6 Structural/Functional Relationships in Glaucoma

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HISTORY OF STRUCTURE / FUNCTION RELATIONSHIPS IN GLAUCOMA

The relationship of the structural integrity of the optic nerve and the functional status of the visual system has been actively investigated since the invention of the direct ophthalmoscope more than 150 years ago. The ability to assess both the structure and function of the optic nerve has evolved, becoming more clinically practical and efficient with greater sensitivity and specificity for detection of disease. However, the evolution of structural and function diagnostics have not always developed in concert. As visual field documentation has become more sensitive and more precise, we have increasingly used functional testing for diagnosis and monitoring of the glaucomatous optic nerve. Over the last century and a half, there have been many advances in functional detection of disease and assessment of progression. Clinicians have relied on the most efficient, sensitive, and specific test method (functional or structural) that was available at any given time. Therefore, even if a structural change is antecedent to a functional change, sensitive functional testing has developed more quickly and been implemented to a greater extent into clinical practice. Yet even von Graefe hinted at the relationship of visual field documentation and optic nerve changes.[1] Further illumination regarding the relationship between the appearance of the optic nerve and visual field deficits associated with glaucoma were founded through the pioneering efforts of Jaeger, Weber, Mackenzie, and others.[2]

In addition to exploiting the best available testing paradigms of any particular era, the recent understanding that measurable functional and structural changes of optic nerve may not occur simultaneously has once again forced us to rethink the structure-function relationship. The understanding that early in the disease structural optic nerve alterations may be more easily observed has led to intense interest in objective optic nerve analysis. While late in the course of the disease, functional changes may be a better barometer of optic nerve health. However, functional tests have continually improved, becoming more sensitive to early change and narrowing the gap between observable functional loss and its precedent structural alteration. This chapter will review the history of the structure-function relationship and discuss the various diagnostic tests that have been used to evaluate the glaucomatous optic nerve. In addition, recent longitudinal studies that shed more light on the relationship between structure and function will be reviewed.

Over the last 40 years, a number of investigators reported a strong relationship between the appearance of the optic nerve and retinal nerve fiber layer and visual field deficits in patients with glaucoma.[3-11] Drance[3-5] reported that he was correctly able to determine whether an eye had glaucomatous visual field loss on the basis of the appearance of the optic nerve with 85% sensitivity and 80% specificity. Other studies have reported similar results.[12, 13] In addition, several investigators have also reported that changes in the optic nerve head precede visual field loss.[14-17] Susanna and Drance[18] conducted a prospective, longitudinal study of the false positives and true negatives of predicting the visual field status on the basis of optic nerve appearance. This investigation suggested that, in some cases, there were early optic nerve changes that preceded visual field loss. Hart et al[15] and Gloster[19] reported an increase in the prevalence of glaucomatous visual field loss with increasing cup/disc ratios. In addition, Hart et al[15] also reported that high cup/disc ratios strongly correlated with later development of visual field loss. Taken together, these studies provided strong evidence that optic nerve structural anomalies were highly correlated with visual function deficits.

In recent decades, more investigations have examined the relationship between clinically observable structural abnormalities of the optic disc and perimetric changes. These investigations have focused on a variety of different features of the optic nerve and the surrounding nerve fiber layer. In addition, localized topographic changes have been associated with regional functional changes. Holmin[20] evaluated the ability of readers to classify a quadrant of the optic nerve in disc photographs and predict whether a visual field deficit was present. Good agreement was found among the readers, who demonstrated 75% sensitivity and 85% specificity for predicting visual field loss in the superior and inferior hemifields on the basis of optic disc appearance. Lewis et al[21] examined the ability to predict early, moderate, and advanced glaucomatous visual field loss from the appearance of the optic disc in primary open-angle glaucoma and low-tension glaucoma. The severity of visual field loss could be accurately predicted about 50% of the time. Overprediction and underprediction of visual field loss occurred approximately equally, although there were large individual differences among observers.

