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Clustered Trend-Type Analysis to Detect Progression of Visual Field Defects in Patients with Open-Angle Glaucoma

Takeo Fukuchi, Takaiko Yoshino, Masaaki Seki, Tetsuya Togano, Hideko Sawada and Haruki Abe
Division of Ophthalmology and Visual Science, Graduated School of Medical and Dental Sciences, Niigata University Japan

1. Introduction

Glaucoma remains one of the leading causes of acquired blindness worldwide (Thylefors & Negrel, 1994; Quigley & Broman, 2006). Open-angle glaucoma (OAG) including primary open-angle glaucoma (POAG), and normal-tension glaucoma (NTG), is the most common type of glaucoma and is just a representative chronic disease such as hyptertension and diabetes mellitus (Schwartz & Quigley, 2008; Quigley, 2011). Because the ultimate goal of glaucoma treatment is to maintain long-term visual function, glaucomatous patients require essentially lifelong follow-up. Thus, we need an approach to glaucoma management that considers patients' present visual functions as well as their future prognosis.

The pathogenesis of glaucomatous optic neuropathy as well as the details of its long-term progression have not beeen clered yet. Many clinical trials have confirmed the importance of intraocular pressure (IOP) in the development and progression of OAG (Kass et al., 2002; Gordon et al, 2002; Heijl et al. 2002; 2003; Leske et al, 1999; 2003; Collaborative normal-tension glaucoma study group, 1998; 2001; Anderson et al, 2003; The AGIS Investigators, 1994; 2000; Katz, 1999; Musch et al, 2009; Parrish et al, 2009; Chauhan et al, 2008). These studies have shown that lowering IOP reduces the risk of developing OAG and slows its progression. The aim of current glaucoma treatment approaches is to maintain patients' visual function for as long as possible by reducing IOP. In addition to visual function, of course, we monitor patients' IOP, optic discs, and retinal changes. Since preservation of visual fields is the final outcome in glaucoma management, ongoing evaluation of patients' visual fields must be the most important activity in clinical practice. Recently, the morphological evaluation of optic disc cupping, retinal nerve fiber layer defects, and the retinal ganglion cell complex by imaging systems such as optical coherence tomography (OCT) has become popular (Wollstein et al, 2005; Tan O et al, 2009). After all these systems provide only the ability to reliably and safely detect or predict glaucoma progression beside monitering visual field and visual acuity (Hood & Kordon, 2007; Harwerth et al, 2010; Parrish et al, 2009).

Standard automated perimetry (SAP) is used to examine and evaluate visual fields, but the technique is difficult to perform and have still has many problems. Furthermore, there is

currently no consensus on the proper method of evaluating visual field progression despite the fact that it is one of the most important aspects of glaucoma management. Spry and Johnson (2002) grouped procedures for detection of glaucomatous visual field defects into four categories: 1) subjective clinical judgment, 2) defect classification systems, 3) trend analyses, and 4) event analyses. Clinical judgment consists of the simple subjective observation of sequential visual field test results and is the oldest method of identifying visual field progression. Though it is, easy to perform, requires no additional instruments, and is useful in clinical practice, it is a subjective, inexact method and is not suitable for evaluating the details of long-standing glaucoma progression. Defect classification systems have often been used in major clinical trials for glaucoma, including the Advanced Intervention Glaucoma Study (AIGS) (The AGIS Investigators, 1994; 2000), and the Collaborative Initial Treatment Study (CIGTS) (Katz, 1999; Musch et al, 2009; Parrish et al, 2009). These systems seem to be more reliable than the others at detecting progression (Mayama et al, 2004). However, each clinical trial set different progression criteria, and various individual criteria were suitable only for specific populations or disease stages (Heijl et al, 2008a). Event-type analysis (Hitchings 1994; Casas-Llera et al, 2009) and trend-type analysis (Holmin & Krakau, 1980; 1982; McNaught et al, 1995; Wild et al, 1989) have often been used in clinical practice since SAP instruments were introduced. Event-type analysis uses 2 or 3 visual field tests to establish a baseline, then compares subsequent tests to this baseline. Progression is considered to have taken place when definite sensitivity loss occurs, usually 2 or 3 dB from baseline. Cases with rapid progression can be picked up with this method earlier than with trend-type analysis. Because of variability in test results, however, the decision that a case has progressed is often reversed by subsequently improved results. A more common method of evaluating progression is trend-type analysis, which uses linear-regression analysis between multiple test results against time course. When the regression line has a significantly negative slope, we consider progression to have occurred. While trend-type analysis is more statistically reliable than event-type analysis, it requires longer follow-up periods and more test results. Some investigations have confirmed that trend-type analysis ideally requires 6 to 7 or more test results (Holmin & Krakau, 1982; Katz et al, 1997; Spry et al, 2000; Chauhan et al, 2008). Thus, for this type of analysis they recommended performing at least 3 visual field examinations within 2 to 3 years from the start of follow-up (Chauhan et al, 2008).

Cases rarely progress rapidly; OAG in particular usually progresses slowly but predictably, generally requiring careful examinations for over 10 years (Collaborative normal-tension group study group, 2001). Two factors that are critical in monitoring the status of glaucomatous patients are ascertaining whether or not their visual field defects have progressed and the rate of progression (Johnson, 2010). It may be possible to predict the state of a patient's visual fields as well as their quality of vision (QOV) if their condition continues to progress at a similar rate. Alternatively, we may evaluate the effects of additional treatments, medication changes, or glaucoma surgery by comparing progression rates between pre- and post-intervention. Although the time interval between the start of progression and its assessment during follow-up should depend on the speed of disease progression, defect classification systems and event-type analysis are only used to evaluate the extent of progression in the glaucomatous eyes. In this regard, trend-type analysis has a significant advantage relative to the other methods in terms of detecting visual field progression.

