**Hierarchical Cluster Analysis of Progression Patterns in Open-Angle Glaucoma Patients With Medical Treatment**

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**PURPOSE.** To classify medically treated open-angle glaucoma (OAG) by the pattern of progression using hierarchical cluster analysis, and to determine OAG progression characteristics by comparing clusters.

**METHODS.** Ninety-five eyes of 95 OAG patients who received medical treatment, and who had undergone visual field (VF) testing at least once per year for 5 or more years. OAG was classified into subgroups using hierarchical cluster analysis based on the following five variables: baseline mean deviation (MD), baseline visual field index (VFI), MD slope, VFI slope, and Glaucoma Progression Analysis (GPA) printout. After that, other parameters were compared between clusters.

**RESULTS.** Two clusters were made after a hierarchical cluster analysis. Cluster 1 showed −0.06 ± 2.43 dB baseline MD, 92.58% ± 6.27% baseline VFI, −0.28 ± 0.38 dB per year MD slope, −0.52% ± 0.81% per year VFI slope, and all “no progression” cases in GPA printout, whereas cluster 2 showed −0.68 ± 3.81 baseline MD, 77.54% ± 12.98 baseline VFI, −0.72 ± 0.55 MD slope, −2.22 ± 1.89 VFI slope, and seven “possible” and four “likely” progression cases in GPA printout. There were no significant differences in age, sex, mean IOP, central corneal thickness, and axial length between clusters. However, cluster 2 included more high-tension glaucoma patients and used a greater number of antiglaucoma eye drop significantly compared with cluster 1.

**CONCLUSIONS.** Hierarchical cluster analysis of progression patterns divided OAG into slow and fast progression groups, evidenced by assessing the parameters of glaucomatous progression in VF testing. In the fast progression group, the prevalence of high-tension glaucoma was greater and the number of antiglaucoma medications administered was increased versus the slow progression group.

Keywords: hierarchical cluster analysis, open-angle glaucoma, progression

Open-angle glaucoma (OAG) is a chronic, progressive optic neuropathy with a characteristic optic nerve appearance and associated visual field (VF) defects.1 Although VF defects usually progress relatively slowly, it is clinically important to identify patients who show more rapid OAG progression and to define factors that contribute to rapid progression. Many previous studies have demonstrated that progression rates vary widely among patients.2–6 For example, in the Early Manifest Glaucoma Trial (EMGT), which was a major randomized clinical trial, the mean progression rate was −1.08 dB per year overall, −1.31 dB per year in high-tension glaucoma (HTG), −0.36 dB per year in normal-tension glaucoma (NTG), and −3.13 dB per year in pseudoexfoliation glaucoma (PEXG).7 Based on several previous studies, increased IOP, older age, decreased central corneal thickness (CCT), lower ocular perfusion pressure, and pseudoexfoliation syndrome have been demonstrated to be risk factors of glaucomatous VF defect progression.6,8–10 However, most previous studies have investigated glaucomatous progression only by calculating progression rates or evaluating risk factors. Attempts to assess and compare OAG progression patterns were not located by us in the literature. The present study used hierarchical cluster analysis to classify medically treated OAG patients by glaucoma progression patterns characterized by rapidity of VF deficit development, and to compare the characteristics of slow- versus fast-progressing OAG.

**METHODS**

**Subjects**

The clinical records of OAG patients seen at the glaucoma clinic of Severance Hospital at Yonsei University College of Medicine between April 2004 and January 2012 were retrospectively reviewed. This study followed the tenets of the Declaration of Helsinki and was approved by the institutional review board of our institute. We included patients with glaucomatous optic neuropathy and glaucomatous VF defect, who also had open-angled anterior chamber and had undergone VF testing (30-2 SITA Standard algorithm, Humphrey Visual Field Analyzer; Carl Zeiss Meditec, Inc, Dublin, CA) with visual field data available for review. The study included 95 patients (95 eyes) who were treated with medical therapy and had undergone VF testing at least once per year for 5 or more years. Exclusion criteria included patients with a history of other eye pathologies,镰状贫血, or angle-closure glaucoma.
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Table 1. Demographics of Subjects