Several investigators have also reported strong correlations between neuroretinal rim thickness and visual field deficits, both for overall measures and for localized regions.[22-28] Weber et al[29] found good topographic correlations in patients with focal optic nerve damage between the affected region of the neuroretinal rim of the optic nerve and visual field deficits. Neuroretinal rim thickness, either average rim thickness or localized rim thickness, appears to be the most consistent optic disc parameter to correlate with visual field measures across a large number of investigations.

Although longitudinal investigations of structural and functional losses in glaucoma are not common, those that have been published indicate that structural changes of the optic disc or retinal nerve fiber layer usually occur prior to visual field loss as determined by conventional white-on-white perimetry.[27, 30-35]

Historically, it has been generally believed that structural abnormalities of the optic nerve and retinal nerve fiber layer precede visual function loss, particularly using standard automated perimetry. However, the advent of new visual function test procedures that are more sensitive than standard automated perimetry (SAP) opens the possibility that some visual function deficits may be concurrent with or prior to observable structural glaucomatous damage. Presently, optic nerve head analysis is also rapidly evolving, and more sensitive techniques have become available. This will presumably allow earlier detection of glaucomatous structural changes, permitting observable structural change to predate functional consequences. To date, no prospective longitudinal investigations have directly compared the temporal relationship of structural and functional glaucomatous changes for the new, more sensitive visual function test procedures and more advanced structural analysis methods.

OPTIC NERVE IMAGE ANALYSIS AND FUNCTIONAL LOSS

A number of investigations have evaluated the relationship between optic nerve parameters determined using objective image analysis and visual fields. Caprioli and Miller[36] found significant correlations for cup/disc ratio, disc rim area, and cup volume (Rodenstock Scanning Laser Ophthalmoscope) and visual field indices (mean defect and loss variance). Using the Heidelberg Retina Tomograph (HRT), Brigatti and Caprioli[37] found even stronger correlations between optic disc parameters and visual field indices. In particular, the correlation of the third central moment of the frequency distribution of depth values (cup shape) with both mean deviation and corrected pattern standard deviation were quite high. Lee et al[38] examined the relationship between HRT optic nerve measurements and visual field indices. Rim area, rim volume, and mean retinal nerve fiber layer height were all significantly correlated with both mean deviation and corrected pattern standard deviation. The cup shape was also significantly correlated with mean deviation. The highest correlation was between rim area and mean deviation. There was also a strong correlation between rim area of the superior and inferior sections of the optic nerve and the corresponding visual field hemifields.

Iester and colleagues[39, 40] also reported good correlations between HRT optic nerve parameters and visual field indices. Rim area was found to be the best optic nerve predictor of mean deviation. In addition, they found that superior and inferior optic nerve measures were significantly correlated with visual field indices for the corresponding visual field hemifields. Tole et al[41] also reported significant correlations between HRT optic disc measurements and visual field indices.

Emdadi et al[42] performed HRT measurements in patients with focal glaucomatous visual field loss and conducted a quantitative comparison of the topography of optic disc characteristics with the focal visual field deficits. Approximately half of the patients demonstrated diffuse optic disc damage despite having a focal visual field defect. About 25% to 35% of patients had focal optic nerve deficits, and about 15% had no detectable optic disc deficit. These findings suggest that distinct topographic relationships between optic disc damage and visual field loss are not always strongly correlated. However, in a subsequent study of patients with both focal optic disc damage and focal visual field loss[43] a strong relationship was found between damaged optic disc sectors and the location of visual field loss. Kamal et al[44] evaluated a small group of ocular hypertensive patients who had converted to glaucomatous visual field loss in comparison to a small group of normal control eyes. Significant optic disc changes were noted in the ocular hypertensives converting to glaucoma. In addition, the HRT optic disc changes were noted prior to the development of confirmed visual field change.