Both event-type and trend-type analyses can be performed on whole visual fields or on individual test points. Mean deviation (MD) slope, derived the Humphrey Visual Field

Analyzer's (HFA) Statpac 2, is a typical method used to perform trend-type analyses of entire visual fields. Glaucoma Progression Analysis (GPA) for HFA is one way of performing point-by-point event-type analysis. Modified methods of point-by-point event-type analysis have been used to detect progression in the Collaborative Normal-Tension Glaucoma Study (CNTGS) (Collaborative normal-tension group study group, 1998; 2001; Anderson et al, 2003) and the Early Manifest Glaucoma Trial (EMGT) (Leske et al, 1999; 2003; Heijl et al, 2002; 2003). Point-by-point trend-type analyses can be conducted using PROGRESSOR (Fitzke & Hitchings, 1996; Viswanathan et al, 1997), software package for Windows-based personal computers. Analysis of the entire visual field generally has high specificity but low sensitivity because changes in small, localized areas are averaged in with remaining stable areas (Heijl et al, 1986; 1987; Chauhan et al, 1990) . For example, the HFA 30-2 program derives MD by averaging 76 test point values, meaning that this system evaluates 76 points equally. In contrast, point-by-point methods generally have high sensitivity but low specificity (O'Brien & Schwartz, 1990; Smith et al, 1996). There is no consensus on how to use the results of these tests in clinical practice, particularly if we detect progression in only few test points. We may have to establish criteria that enable us to identify an exact progression using point-by-point analysis. Many investigators have recommended cluster- or sector-based visual field analyses as methods that are intermediate between whole visual field and point-by-point approaches (Katz et al, 1997; Nouri-Mahdavi et al, 1997; Mayama et al, 2004). These may be more sensitive than whole visual field techniques and more specific than those using point-by-point assessment. Each OAG patient presents with a different patterns of progression and visual field defects. In addition, each visual field area may contribute differently to patients' QOV (Sawada et al, 2010). In general, lower visual field problems cause greater subjective difficulty than trouble with the upper field. In addition, the central visual field is likely more important than peripheral fields (Gutierrez P et al, 1997; Parrish et al, 1997; McKean-Cowdin et al, 2007; Sumi et al, 2003; Sawada et al, 2011). It may prove beneficial to be able to use clusterization or sectorization to identify not just specific points but also areas of the visual field.

In this study, we used HFA to perform a cluster-based trend-type analysis of OAG patients with long-term follow-up of up to 20 years. We evaluated the usefulness and reliability of this method in detecting progression of visual field defects. We also used this method to evaluate the patterns of longstanding OAG disease progression.

2. Patients and methods

2.1 Patient selection

One eye each from 328 OAG patients were evaluated in this study based on the inclusion and exclusion criteria listed below. If a patient's left and right eyes fit the criteria, we selected one eye randomly. All patients were examined and followed up at the Glaucoma Clinic in the Niigata University Medical and Dental Hospital. All patients were Japanese with similar social backgrounds and resided in the same urban area. The study was conducted in accordance with the Declaration of Helsinki and subsequent revisions thereof under approval of Niigata University.

1. Inclusion criteria

- Diagnosis of POAG or NTG by slit-lamp examination, of the optic disc and visual field, with normal anterior chamber angle, based on the Guidelines for Glaucoma from the European Glaucoma Society (2008) and Japan Glaucoma Society (2002).

- Age between 20 and 80 years at initial examination.
- Follow-up data for at least 5 years with at least 7 reliable analyses (fixation losses, pseudo positive and negative below 30%) with a Humphrey Field Analyzer (HFA, Carl Zeiss Meditec Inc., Dublin, CA) using the Full-Threshold 30-2 program after exclusion of the first 2 or 3 visual field results to minimize learning effects. This was because our preliminary study and previous reports (Holmin, 1982; Katz, 1997; Spry, 2000; Chauhan, 2008) showed that at least 5 or 6 sets of examination test results were necessary for exact trend-type analysis. No reliable, unexpected, or unreasonable results were excluded.
- Reproducible glaucomatous visual field defects based on Anderson and Patella's criteria (Anderson & Patella, 1999) in at least one eye at both the initial and last examinations.

We focused only on whether visual field defect progression was detected in each eye or not. Thus, this study did not take into account patients' medications, surgeries, or IOP during follow-up. However, we excluded eyes that demonstrated loss of visual function within the study period, for instance due to cataract progression, hypotony maculopathy, or bullous keratopathy. Cataract surgery was permitted, but if the visual field changed remarkably before or after surgery, the patient was excluded from the study.

2. Exclusion criteria

- Refractive errors (spherical equivalent powers less than –6D or more than +6D).
- Corrected visual acuity under 20/40.
- A significant cataract that could possibly influence visual acuity and visual field. Eyes with reductions of 3 or more steps in corrected visual acuity due to cataract progression were also excluded.
- Overlap with other types of glaucoma, such as primary angle-closure glaucoma, pseudoexfoliation glaucoma, and steroid-induced glaucoma, even if there was only the possibility of overlap. We also excluded cases with shallow anterior chambers under grade 2 based on van Herick's or Shaffer's classifications.
- Combinations of congenital optic disc anomalies (tilted disc syndrome, optic nerve hypoplasia, optic disc pits, or coloboma) or retinal diseases (diabetic retinopathy, retinal vein or artery occlusion, acquired macular degeneration, central serous chorioretinopathy, etc.).
- Possibility of other optic nerve diseases (optic neuritis, anterior ischemic optic neuropathy, etc.)
- Intracranial legions or trauma, possibly associated with visual field defects.