<table>
<thead>
<tr>
<th>Variables</th>
<th>OAG, n = 95</th>
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</thead>
<tbody>
<tr>
<td>Age (range)</td>
<td>56.1 ± 14.7 (26–79)</td>
</tr>
<tr>
<td>Sex, female/male (%)</td>
<td>35 (37)/60 (63)</td>
</tr>
<tr>
<td>Diagnosis, NTG/HTG (%)</td>
<td>43 (45)/52 (55)</td>
</tr>
<tr>
<td>Follow-up period, y</td>
<td>5.8 ± 0.6</td>
</tr>
<tr>
<td>No. of VF tests</td>
<td>6.73 ± 1.76</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD or n (%), as appropriate.

Zeiss Meditec, Inc., Dublin, CA, USA) at least once per year for 5 years or more. HTG was defined when untreated IOP was more than 21 mm Hg, and NTG was diagnosed when a maximum untreated IOP was always 21 mm Hg or lower with three repeated measurements taken during separate follow-up visits. All eligible eyes had been treated medically under a glaucoma specialist’s (CYK) care, and were required to have best corrected visual acuity (BCVA) of 20/40 or better on a Snellen acuity chart at baseline. If both eyes of the same patient were eligible, the eye with the greater number of VF tests was enrolled. We excluded subjects who were unfamiliar with automated VF testing, without reliable baseline VF test results, who had any type of incisional or laser ocular surgery during the study period, and subjects whose conditions would likely affect VF testing (except for glaucoma and mild cataract). We also excluded PEXG patients.

All patients underwent a complete ophthalmologic examination at baseline assessment including BCVA, IOP, slit-lamp biomicroscopy, VF testing, ultrasonic pachymetry (DGH-1000 pachymeter; DGH Technology, Inc., Frazer, PA, USA) to measure CCT, IOL Master ocular biometric device (Carl Zeiss Meditec, Jena, Germany) for axial length (AL) assessment, color disc photography, and dilated-fundus examination with a 90-dioptr lens. Some of these examinations were repeated at 3- to 12-month intervals, as necessary. IOP was assessed using Goldmann applanation tonometer, and we applied standard definitions of peak IOP, mean IOP, and IOP fluctuation.11 Peak IOP was defined as the highest IOP measurement, and mean IOP was the average of all pressure measurements taken every 3 months during follow-up. IOP fluctuation was defined as the SD of the mean values. Other clinical histories about antiglaucoma eye drop use during the study period were collected from patient charts. Combination antiglaucoma eye drops were considered as two eye drops when the average number of medications was calculated.

Visual Field Analysis

A glaucomatous VF defect was defined as the presence of (1) a cluster of 5 or more locations depressed at the P less than 0.05 level, one of which had to be depressed at the P less than 0.01 level on a pattern deviation plot; (2) an abnormal glaucoma hemifield test; or (3) a pattern SD value that was significant at the P less than 0.05 level on two consecutive baseline VF tests.12 All VF tests required reliability indices better than 20% to be included, and unreliable VF tests were excluded. All patients were also experienced in VF testing. From VF tests, we used five variables that are related to VF progression for a hierarchical cluster analysis: baseline mean deviation (MD) (dB), baseline visual field index (VFI) (%), MD slope (dB/year), VFI slope (%/year), and Glaucoma Progression Analysis (GPA) printout.

Baseline MD and VFI were adopted from the first VF test in this study period. MD slope and VFI slope were calculated by linear regression analysis of the MD and VFI values over time, respectively, for at least five VF tests for each patient. GPA printout was obtained using the Humphrey VF Analyzer software. The GPA methodology was based on the EMGT study.13 The GPA established a baseline by averaging results of the first two examinations and successive follow-up examinations were compared with baseline data. Presence of progression was considered as “possible” when there was significant deterioration at the same 3 or more points on two consecutive tests, and as “likely” when such deterioration occurred over three consecutive tests.