Several investigators have examined the relationship between quantitative optic disc measurements obtained with a confocal scanning laser ophthalmoscope and short-wavelength automated perimetry (SWAP) and motion sensitivity. Yamagishi et al[45] evaluated the relationship between focal optic disc damage as determined by Heidelberg Retina Tomograph images, and localized visual field deficits for SWAP in glaucoma. There was a strong topographic relationship between the SWAP visual field deficits and damaged nerve rim sectors. In addition, Teesalu and colleagues[46, 47] compared SWAP visual field sensitivity to several optic disc parameters and retinal nerve fiber layer height obtained from the Heidelberg Retina Tomograph. They found high correlations for SWAP visual field indices and hemifield values in comparison to several optic disc parameters (cup shape measure, rim volume, rim area) and retinal nerve fiber layer measures (retinal nerve fiber layer height and retinal nerve fiber layer cross-sectional area).

The topographic relationship between motion perimetry deficits and optic disc abnormalities was examined by Bosworth et al[48] in patients with focal optic nerve damage and focal motion perimetry losses. Comparisons were also made to SWAP and standard automated perimetry deficits. A strong topographic relationship was observed between optic disc abnormalities and motion perimetry deficits. These topographic correlations were also found for standard automated perimetry and SWAP. Thus, focal notching of the optic nerve is probably independent of specific subsets of retinal ganglion cells because all three visual function tests showed similar topographic relationships to the optic nerve and each visual function test is believed to be mediated by different groups of retinal ganglion cells.

Although these investigations all report strong relationships between focal functional deficits and focal optic nerve deficits, it should be kept in mind that a large proportion of glaucomatous optic nerve damage is characterized by diffuse thinning of the neuroretinal rim, where topographic structure/function relationships are not expected to be as strong.

CRITERIA FOR ASSESSING VISUAL FUNCTION LOSS IN GLAUCOMA

In an effort to better understand the relationship between structure and function, it should be realized that assessing loss, either structural or functional, involves a number of investigator-driven choices. These choices or criteria have evolved over several decades for automated perimetry and are presently being developed for automated optic nerve head analysis. The Structure and Function Evaluation (SAFE) study was a prospective, collaborative investigation of a large population of ocular hypertensives, glaucoma suspects, and early glaucoma patients.[10] To date, there have been two publications from the SAFE study. The first manuscript described the development of a system or set of criteria for determination of visual field loss in ocular hypertension and early glaucoma. The findings indicated that it is possible to derive criteria with high specificity for detecting the development of early glaucomatous visual field loss that can be applied to both SAP and SWAP results. Both the evaluation of individual visual field locations and analyses based on nerve fiber bundle patterns appear to have the best overall performance. Specificities of 98% to 100% were achieved by using these analyses in conjunction with requiring all potential changes to be confirmed on two successive visual field examinations. Previous investigations have also found that to maintain high specificity, it is necessary to confirm suspected changes with additional examinations.[49] These findings indicate that it is possible to attain high specificity with confirmation on two successive visual field examinations. However, most of the SAFE results were based on the evaluation of ocular hypertensive patients, who have lower test-retest variability than glaucoma patients. Clustered abnormal points provided a slight improvement in specificity, but nothing that was as significant as confirmed abnormalities.

Six criteria were found to have high specificity, and of these six, two of them (GHT [glaucoma hemifield test] outside normal limits and four pattern deviation locations that were worse than the 5% probability level) had the highest percentage of abnormal results detected for SAP. The GHT outside normal limits also detected a higher number of new SWAP deficits. The establishment of these criteria for the development of glaucomatous visual field loss allows them to be used in conjunction with analysis of structural features of the optic nerve to determine the relationship between structural and functional losses in glaucoma.

DOES STRUCTURAL CHANGE PREDICT FUTURE FUNCTIONAL DEFICITS?

