# THE NERVE FIBER LAYER

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# ITS VALUE IN THE DIAGNOSIS AND MANAGEMENT OF GLAUCOMA

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## I. Introduction

In the past six months, many of the faculty and also my fellow students have inquired about the subject of my senior research. When I answered that I was doing a literature search on nerve fiber layer (NFL) defects and their involvement in glaucoma, more often than not my answer was met with a blank stare. I guess this reaction really does not surprise me. After all, I knew very little about the evaluation of the NFL before my experience with glaucoma patients at the Topeka Veterans Administration Medical Center. Yet the idea of using retinal NFL evaluation in the diagnosis and management of glaucoma is hardly a new concept. Vogt first used a red-free light source to examine and describe the NFL as long ago as 1913. (1,2) Of course, the knowledge and instrumentation that is available to us today is far superior to what was available at that time.

I am not exactly sure why clinicians today are not more willing and able to add the evaluation of the NFL to their arsenal of diagnostic procedures for glaucoma. In 1973, Hoyt and associates reported that red-free fundus photographs of the NFL could show glaucomatous abnormalities as subtle losses of nerve fibers in the presence of normal optic discs and visual fields. (3) This has subsequently been confirmed by other investigators who have used red-free photographs of NFL to help diagnose glaucoma. The purpose of my literature search is to define NFL dropout, describe how it can be applied in clinic, and investigate its usefulness in glaucoma management.

## II. Normal NFL Appearance

The clinical appearance of the retinal NFL is that of fine linear silver striations that represent reflections off of the NFL bundles. (2,4,5) The generation of these linear white reflexes occurs as a result of ocular structure. Light passes through the internal limiting membrane and is differentially reflected back to the viewer from the nerve bundles. The brightness of these striations is directly related to the thickness of the NFL bundles. (5) The dividing dark zones between these light striations represent the linear arrangement of Mueller cell processes that form the lateral borders of each bundle. These dividing septa of glial tissue do not reflect light as well and represent the dark lines seen between the bright striations. (5) A normal NFL pattern is thus seen as a bright-dark-bright pattern which corresponds to the known pattern of nerve pathways across the retinal. (2)

The NFL is slightly more evident in the inferior arcades than the superior arcades. (6) However, for the NFL pattern to be detectable in any area of the retina, it is important that the tissue posterior to the NFL reflect as little light as possible. The more darkly colored the retinal pigment epithelium and the choroid, the better the NFL reflexes are seen. (5) Thus, the visibility of retinal NFL varies considerably even among normal individuals and is most easily seen in those with moderate to heavy pigmentation. (2)

Retinal nerve fiber layer is also most easily viewed in the peripapillary area. The brightness of the NFL fades further away from the optic nerve head because the NFL becomes thinner as the retinal

periphery is approached. (2) Two disc diameters out from the nerve head, the NFL begins to thin variably, giving a feathered-out appearance. (7) Only within two disc diameters of the nerve head can the RNFL be evaluated reliably and accurately for glaucomatous defects. Also typical of a normal NFL appearance is the whitish haze that these axons of the anterior retina cast over the underlying retinal vessels, retinal pigment epithelium and the choroidal structures. (2) If retinal vessels have bright highlights crossing and partially covering them, then the NFL is present to some degree. (7)

## III. Anatomical Consideration of the NFL

To use the examination of the RNFL effectively, it is important to understand the anatomy of the retina and the origin of the NFL striations. It is quite clear that the bright striations that are visible in the posterior pole of the eye correspond generally to the pattern of nerve fiber bundles of the retina. In fact, studies show that for the most part, one striation is the equivalent of one NFL bundle. This rule of thumb does break down however, in areas of the retina where the NFL is the thickest. (5) Histiologic studies of the human eye confirm that as ganglion cells from the periphery converge toward the disc, the thickness of the the NFL increases. At the superior and inferior poles of the nerve head the NFL is the most dense. (5)

It has been found that approximately one million retinal nerve fibers converge to the optic nerve head in the normal and young human eye. (8) These axons form nerve bundles as they pass through the retina over the small retinal blood vessels and compose the NFL. After traversing the optic nerve, optic chiasm, and the optic tract, the ganglion cell axon ends in the lateral geniculate body. No break in the pathway occurs prior to this final synapse. (6) When damaged, an axon undergoes both orthograde and retrograde degeneration. Consequently, a lesion of the retinal ganglion cell axon in any part of the anterior visual pathway will cause degenerative changes in the retinal NFL. (2)