2.2 Study visits

Patients were observed approximately every 3 months. Study visits included IOP measurements with the Goldmann Applanation Tonometer. Perimetry was performed with an HFA using the Full-Threshold 30-2 program at least once a year. Patients also underwent best-corrected visual acuity measurements and standard eye examinations, including slit-lamp and ophthalmoscopic examinations.

2.3 Analysis of visual fields

The central 30 degrees of patients' visual fields were evaluated for defects using the mean deviation slope (MDS) of the HFA. In this study, the MDS is referred to as "the total MDS". The 76 test points of the HFA central 30-2 full-threshold program were classified into upper and lower visual fields and into 10 visual field clusters (Fig. 1). Clusterization in this study

was based on Suzuki's sectorization (Suzuki et al, 1993; 2001). Originally Suzuki et al. used mathematical calculations to divide the entire central 30-degree field into 15 sectors. We adapted original clusters in central 1 and 9, paracentral 2 and 10, and nasal 3 and 12. In addition to upper clusters, lower and temporal clusters were set by collecting 1 to 3 original sectors. We then calculated the average of total deviations in each cluster and performed a linear regression analysis using a Windows-based PC program, HfaFiles ver.5 (Beeline Co., Tokyo, Japan, URL; http://www.beline.co.jp). In this study, the MDS in upper or lower visual fields was called the hemi-MDS. In addition, the MDS in each cluster was designated as the clustered MDS. If the eyes showed a statistically significant negative correlation with time progress, visual field progression was defined as having occurred. When eyes had a negative total MDS value (<0 dB/yr) and a p-value <0.05, they were considered to have statistically significant progression of the whole visual field. Similarly, significant progression in either upper or lower field was identified as progression in the hemi-MDS. Furthermore, we considered clustered MDS progression to have occurred if significant progression was observed in at least 1 of the 10 clusters.

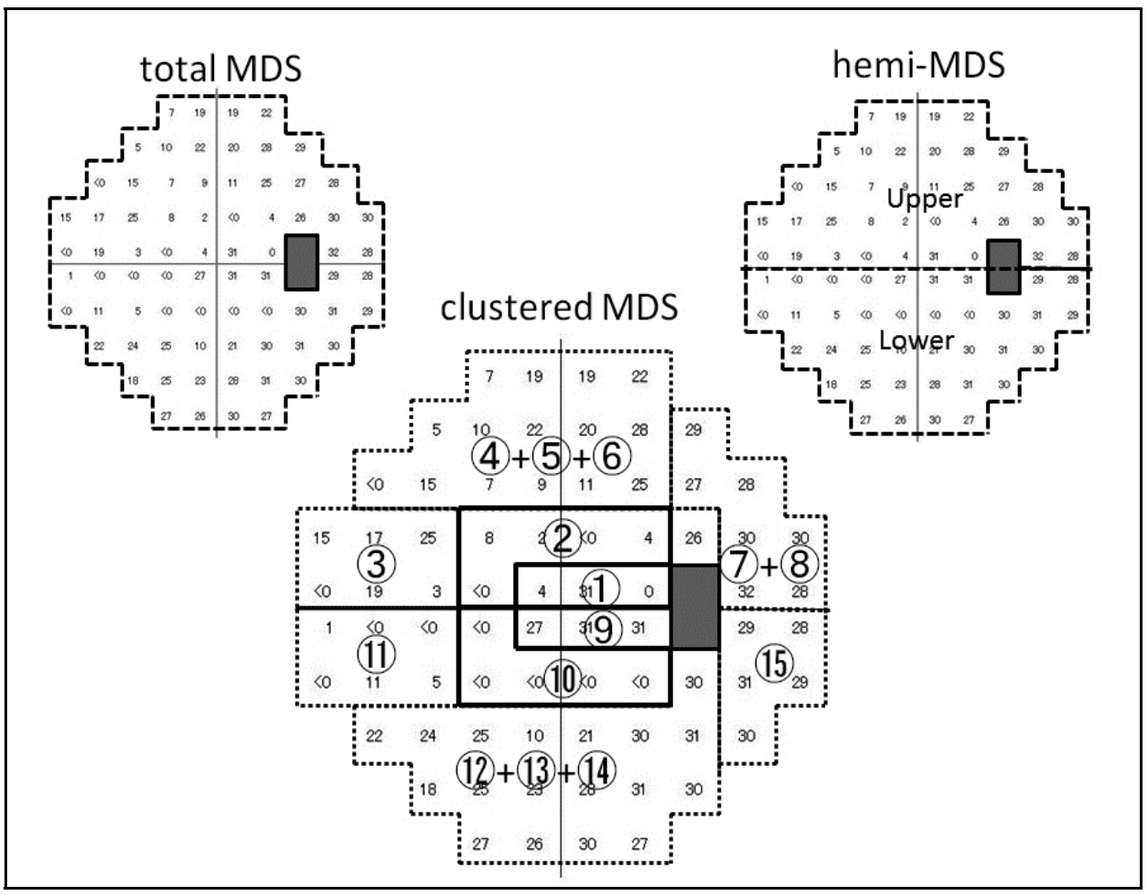


Fig. 1. Setting of the 76 test points of the HFA central 30-2 full-threshold program for 3 types of trend-type analysis, the total MDS, the hemi-MDS and the clustered MDS.

The progression probabilities as determined by hemi and clustered MDS were compared with that of the total MDS. Additionally, hemi-MDS, clustered MDS, and the total MDS were compared in terms of progression rate and severity of the visual field defect. Progression rate was graded by the total MDS and severity was determined based on MD at the initial follow-up.