Statistical Analysis

To classify VF progression patterns in OAG, a hierarchical cluster analysis was performed using the proc cluster procedure from SAS software (SAS Institute, Inc., Cary, NC, USA) (see Supplementary Appendix S1 for SAS code). Specifically, the agglomerative technique was performed to group OAG eyes into homogeneous subgroups, in which it begins by considering each eye to be cluster by itself, and continues until similar clusters merge together. Of all 11 methods (AVERAGE, CENTROID, COMPLETE, DENSITY, EML, FLEXIBLE, MCQUITTY, MEDIAN, SINGLE, TWOSTAGE, and WARD method), Ward’s minimum variance method was used as clustering criterion, which has the advantage of minimizing the total within-cluster variance. All variables were standardized before clustering. To determine the optimal number (k) of clusters, we used the pseudo $R^2$ statistic; the pseudo $R^2$ statistic provides an indication of the appropriate number of clusters through local troughs in its value. This is seen by a small value of the pseudo $R^2$ statistic for a given cluster level followed by a larger pseudo $R^2$ value for the next cluster fusion. After deciding the optimal number of clusters, the cluster progression characters were analyzed and compared according to the five primary VF variables and other selected demographic and ocular biometric parameters. Independent two-sample t-test and $\chi^2$ test were used to analyze differences between clusters.

We used SAS software version 9.2 (SAS Institute, Inc.) for all statistical analyses and $P$ less than 0.05 was considered statistically significant.

Results

Ninety-five eyes of 95 OAG patients were enrolled in this study. The mean age at baseline was 56.1 ± 14.7 years (range 26–79 years). There were more men (63%) and slightly more HTG (55%) than NTG cases diagnosed. Mean observation period was 5.8 ± 0.6 years and the mean number of examined VF tests was 6.73 ± 1.76 (Table 1).

Using a hierarchical cluster analysis, all subjects were classified by the five variables that represent the pattern of VF deficit progression in glaucoma. To determine the number of clusters that best fit the data, we found the small pseudo $R^2$ statistics followed by a much larger value. The two-cluster solution in this analysis had a pseudo $R^2$ value of 12.430

<table>
<thead>
<tr>
<th>No. of Clusters</th>
<th>Pseudo $R^2$ Statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>30.586</td>
</tr>
<tr>
<td>4</td>
<td>29.974</td>
</tr>
<tr>
<td>3</td>
<td>14.456</td>
</tr>
<tr>
<td>2</td>
<td>12.430</td>
</tr>
<tr>
<td>1</td>
<td>30.876</td>
</tr>
</tbody>
</table>

* Pseudo $R^2$ statistic indicates the appropriate number of clusters. A potentially optimal number of clusters is indicated when a small pseudo $R^2$ statistic is followed by a much larger value.
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The progression pattern of cluster 1 was characterized by $-0.06 \pm 2.43$ dB baseline MD, $92.58\% \pm 6.27\%$ baseline VFI, $-0.28 \pm 0.38$ dB per year MD slope, $-0.52\% \pm 0.81\%$ per year VFI slope, and all eyes were "no progression" in the GPA printout. On the other hand, the 28 eyes in cluster 2 showed $-8.68 \pm 3.81$ dB baseline MD, $77.54\% \pm 12.98\%$ baseline VFI, $-0.72 \pm 0.55$ dB per year MD slope, $-2.22\% \pm 1.89\%$ per year VFI slope, and 7 "possible progression" and 4 "likely progression" cases in the GPA printout. There were significant differences in all variables between cluster 1 versus 2 (Table 3). Figure 2 shows the distributions of four variables (except GPA printout) used for hierarchical cluster analysis of the two clusters. There were largely overlapping portions in all of the four variables; however, substantial distinctions were found between interquartile ranges of two clusters, especially in the baseline VFI.