Although the configuration of nerve fibers within the retina has long been understood, the correct orientation of retinal nerve fibers in the optic nerve head has been the subject of considerable debate. Prior to 1930, the common view was the nerve fibers from the peripheral retina entered the central portion of the optic nerve head. (1) It has since been established that the reverse is true: nerve fibers from the far retina enter the peripheral optic nerve head while more central fibers occupy the central position in the nerve. (1,2,5,8,9) Therefore, nerve fiber atrophy that is more proximal to the optic disc, where the NFL is most easily and effectively observed clinically, is most directly related to cupping formation. (9)

Initially in glaucoma, the superior and inferior poles of the optic nerve lose fibers at a selectively greater rate, leading to an hour-glass-shaped atrophy at the nerve head. Since the topographic location of optic nerve fibers and their retinal site of origin are known, it is possible to relate the pattern of nerve atrophy at the disc to that which occurs in the retina. The axons which converge to superior and inferior poles of the nerve head originate in the superior and inferior arcuate perimacular areas of the retina. (8)

Eventually, this neuronal loss in the retina and at the nerve head appears as an associated field loss in the arcuate areas. (5) It is convenient that the temporal NFL which can prove to be the most useful in early prediction of these defects is also the easiest area to examine. When the anatomy of the retina is considered, the best visibility of the NFL and the most effective location to examine it is in the temporal arcuate areas within two disc diameters of the nerve head.

## IV. The Abnormal Nerve Fiber Layer

Although studies of the exact relationship between NFL atrophy and visual field loss continue, it has become evident that visual field defects become apparent as a direct result of the loss of optic nerve fibers. More importantly, these defects are not detectable until years after the initial loss of the neuronal tissue. (5) The method of subjective clinical examination of the NFL is not precise enough to determine whether damage in the NFL occurs axon by axon or bundle by bundle. Actually it is not really even known whether axons stay in the same bundle throughout their course to the optic nerve head. (8) Yet by the time that glaucoma is advanced enough for us to see classic changes, such as cup-to disc ratio and visual field loss, Quigley has estimated that approximately 50% of retinal ganglion axons are lost. (10)

Quigley found that lesions causing less that 50% decrease in NFL were generally not visible at the retina, while those involving greater that 50% of them were detectable. Of course, defects that are visible in a zone of thick NFL represent a greater loss of neuronal tissue than a detectable defect in a zone of thinner NFL. (5) At the same time, defects in the NFL can be best appreciated before the development of substantial field loss. Once this occurs, the NFL has practically disappeared, at least for the purposes of our detection techniques. Thus, current methods of NFL assessment are most suitable for monitoring very early neuronal loss and glaucoma detection. (11) At the same time, quite a degree of axonal loss must occur before NFL defects can be detected. (5)

To aid in the evaluation of glaucoma and other disorders, it has long been the aim of investigators to assess the amount of functional neuronal tissue. (12) Nerve fiber layer atrophy has been widely recognized as an essential clinical finding suggesting functional damage, however this atrophy also typically occurs in the aging eye. (9) It would be clinically useful to be able to assess and quantitate the normal age-related loss of nerve fibers. Caprioli estimated that the average normal loss of nerve fibers in the retina is 5,600 each year. (1) Because 50% loss of nerve fibers must occur before nerve fiber atrophy becomes evident, atrophy in the inferior temporal area, where the NFL is the thickest, cannot possibly be solely due to aging loss. (5,8,9).

While NFL atrophy indicates a major loss of fibers, it is possible that considerable visual function still remains. (5) Keep in mind that only a few papillomacular bundles are needed for good Snellen Acuity. (2) Often NFL striations are no longer visible in eyes with advanced glaucoma damage. (5) These eyes have suffered a profound loss of neuronal tissue, thus they have few fibers in reserve. Eyes with advanced glaucoma may suffer damage at lower IOP's, perhaps this

results from the small number of fibers remaining in such eyes, rather than an increased susceptibility. In other words, loss of further number of fibers may have a greater effect on visual acuity and remaining fields than would the loss of the same number of axons in an eye with a large number of axons remaining. (8)