2.4 Statistical analysis

The MacNemar test was used to compare the total MDS and the hemi- or the clustered MDS. The MacNemar test was also used to compare upper and lower MDS and the MDS of each cluster in the clustered MDS.

3. Results

3.1 Patients profiles

Subject characteristics are shown in Table 1. Subjects were 56.3 ± 11.3 (25–78) years old (average ± standard deviation, range) and had a mean initial MD of –7.69 ± 6.79 (+2.13 to –29.50) dB. They were followed up for 11.6 ± 4.09 (5–22) years. The mean number of valid examinations was 13.2 ± 6.05 (7–52).

	OAG
Cases	328 eyes from 328 subjects
gender (male / female)	162/166
right / left eyes	173/155
age at initial examination	56.2 ± 11.8 (25–78) yr-old
mean deviation at initial examination	–7.69 ± 6.79 (+2.13 to –29.50) dB
follow-up duration	11.6 ± 4.1 (5–22) years
number of visual field examinations	13.2 ± 6.1 (7–52) times

Table 1. Patient profiles used in this study

3.2 An example of 3 types of trend-type analyses

An example of trend-type analyses based on the entire 30-degree field, upper or lower hemifield, and 10 clustered fields are shown in Fig. 2. The subject was 56-yr-old male with NTG and a baseline IOP of 19 mmHg, followed up for 9 years. In his right eye, while the total MDS was –0.20 dB/yr, the upper and lower MDS were -0.23 dB/yr and –0.19 dB/yr, respectively. In this case, 3 MDS indexes, the total, upper and lower MDS, were not statistically significant, so neither the total MDS nor hemi-MDS could be used to determine whether visual field progression had occurred. However, the clustered MDS in area 1 was –1.12 dB/yr (p = 4.17%), that in area 11 was –0.88 dB/yr (p = 0.07%) and that in area 7 and 8 was –0.81 dB/yr (p = 0.14%). His right visual field had deteriorated locally and was evaluated as showing statistically significant progressive loss based only on the clustered MDS.

3.3 Overall results

All 328 eyes were analyzed in the same manner. Progression was seen in 228 eyes (69.3%) based on total MDS, 242 eyes (73.6%) based on hemi-MDS, and 303 (92.1%) eyes based on

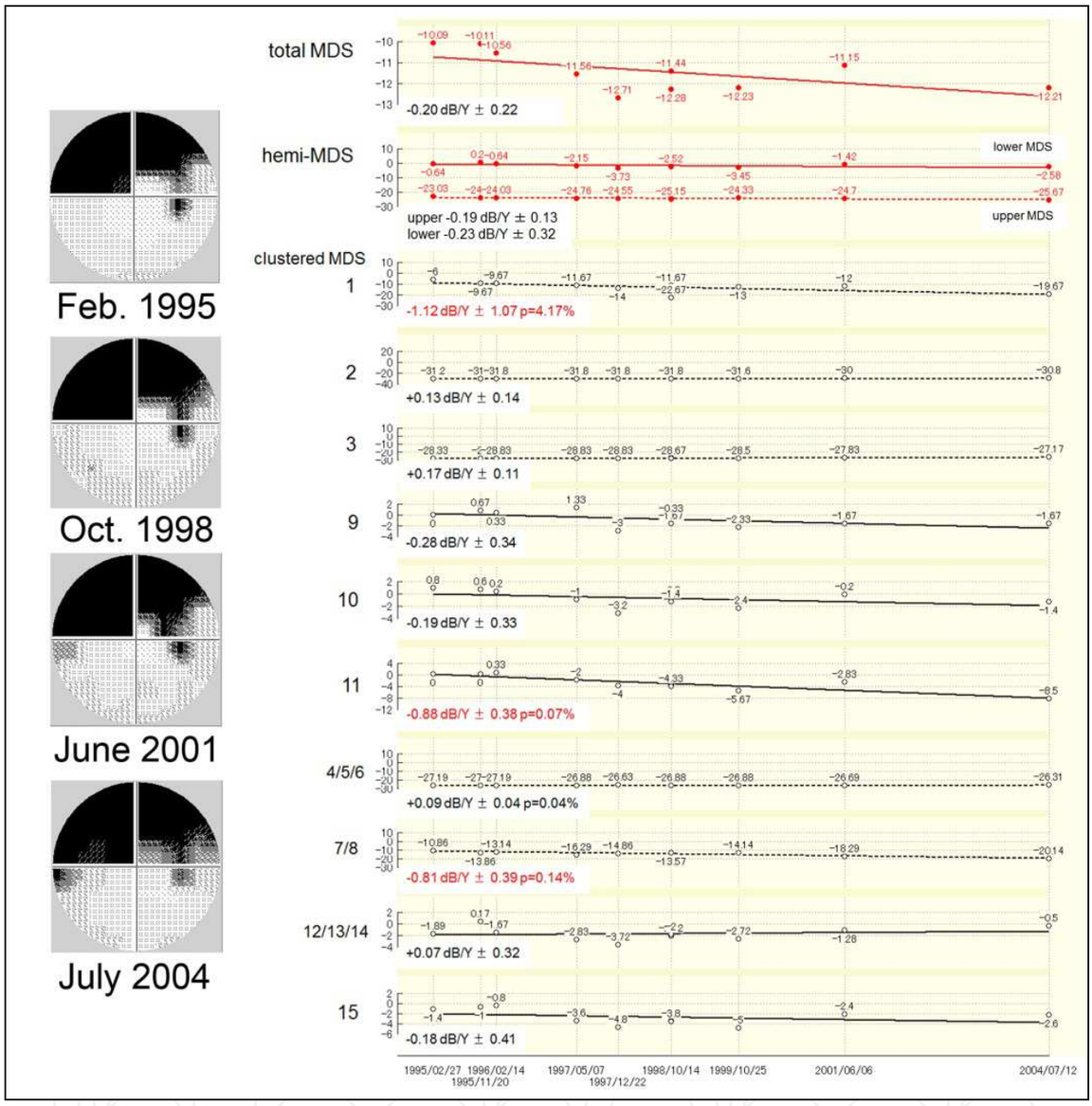


Fig. 2. An example of 3 types of trend-type analysis that were performed in a patient with NTG