Comparisons of patient demographics and other select optical biometrics between the two clusters are shown in Table 4. There were no significant differences in age, sex, CCT, AL, mean IOP, peak IOP and IOP fluctuation between the two groups. However, HTG was present in 71% of patients in cluster 2 versus only 48% of patients in cluster 1 ($P = 0.035$). The average number of antiglaucoma eye drop medications used during follow-up was $2.29 \pm 1.21$ in cluster 2, which was significantly higher than $1.42 \pm 0.88$ medications used in cluster 1 ($P = 0.001$).

**DISCUSSION**

We investigated VF deficit progression patterns in medically treated OAG patients. A hierarchical cluster analysis was used to analyze progression patterns, which is a useful statistical tool to investigate disorders by classifying subjects into homogeneous subgroups based on similar characteristics. Hierarchical cluster analysis suggested classifying the progression of OAG into two groups based on five variables from VF testing. Cluster 1 showed significantly better baseline MD and VFI values, and less-steep MD and VFI slopes than cluster 2. Cluster 1 also had "no progression" in all GPA printouts, whereas cluster 2 had seven "possible progression" and four "likely progression" cases. Therefore, cluster 1 and cluster 2 were represented as the slow- and fast-progression groups, respectively.

There were no differences in age, sex, CCT, AL, and IOP variables (mean, peak, and fluctuation) between the two clusters. Although there exists disagreement on the effect of sex and AL on OAG progression, most previous studies that investigated OAG risk factors have suggested that older age, thinner CCT, and higher IOP variables are related to the VF deficit progression in OAG. In this study, we took a different approach to assessing OAG risk factors by analyzing the VF deficit progression patterns first; we did not find a similar effect of those risk factors on OAG progression. IOP variables, which are well-established OAG risk factors, were not significantly different between the two groups, although the fast-progression group trended toward slightly higher mean IOP, peak IOP, and IOP fluctuation than the slow-progression group.

Between two groups, two other significant differences were observed. First, the fast-progression group had larger proportion of HTG patients than the slow-progression group ($P = 0.035$). Although the HTG and NTG classifications are still used during follow-up was $2.29 \pm 1.21$ in cluster 2, which was significantly higher than $1.42 \pm 0.88$ medications used in cluster 1 ($P = 0.001$).

**Table 3. Comparisons of VF Progression Patterns Between Two Clusters Obtained by a Hierarchical Cluster Analysis**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Cluster 1, $n = 67$</th>
<th>Cluster 2, $n = 28$</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MD, dB</td>
<td>$-4.05 \pm 2.43$</td>
<td>$-8.68 \pm 3.81$</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>VFI, %</td>
<td>$92.58 \pm 6.26$</td>
<td>$77.54 \pm 12.98$</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>MD slope, dB/y</td>
<td>$-0.28 \pm 0.38$</td>
<td>$-0.72 \pm 0.55$</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>VFI slope, %/y</td>
<td>$-0.52 \pm 0.81$</td>
<td>$-2.22 \pm 1.89$</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>GPA printout, no/possible/likely progression</td>
<td>67 (100)/0 (0)/0 (0)</td>
<td>17 (60.7)/7 (25)/4 (14.3)</td>
<td>$&lt;0.001$</td>
</tr>
</tbody>
</table>

Data are expressed as mean $\pm$ SD or n (%).
widely used in clinical care, HTG and NTG are currently considered as a single disease because of their similar properties.\textsuperscript{18–20} This convention was supported by our study, in which HTG and NTG cases were mixed within each cluster. IOP is the only factor that could differentiate HTG and NTG. In the EMGT, the mean progression rate in HTG was \(-1.31\) dB per year, which was more rapid than \(-0.36\) dB per year in NTG.\textsuperscript{7} Thus, our data are consistent with the EMGT in that the fast-progression group had a higher frequency of HTG patients. However, our study investigated medically treated OAG patients whose IOPs were within the normal range, whereas the EMGT examined the natural course of OAG. Because there were no significant differences in all IOP variables between the two study groups, we speculate that pretreatment IOP might