## V. Abnormal NFL Appearance

Hoyt and his co-workers categorized NFL defects acquired from glaucoma into the following groups: slit defects, wedge defects, diffuse atrophy, and total atrophy. (1,13) Slit and wedge defects, also grouped into the category of local defects, usually are detected first. (7,8) Yet part of the reason that some claim that localized defects occur earlier may be attributed to the fact that localized defects are easier to spot than diffuse atrophy. (5,11) Actually, Sommer and Katz found that when they charted the evolution of NFL abnormalities in glaucoma patients, most often some degree of diffuse thinning, mainly in the arcuate zone, was usually the initial appearance of NFL loss. (11)

Generally speaking, defects in the NFL appear as an area where the normal striated appearance is absent. The boundaries of the defect conform to the arcuate pattern of the NFL bundles as they converge toward the optic disc. Because the boundaries of diffuse drop-out are so difficult to distinguish, these defects are not usually detected until late in the progression of NFL atrophy. (4) It is these diffuse or generalized defects in the NFL that become most obvious in patients whose glaucoma has progressed to the point that localized defects are easily identifiable and field loss is already occurring. (1) In glaucoma suspects, on the other hand, a clinician is more likely to detect localized NFL defects. (1,4) These localized changes are also associated with thinning rim tissue and paracentral scotomas. (1) Another interesting differentiation is that normal tension glaucoma patients tended to present with localized NFL defects and high-tension glaucoma patients more characteristically show diffuse defects. (3)

Focal or localized atrophy can present in the form of slit defects or wedge defects. Quigley states that tiny slit-like dark zones can be seen in the NFL of 15% of normal eyes. It is obvious that there is a need to differentiate between physiological presentation and pathological slit defects. Baun concluded in his studies that a dark slit of <1 vein wide could be considered as physiological variation and those >1 vein width should be considered a pathological finding. (14) The slit defects are thought to represent focal damage of several adjacent ganglion cell axons in the optic nerve. (2) One theory is that all fibers in the particular bundle are lost, but adjacent bundles remain intact. (8) With time, focal defects tend to deepen and expand. (11) Relatively focal early damage in some studies would seem to be compatible with the earliest visual field defects, paracentral scotomas. (1,8) As the loss of ganglion cells progress, the slit defects become wedge-shaped defects. The wide end of the wedge defect is usually closer to the optic nerve head and is often associated with a notch in the rim tissue and a corresponding visual field defect. (2) These groupings of NFL loss are more obvious and thus are easier to detect. (5)

Diffuse defects, although they are more difficult to identify, are the most common type of NFL atrophy. (2) Once again since there is a

specific topographic arrangement of RNFL in the optic nerve, diffuse loss of axons in the nerve head will also show as a diffuse loss of nerve fibers in the retina and a related generalized depression of visual function. (1,5) The appearance of a diffuse defect is a general thinned or raked appearance of the NFL striations. (2) One theory of this type of loss is that many nerve fiber bundles are all losing a few of their axons. Obviously, this type of loss will be less evident than wide areas of defect with sharply demarcated boundaries. (8) With diffuse atrophy, retinal vessels and other underlying structures become more prominent. (2) Along with this further loss of the normal striated NFL pattern, a darkening of the fundus occurs. (11) In fact, instead of being the darkest area in the fundus, the papillomacular bundle becomes more prominent and is brighter than the inferior and superior arcuate bundles. (8)

The final stage in the progression of NFL atrophy is total atrophy. This, of course, occurs in cases of far-advanced glaucoma and is usually associated with severe visual field loss and advanced cupping. (1,15) Ultimately, little if any, NFL exists. The fundus becomes dark and granular and sometimes there appears to be very faint and widely-spaced striations, but eventually all striations are lost. The underlying retinal vessels are darker, redder, and they seem to stand in relief against a dull or mat-like retinal background. (2) Additionally, the vessel walls appear to have a white border because of the loss of surrounding NFL. (7) Even when no striations are visible, it is important to remember that the eye most likely still has some functional fibers and thus a degree of visual field remaining. Most likely, it is merely photographic resolution that prevents us from seeing the striations. (15)