clustered MDS (Table 2). Upper and lower MDS were quite similar in terms of their ability to detect progression (185 eyes, 56.2% by upper MDS and 178 eyes, 54.1% by lower MDS). Table 2 also lists the number of eyes showing progression as determined by clustered MDS. Overall, the probability of visual field defect progression was highest in clusters 2 and 10, and then in clusters 4, 5, and 6. Conversely, progression was seen least frequently in cluster 15, then cluster 9. When comparing the same clusters of the upper and lower fields, the difference between clusters 1 and 9 was significant statistically by the McNemer test ($p = 0.0003$). Similarly, the p-values for comparison of different cluster sets were 0.211 for clusters 2 and 10, 1.000 for 3 and 11, 0.238 for 4, 5, and 6 compared to 12, 13, and 14, and 0.000 for 7 and 8 compared to 15.

OAG (n = 328)	# of eyes showing progression	P
total MDS	228 (69.3%)	
hemi-MDS	242 (73.6%)	0.014
upper	185 (56.2%)	0.589 / lower
lower	178 (54.1%)	
clustered MDS	303 (92.1%)	0.000
cluster 1	128 (38.9%)	0.006 / cluster 9
cluster 2	149 (45.3%)	0.211 / cluster 10
cluster 3	134 (40.7%)	1.000 / cluster 11
clusters 4, 5, & 6	142 (43.2%)	0.238 / clusters 12, 13, & 14
clusters 7 & 8	111 (33.7%)	0.000 / cluster 15
cluster 9	96 (29.2%)	
cluster 10	165 (50.2%)	
cluster 11	134 (40.7%)	
clusters 12, 13, & 14	127 (38.6%)	
cluster 15	76 (23.1%)	

Table 2. Incidence of progression determined by 3 types of trend analyses（MDS: mean deviation slope）

3.4 Results by disease severity or progression rate

The number of eyes showing progression, as determined by the total, hemi- and clustered MDS, are shown categorized by MD stages (Table 3) and by total MDS (Table 4). The MD indicates the severity of visual field defects and the disease stage of OAG, and the total MDS marks the speed of progression in OAG. The number of eyes identified as showing progression was statistically similar between the total and hemi-MDS based on the McNemer test. Clustered MDS identified many more eyes exhibiting progression than the total or hemi-MDS in all eyes except for the eyes

initial MD (dB)	eyes	by total MDS	by hemi MDS	p	By clustered MDS	p
MD ≧ 0 dB	28	25 (89.3%)	24 (85.7%)	1.000	26 (92.2%)	1.000
0 > MD ≧ –2.5 dB	59	47 (79.7%)	49 (83.1%)	0.625	58 (98.3%)	0.001
–2.5 > MD ≧ –5.0 dB	61	41 (67.2%)	41 (67.2%)	1.000	55 (90.2%)	0.000
–5.0 > MD ≧ –7.5 dB	44	29 (65.9%)	34 (77.3%)	0.125	43 (97.7%)	0.000
–7.5 > MD ≧ –10.0 dB	31	26 (83.5%)	28 (90.3%)	0.500	29 (93.5%)	0.250
–10.0 > MD ≧ –15.0 dB	55	34 (61.8%)	36 (65.5%)	0.687	50 (90.9%)	0.000
–15.0 > MD ≧ –20.0 dB	28	17 (60.7%)	20 (71.4%)	0.250	25 (89.3%)	0.008
MD > –20.0 dB	22	9 (40.9%)	10 (45.5%)	1.000	17 (77.3%)	0.008

Table 3. Incidence of progression determined by 3 types of trend analysis; Categorization by initial MD as the severity of visual field defect at the start of follow-up

One of the main purposes of this report was to verify the advantages of cluster-based analysis in detecting progression and understanding glaucomatous visual fields. First, we

analyzed progression rates obtained by evaluating 30-degree whole fields (Table 3). In eyes with rapid progression under –0.7 dB/year of the total MD slope, all 3 methods showed a similar ability to identify progression of visual field defects in OAG. Clustered trend-type analysis was more effective in eyes with slower progression, particularly over –0.2 dB/year.

total MDS (dB/yr)	eyes	by total MDS	by hemi MDS	p	by clustered MDS	p
MDS ≧ 0 dB/yr	22	0 (0%)	0 (0%)	-	7 (31.8%)	0.016
0 > MDS ≧ -0.1 dB/yr	29	1 (3.4%)	1 (3.4%)	1.000	22 (78.9%)	0.000
–0.1 > MDS ≧ –0.2 dB/yr	45	23 (51.1%)	27 (60.0%)	0.289	42 (93.3%)	0.000
–0.2 > MDS ≧ –0.3 dB/yr	50	36 (72.0%)	42 (84.0%)	0.109	50 (100%)	0.000
–0.3 > MDS ≧ –0.5 dB/yr	79	73 (92.4%)	73 (92.4%)	1.000	79 (100%)	0.031
–0.5 > MDS ≧ –0.7 dB/yr	44	40 (90.9%)	40 (90.9%)	0.125	44 (100%)	0.008
–0.7 > MDS ≧ –1.0 dB/yr	36	36 (100%)	36 (100%)	1.000	36 (100%)	1.0000
MDS > –1.0 dB/yr	23	23 (100%)	23 (100%)	1.000	23 (100%)	1.0000

Table 4. Incidence of progression determined by 3 types of trend analysis; Categorization by total MDS (indicating progression rate of visual field defects)

We also classified disease severity by initial total MD and then compared the 3 methods (Table 4). For all visual field stages except for eyes with initial MD over 0 dB and between –7.5 and –10.0 dB, clustered analysis was superior to total and hemifield analysis at detecting progression. It is generally difficult to identify progression of visual field defects in severely affected eyes (MD < –20 dB) using total MD slope due to appearance of a "floor effect." From the results, probability of progression decreased even with clustered analysis, but it picked up 17 from 22 eyes (77.3%) as progression. Clustered analysis may be able to evaluate progression using each residual visual field area even in these severe cases.