The second SAFE publication examined the relationship between pre-existing glaucomatous optic neuropathy and the later development of functional abnormalities.[11] The criteria established in the first publication were used to define functional abnormalities. The findings indicated a strong, statistically significant relationship between the presence of glaucomatous optic disc damage at baseline and the subsequent development of SAP visual field loss at some later point in time. The optic nerves were evaluated by masked observers examining simultaneous stereophotographs, obtained at baseline and annually. A similar trend was found for the presence of glaucomatous optic discs at baseline and the presence of SWAP deficits at baseline or development of SWAP deficits during the follow-up period. There were a large number of cases in which the affected visual field hemifield(s) and optic disc hemisector(s) were in correspondence, and an equally large number of cases in which the extent of optic disc damage extended to two hemisectors when the visual field loss was restricted to one hemifield. There were a very small number of cases in which the extent of visual field loss was greater than the degree of optic disc damage.

In addition, in eyes that demonstrated progression of optic disc damage, most developed glaucomatous visual field loss at or subsequent to the time at which the optic disc changes were noted. Taken together, these results provide compelling evidence that visible glaucomatous optic disc changes occur prior to measurable glaucomatous visual field loss, and that glaucomatous optic disc changes are predictive of future visual field loss as measured with current techniques.

In the group that did not demonstrate visual field loss for SAP or SWAP, there were a large number of optic discs that were judged to be glaucomatous. Many of these cases are likely to represent future visual field “conversions” that have not yet manifested themselves during the follow-up interval. A more comprehensive determination of the strength of the relationship between structural and functional damage in glaucoma may require as much as 10 years or more of longitudinal follow-up. Other investigations have concluded that glaucomatous optic disc changes precede visual field loss and that optic disc changes are predictive of future visual field deficits; however, most have been cross-sectional or retrospective. These results from longitudinal monitoring of a large cohort of well-defined patients are consistent with the findings of prior studies and provide strong support for observable structural optic disc abnormalities being a predictor of future glaucomatous visual field deficits. These findings also support the need for standardized and automated optic nerve analysis in the management of glaucoma patients.

CONCLUSION

A large number of studies have demonstrated good correlations between structural alterations of the optic nerve head and retinal nerve fiber layer and visual function deficits produced by glaucoma. Structural and functional glaucomatous damage appears to be topographically related, especially in cases of predominantly focal damage. There is also evidence from prior studies that optic nerve and retinal nerve fiber layer damage usually can be observed prior to visual field loss, at least for standard automated perimetry. Recent investigations indicate that technological advances in both the measurement of structural properties of the optic disc and retinal nerve fiber layer and the evaluation of new visual function characteristics have improved the sensitivity and reliability of noninvasive methods of assessing glaucomatous damage.

There are several shortcomings associated with many investigations of structure/function relationships in glaucoma to date. First, the majority of investigations have involved relatively small numbers of patients. In many instances, inclusion and exclusion criteria are not well defined. Secondly, the vast majority of investigations are cross-sectional. There are very few longitudinal investigations of structure/function relationships, and many of such studies have been conducted retrospectively rather than prospectively. Finally, many of the early studies in particular suffer from methodological flaws, selection biases, and other problems associated with the research design or analysis methods.

Evaluation of a large, prospectively collected data set of functional and structural optic nerve measures in glaucoma patients strengthens the understanding of these issues. There are two fundamental questions to be answered. First, is a structural abnormality predictive of future glaucomatous visual field loss? If so, what is the strength of this relationship? Secondly, what is the relationship between structural optic nerve changes and visual function changes in glaucoma?

In the SAFE study, a strong relationship exists between glaucomatous optic disc damage at study entry and the subsequent development of a confirmed glaucomatous SAP visual field defect. A higher percentage of glaucomatous optic discs were also found in patients with SWAP deficits at baseline and in those who later developed SWAP deficits. These findings support the premise that a glaucomatous optic disc is predictive of the subsequent development of glaucomatous visual field loss.

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