visual field test. Including preperimetric glaucoma, the proportion of glaucoma would be much higher because most subjects showed early RNFLD on red-free photography. Moreover, 96% of referred subjects had IOP within the normal range (≤21 mm Hg). Taken together, most of the RNFLD group in the present study would be related to glaucoma, especially NTG.

The reported prevalence of SCI ranges from 8% to 28%. In our study, 1077 (24.5%) of the 4395 subjects had cerebral SVD, which is consistent with the findings of previous studies. After the subjects were divided into two groups according to the presence or absence of RNFLD, the percentage of cerebral SVD in the RNFLD group was 37.8% (90/238 subjects), compared with 23.7% (987/4157 subjects) in the non-RNFLD group (P < 0.001). This result is also similar to those of previous studies in which the prevalence of SCI or WML was reported as 34% to 40% in NTG patients.

In the present study, we detected an association between RNFLD and the presence of cerebral SVD. After adjusting for other risk factors, the odds ratio of cerebral SVD was 1.58 (P = 0.003). Subgroup analysis results demonstrated that the SWML and LI_WML group were still associated with the presence of RNFLD (P = 0.007 and P = 0.009, respectively). However, the SLI group was not related significantly with the presence of RNFLD. These results imply that the pathogenesis of RNFLD may be similar to WML, but not LI. Previous studies indicated that WML and LI are disparate forms of cerebral SVD evidencing different time course and risk factors. Acute ischemic...
damage of small focal regions in perforating arteriole territories appeared to cause LI, whereas chronic ischemic damage results in WML. Therefore, it appears that RNFLD shares the chronic aspect of cerebral SVD.

In our study, the most common location of cerebral SVD was the periventricular area. It had no topographic correspondence to the presence or the location of RNFLD. It has been assumed that cerebral SVD may be linked to cerebral ischemia and the periventricular area known to be vulnerable to ischemic insult. This may indirectly suggest a role of vascular insufficiency or related factors in the pathogenesis of RNFLD or NTG. Further studies are warranted in the future in regard to this matter.

Having hypertension and being of the male sex and older put subjects more at risk for RNFLD in the present study. Hypertension has been tentatively associated with RNFLD as well as open-angle glaucoma, including NTG. Because hypertension is regarded as an important disease related to the pathogenesis of cerebral SVD, it may be a confounding factor in the association between RNFLD and cerebral SVD. However, the association between RNFLD and cerebral SVD was still significant in a multivariate analysis that included hypertension as a parameter. To the best of our knowledge, there have been no reports regarding the association between RNFLD and being male, although several studies have predicted that being of the male sex would correlate with higher prevalence of open-angle glaucoma. Those results may explain some facets of our results, although further studies are clearly warranted to confirm our findings.

This study was limited in several ways. First, due to the study's retrospective cross-sectional design, it is possible that some of the cases of RNFLD were caused by other previous ocular diseases, such as optic disc drusen, toxoplasmotic retinochoroidal scars, cotton-wool spots, longstanding papilledema, or multiple sclerosis with optic neuritis. However, owing to their comparatively low frequencies, RNFLD is regarded as the most dependable early sign of glaucoma, which may be present despite a normal optic disc and intact visual field. Moreover, concomitant medications were not included and controlled in analysis because of the retrospective design of the present study. Second, possible selection biases should be considered because all subjects voluntarily received health-screening examinations, including brain MRI and fundus photography. The subjects included in present study all were concerned about their own health; this may have introduced bias. Third, we used a semiquantitative scale for the grading of WML, vascular stenosis, and RNFLD. These grading systems may not provide an accurate estimation of the severity of the lesion; however, we also assessed the presence of the lesion and the association between the presence of RNFLD and other factors. Thus, the possible effects of misclassification should be minimal, if not negligible. Finally, we could not estimate the statistical power, since the present study was of retrospective cross-sectional design. However, our P values were low enough to imply an association between RNFLD and cerebral SVD.

Our data do not suggest that all patients with RNFLD should be evaluated with brain MRI for the detection of cerebral SVD, or vice versa. The principal objective of this study was to determine whether RNFLD was associated with cerebral SVD in a large population. The clinical importance of cerebral SVD should be established before analysis of the cost-effectiveness.
of brain imaging in patients with RNFLD is conducted. Further studies by neurologists and ophthalmologists are clearly necessary to determine the clinical relevance of the association between RNFLD and cerebral SVD.

In conclusion, RNFLD detected via fundus photography was related to cerebral SVD, particularly the subgroup of SWML and LI_WML, detected with MRI. Having hypertension and being male and older were risk factors for RNFLD in the general population.

References