3.5 Comparison among the 4 groups classified by total and clustered MDS

The final step in our analysis was to separate the eyes into 4 groups based on prevalence of progression as determined by total and clustered MDS (Table 5). All 228 eyes identified as showing progression by total MDS were also detected by clustered MDS. Thus, we compared 3 groups with each other (Table 5). Twenty-five eyes without any progression tended to have shorter follow-up terms, fewer test times, more severe initial MD, and greater total MDS than those with statistically exact progression as determined both by total and clustered MDS.

4. Discussion

The main purposes of visual field testing are threefold: 1) to detect early sensitivity deficits, 2) to aid differential diagnosis by identifying spatial patterns characteristic of sensitivity loss, and 3) to monitor patterns for evidence of progression, stability, or improvement of visual field deficits (Spry & Johnson, 2002). More than two decades have passed since SAP was introduced into clinical practice to manage and monitor glaucoma. Numerous clinical data from glaucomatous patients have been accumulated using this technique. The longer the follow-up period, the more we are able to understand about both the pathogenesis and disease course of OAG. The purpose of this study was to verify the usefulness and necessity

	Progression by total MDS			
	Yes		No	
	Progression by clustered MDS			
	Yes	No	Yes	No
n=	228	0	75	25
initial age	56.8±11.1	-	55.3±11.6	54.2±11.0
p	-		0.3261	0.2739
follow-up duration	12.3±4.2	-	10.2±3.5	10.5±3.8
p	-		0.0001	0.0349
test times	13.8±5.9	-	12.4±7.0	10.6±2.8
p	-		0.1154	0.0000
initial MD	–6.72±6.22	-	–9.42±7.27	–11.30±8.30
p	-		0.0047	0.0124
total MDS	–0.54±0.34	-	–0.18±0.19	0.03±0.12
p	-		0.0000	0.0000

Table 5. Four groups' classification by incidence of progression as determined by total MDS and clustered MDS.

of cluster-based trend-type analysis in identifying progression of visual field defects in glaucomatous patients, and to use this method to elucidate the long-term disease course or manners of OAG. Numerous studies have shown that clusterization or sectorization is recommended because of their usefulness in evaluating individual test results as well as disease progression (Katz et al, 1997; Nouri-Mahdavi et al, 1997; Mayama et al, 2004). Furthermore, analysis of clinical data from patients followed up for as many as 20 years demonstrates other advantages: 1) cluster-based analysis is particularly useful for detecting local and minimal changes in glaucomatous visual fields, 2) detecting defects anywhere in the visual field is necessary for maintaining lifelong QOV in OAG, and 3) understanding OAG disease progression requires evaluation of both whole and local visual fields.

This study used HfaFiles ver.5 (Beeline Co., Tokyo, Japan), a Windows-based PC program. Similar programs are available for managing and analyzing SAP results for clinical and research use. They generally tend to be easy to use and enough to manage for glaucomatous patients. HfaFiles ver.5 can store numerous HFA test results; in our clinic it maintains complete test results from the beginning of our use of HFA in 1988. It can also calculate various visual field parameters such as MD slope and staging data, as well as grading scores such as those from the AGIS and CIGTS. This program is useful both in the clinic and the laboratory. Standard settings allow calculation of the MD slope of the whole visual field as well as the total deviation (TD) slopes of the upper and lower hemifields. In addition, it has a function for calculating mean total deviations and their time trends after separating test points into clusters or sectors (Fig. 3). We used this function to perform trend-type analysis of the whole visual field, upper or lower hemifields, and 10 clustered visual fields, and then compared them with each other (Fig. 1).

At first, we have to give a name for definition of the cluster setting. After we select the symbol, it should be placed on the HFA test points of each cluster we want to set.

Clusterization in this study was based on Suzuki's sectorization method described (1993; 2001) in the Patients and Methods section. Various such approaches have been used for cluster or sector classification even with HFA (Wirtshafter et al, 1982; Sommer et al, 1987;

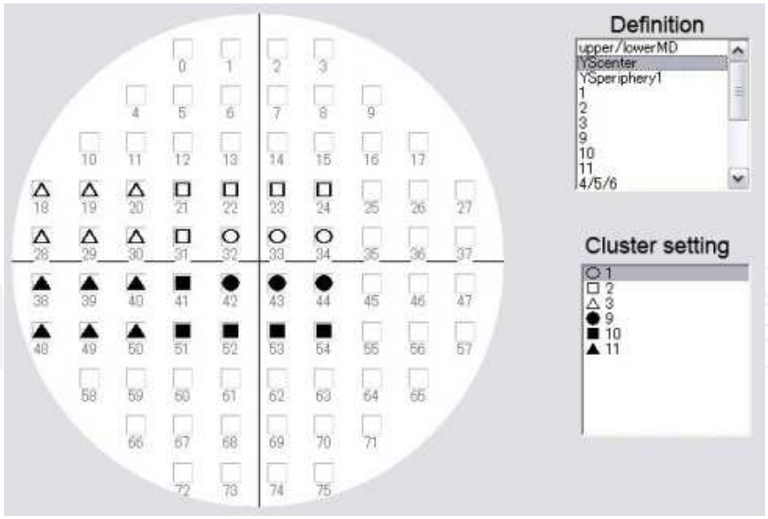


Fig. 3. Setting of the clusters using HfaFiles ver.5 (Beeline Co. Lit., Tokyo, Japan, URL; http://www.beline.co.jp)