FIGURE 2. The distributions of baseline MD (left top), baseline VFI (right top), MD slope (left bottom), and VFI slope (right bottom) from two clusters are shown. Thick line indicates median, box boundaries indicate interquartile range, and open circles indicate outliers.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Cluster 1, (n = 67)</th>
<th>Cluster 2, (n = 28)</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>55.5 ± 14.9</td>
<td>57.5 ± 14.3</td>
<td>0.553</td>
</tr>
<tr>
<td>Sex, female/male</td>
<td>41 (61)/26 (39)</td>
<td>19 (68)/9 (32)</td>
<td>0.539</td>
</tr>
<tr>
<td>Diagnosis, NTG/HTG</td>
<td>35 (52)/32 (48)</td>
<td>8 (29)/20 (71)</td>
<td>0.035</td>
</tr>
<tr>
<td>CCT, (\mu m)</td>
<td>540.12 ± 35.16</td>
<td>545.04 ± 26.25</td>
<td>0.520</td>
</tr>
<tr>
<td>AL, mm</td>
<td>25.09 ± 1.78</td>
<td>24.67 ± 1.83</td>
<td>0.299</td>
</tr>
<tr>
<td>Mean IOP, mm Hg</td>
<td>13.61 ± 2.29</td>
<td>14.11 ± 2.12</td>
<td>0.324</td>
</tr>
<tr>
<td>Peak IOP, mm Hg</td>
<td>17.06 ± 3.24</td>
<td>17.93 ± 3.92</td>
<td>0.266</td>
</tr>
<tr>
<td>IOP fluctuation, mm Hg</td>
<td>1.64 ± 0.49</td>
<td>1.84 ± 0.86</td>
<td>0.242</td>
</tr>
<tr>
<td>Average no. of antiglaucoma eye drops</td>
<td>1.42 ± 0.88</td>
<td>2.29 ± 1.21</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD or \(n\) (%).
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play an important role in OAG progression and prognosis, even though IOP would be reduced by treatment. According to the Collaborative Initial Glaucoma Treatment Study (CIGTS), aggressive IOP-lowering therapy minimizes VF loss.\(^9\) The Advanced Glaucoma Intervention Study (AGIS) identified that low IOP levels (<14 mm Hg) tended to be associated with less VF loss than IOP levels often considered adequate (i.e., 14 to 17.5 mm Hg), although this difference was not statistically significant.\(^9\) Another recent CIGTS report supposed that more aggressive treatment would be needed when elevated IOP was observed.\(^22\) Therefore, it might be that HTG patients who have higher pretreatment IOP should be aggressively treated to obtain a lower target IOP than NTG patients to reduce disease progression.

The average number of antiglaucoma eye drop medications used by the fast-progression group was significantly greater than the slow-progression group (\(P = 0.001\)). Because mean IOP was not significantly different between the two groups, this suggests that a larger number of antiglaucoma eye drops was needed in the fast-progression group to maintain a similar IOP level as the slow-progression group. This difference in medication histories could also mean that there is greater potential IOP fluctuation in the fast-progression group, although a significant difference in IOP fluctuation was not observed between the two groups. Previous studies found that IOP fluctuation is significantly correlated with VF deficit progression.\(^23,24\) AGIS investigators also indicated that greater IOP fluctuation was a significant predictive factor for glaucomatous VF deficit progression.\(^17\) Because IOP measurements were conducted at 3-month intervals in this study, we could not fully evaluate intervisit or diurnal fluctuations. To demonstrate precise IOP fluctuations, additional research, such as 24-hour IOP monitoring would be helpful.

Our investigation was limited by its retrospective design and was not free wholly from selection bias. Another weakness was that 95 subjects is a rather small number of cases to classify into subgroups, and the approximately 6-year follow-up was a relatively short period to sufficiently observe glaucoma progression. However, our primary strong point was the inventive approach of using, for the first time, hierarchical cluster analysis to evaluate VF deficit progression in OAG patients.

In conclusion, hierarchical cluster analysis divided medically treated OAG patients into slow- and fast-progression groups, using VF testing parameters to assess glaucomatous progression. The fast-progression group significantly differed from the slow-progression group by having a larger proportion of HTG patients and by using a larger number of antiglaucoma eye drop medications.

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