Werner et al, 1989; Weber & Ulrich, 1991; Asman & Heijl, 1992; Mandava et al, 1993). Sommer et al. (1987) introduced a method that divided both upper and lower 30-degree hemifields into 5 sectors, then compared mirror image sectors to each other to evaluate HFA test results. The Glaucoma Hemifield Test (GHT) is a standard component of the HFA. GHT uses a different sector classification method but it is similar to that of Sommer et al. (1987). Incidentally, the Octopus Field Analyzer (OFA), another SAP, has a program, "Cluster Trend," for clustered trend-type analysis using standard equipment.

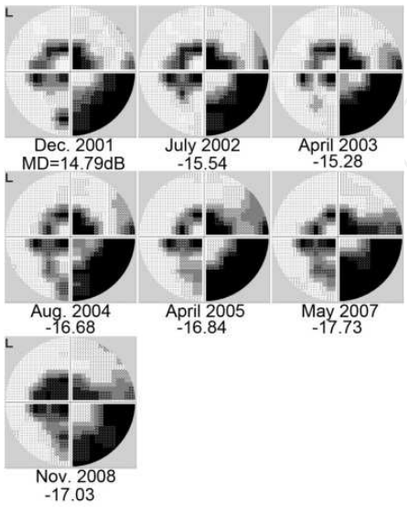
In this study, almost 90% of OAG eyes were classified as showing progression by clustered trend-type analysis after a mean follow-up duration of 11.6 years. This progression percentage was significantly higher than those determined by hemi or total visual fields analysis. The difference between the hemi and total visual field results was statistically significant, but barely so. It is possible that visual field defects in OAG progress very slowly and thus require longer-term follow-up, i.e., over 20 to 30 years. Progression of visual field defect must be more common than that we recognized. Managing OAG over the long-term will thus require us to pay significant attention to affected visual field areas and rate of progression. Mayama et al. (2004) set their original criterion as progression of glaucomatous visual field defects. They then compared the sensitivity and specificity of the methods using trend analysis of TD, MD, mean TD of a sectored visual field, and the original scoring used in the AIGS. They concluded that most of the methods using the TD slope were characterized by high sensitivity, the AIGS method had a very high specificity, and techniques using visual field sectors had reasonable sensitivity and specificity. Similarly, Nouri–Mahdavi et al. (1993) reported that fixed-effects multiple regression analysis of panel data using Octopus field analysis is an appropriate method for evaluating with experienced observers and pointwise univariate regression analysis. Clustered trend-type analysis is an important method for detecting and assessing the rate of progression in each visual field area. Its use in evaluating glaucoma patients is strongly recommended for those in clinical practice.

The probability of progression and difference among clusters are interesting (Table 2). These findings should further our understanding of progression and its patterns in OAG. In

agreement with existing literature, the temporal visual fields showed a low probability of progression. When we compared the upper and lower fields, progression in the paracentral field, cluster 9, was lower than that in cluster 1. In addition, the arcuate (clusters 2 and 10) and nasal (clusters 3 and 11) fields had high incidences of progression that were similar in upper and lower fields. One common feature of glaucoma is that visual acuity is often protected. Morphologically, the macula is situated slightly below horizontal line of the optic disc. Possibly the majority of nerve fibers in cluster 9 arise from the macular bundles.

Our goal in glaucoma management and treatment is the lifelong maintenance of patients' visual function. When we consider the visual field by clusters, as presented in this study, each cluster may have different functions and may work together. For instance, cluster 10 was related primarily to quality of vision (QOV), as were clusters 12, 13, and 14, to a lesser extent. The upper visual field in the better eye is likely to be important for driving. The details of the results will report in near future. Clustered or sectored evaluation of glaucomatous visual field defects and their progression can be used to formulate a management plan for each OAG patient. It is important to consider patients' quality of life (QOL) and QOV both in the present and in the future. For example, cluster 10, the most important area for QOL, is disturbed less frequently than other areas, but nonetheless almost 30% of patients experience progression in this area. Although we have yet to confirm how each area of the visual field responds to glaucoma treatment, particularly IOP reduction, we can hopefully improve OAG patients' QOL by using clustered evaluation such as that employed in this study.

A possible clinical use of clustered trend-type analysis is shown in Fig. 4. and Table 6. She was a 63 yr-old female with NTG followed-up for 9 years. Her left eye showed a remarkable progression to be detected by all 3 trend-type analyses. By clustered analysis, the paracentral clusters 1 and 9, upper nasal cluster 3, and lower peripheral cluster 12, 13 and 14 were indicated as progression. In addition, the progression rate in clusters 1, 9 and 3 was remarkable, under -1.0 dB/yr. The cluster 9, and cluster 12, 13 and 14, more likely relate with subjective disability from our previous study (Sawada et al., 2010). As our expectation,



		MDS (dB/year)	P
total MDS		-0.53 ± 0.30	0.0033
hemi-MDS	upper	-0.39 ± 0.30	0.0172
	lower	-0.54 ± 0.39	0.0123
clustered MDS	**cluster 1**	**-1.71 ± 0.58**	**0.0001**
	cluster 2	+0.27 ± 0.44	
	cluster 3	**--1.29 ± 1.15**	**0.0323**
	clusters 4, 5, & 6	-0.37 ± 0.40	
	clusters 7 & 8	-0.18 ± 0.44	
	cluster 9	**-1.14 ± 0.83**	**0.0133**
	cluster 10	-1.07 ± 0.74	
	cluster 11	+0.01 ± 0.12	
	clusters 12, 13, & 14	**-0.31 ± 0.27**	**0.0278**
	cluster 15	-0.12 ± 0.27	

Fig. 4. and Table 6. A possible clinical use of clustered trend-type analysis.

she complained gradual visual disturbance, particularly around the fixation point. We understood that her left eye needed more aggressive managements to maintain her QOL/QOV. We recommended MMC trabeculectomy for further reduction of IOP after that.

Of course, this study has its limitations. This is a retrospective study, and such does not include clinical information such as IOP and glaucoma treatment interventions. In addition, this study cannot be used to clarify the natural history of OAG. For example, all 3 methods had difficulty detecting progression in cases with under –20 dB . In severe cases we have to consider both reduced sensitivities of our detection methods and the effects of aggressive glaucoma treatments. One of our previous studies showed that follow-up IOPs of Japanese OAG patients were reduced by about 8 to 9% after prostaglandin analogs became available. In this study, many patients had been followed since around 1990. Reduced follow-up IOPs may influence the incidence of progression as well as the areas of progression detected. The optimal methods for identifying progression of visual field defects in OAG have not yet been determined, nor have appropriate progression criteria. Thus, this study could compare the sensitivity but not the specificity of 3 methods of trend-type analysis. Mayama et al. (2004) established their own original criteria for progression and then compared several different methods, including MD slope from the whole field, sectored trend-type analysis, and defect classification systems. They concluded that the sectored trend-type analysis was the most reliable in terms of both sensitivity and specificity. Otherwise AIGS score had low sensitivity but high specificity for instance.

A further task is to establish precisely how to use these types of detection methods in clinical practice. How should we interpret the detection of slight progression in only one temporal cluster? This could hold significance in severe cases in which the temporal areas remained relatively unaffected. If this finding were seen in less advanced cases, we might consider it to be insignificant or perhaps an artifact. As mentioned above, cluster-based analysis is likely to be appropriate as an intermediate method between whole field analysis and that of individual test point. While it is evident that the clustered method is more sensitive than that using the whole field, its specificity might be reduced. We may have to set a significance level of 0.01 rather than 0.05 (Smith et al, 1996). Because this progression detection system with the clustered MDS uses 10 different clusters, the multiplicity possibly becomes a statistical issue to calculate an exact incidence or probability of progression. We might have to set 0.025 for the hemi-MDS and 0.005 for the clustered MDS instead of 0.05 as a significant level by a more strict statistical method like the Bonferroni method. Otherwise some investigators emphasize that setting of additional criteria is recommended, for example the progressive rate in each cluster, to determine whether progression is clinically significant (Noureddin et al, 1991; Birch et al, 1995). Fundamentally clusterization of the fields and the number of test points in each cluster may be critical for methodological accuracy.

When we examine patients' visual fields using these kinds of methods, we often find the clusters showing both impairment and improvement of MD in the same patient. This phenomenon is a reason to reduce the sensitivity of methods using the whole field. Although we have not yet identified the pattern and mechanism of recovery of visual field sensitivity, they possibly relate to neuroprotective effects or activation of the nervous system by glaucoma treatments.

Recent glaucoma research has focused on the correlation between structure and function (Wollstein et al, 2005; Hood & Kordon, 2007; Tan O et al, 2009; Parrish et al, 2009; Harwerth

et al, 2010) . One reason for this is that OCT has become widely available even in clinical practice. When we separate the peripapillary retinal nerve fiber layer into the several sectors, each has a corresponding cluster in the visual field. Cluster-based correlation should be more significant than that between the whole field and retinal nerve fiber layers (Hood & Kordon 2007). Cluster-based observations should be effective both from structural and functional points of view at predicting the progression and prognosis of OAG patients in the future. Future investigations should focus not only on the progression incidence in each cluster but also on the progression rate, as well as on the differences between high-tension glaucoma (HTG) and NTG. In addition, we should analyze the relation with glaucoma treatments. Perhaps the paracentral, arcuate, nasal, and upper or lower peripheral visual fields react differently to IOP reduction.

5. Conclusion

Clustered trend-type analysis of glaucomatous visual field defects is now easier to perform than it used to be, and is useful in evaluating and identifying the progression of glaucoma. It can detect local progression of glaucomatous visual field defects with a higher sensitivity than analysis of the whole field. It may be particularly suitable for the eyes with slow or local progression and for further elucidating the disease course in open-angle glaucoma. It should be considered an important method in the clinical practice setting for predicting QOL and QOV and for establishing treatment plans for glaucomatous patients.

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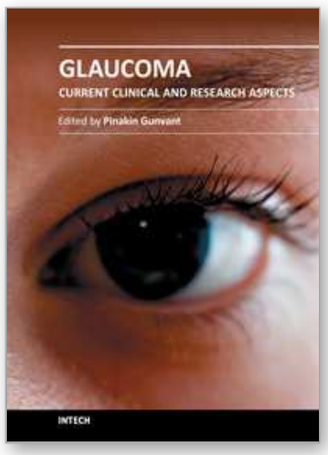

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This book summarizes current literature about research and clinical science in glaucoma and it is a synopsis and translation of the research conducted by individuals who are known in each of their respective areas. The book is divided into two broad sections: basic science and clinical science. The basic science section examines bench- and animal-modeling research in an attempt to understand the pathogenesis of glaucoma. The clinical science section addresses various diagnostic issues and the medical, laser and surgical techniques used in glaucoma management.

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Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
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