## VI. Evaluation of the NFL

Although RNFL evaluation can be taught and learned, it isn't always easy, especially for the novice. Like most optometric techniques, time and practice are required to improve one's ability in NFL evaluation. Quigley and his associates are now developing programs to teach NFL evaluation techniques to clinicians and photographic graders. (8) There is no reason why with a little effort on the part of the examiner, accurate NFL evaluation cannot be mastered. With a few simple tips in mind, a clinician can quickly and easily examine the NFL of his patient. Contrary to what might be believed by some, no expensive or special equipment is necessary. Nerve fiber layer is best viewed by using high-intensity illumination with a direct ophthalmoscope or with a contact lens and slit lamp. (7) Further enhancement is obtained by using a red-free filter. Red-free light brightens the white nerve fiber bundles selectively in comparison with the red retinal pigment epithelium and choroidal background and thereby enhances the visibility of the NFL. (1,2,16)

A maximally dilated pupil and clear ocular media aid in the evaluation process. In addition, initial subtle changes can be best detected by comparing the NFL of the inferior and superior hemispheres and also comparing the appearance of the NFL in one eye to that of the other. (2,11) Diffuse atrophy, although difficult to detect, can best be appreciated by comparing NFL striations to second-order vessels. (11) Normal striations can be easily visualized where they cross at right angles over small vessels. (4) Loss of NFL creates a window defect, so underlying vessels are quite visible and appear

whitened. With atrophy, small tertiary retinal vessels will be visible and the deep layers of the retina will appear dark and granular. (2) Inspecting small vessels closely enables one to differentiate between the lack of striation due to an abnormality in the NFL and the lack of striations due to poor focus. (4)

In watching for diffuse atrophy, it is also helpful to scan the temporal peripapillary area from top to bottom, looking for reversal or other alterations of the normally light-dark pattern. (11) Again localized defects are easier to detect than diffuse atrophy. Recall that slit defects >1 vein width should be considered a normal physiological variant. (14) NFL is most apparent in the peripapillary area from the 11-2 o'clock positions and the 4-7 o'clock from the left optic disc and in the corresponding areas in the right eye. (7) The best practice for learning to detect NFL defects is to first study many normal nerve fiber layers and then those of known glaucoma patients. (11)

## VII. Photography of the Nerve Fiber Layer

As with clinical NFL evaluation, confidence and competence in NFL photography comes from a great deal of practice. At the same time it is still important to remember and understand the anatomy of the retina, especially the NFL. In the human eye, particularly the lightly pigmented, background reflection is minimized by illuminating the retina with green light which is highly absorbed by the RPE. (19) It has been found that a sheet of polarizing film in front of the camera, provides the same excellent visibility of the NFL. (5) Generally, photography of the NFL is most successful with a blue or green light and on high-contrast black and white film. (1)

All researchers of the NFL have developed their own method of photographing the nerve fiber layer. These photographic procedures are usually described in detail in the method section of their respective research articles. (4,7,13,14,16,18) A typical NFL photography set-up includes a fundus camera with a 560 nm short-pass, cut-off filter and Tech Pan Film. (16) Some make photos from the film while others find that studying the negatives under magnification proves to be effective. (4) As with subjective evaluation of the NFL, confidence in the photography comes from spending time taking pictures of and evaluating the photos of normals and also known glaucoma patients. It is most certainly the opinion of the researchers of the NFL, that NFL photography and evaluation is not beyond the scope of the ability of the typical optometry office. All it takes to get started is a good fundus camera and about $100 in supplies from the camera store.

## VIII. NFL as a Diagnostic Tool

Glaucomatous damage causes morphological changes at the optic nerve head and in the NFL and psychophysical deficits that are detectable by perimetry or other functional tests. However, the question to the extent to which morphological changes correlate with functional deficits is controversial. Quite a number of studies have described a moderate to fairly good correlation between RNFL loss and visual field indices. (12) Histology studies and clinical observations suggest that the optic nerve and the NFL may undergo significant structural

alteration before visual field loss becomes manifest. In addition, these NFL changes have been found to correspond to visual field deficits in terms of their depth and location. (3)

Many have noted that NFL defects are observed in some with glaucoma before visual field loss and that they may be an additional sensitive indicator of incipient optic nerve damage. (1,5,9,19) In fact, NFL abnormalities developed in many patients at least 4 to 6 years before any field loss became apparent. (2,4,11,19) Especially when the NFL abnormality was limited to a single hemisphere, it almost invariably corresponded to the location of the field defect. (11) For all of the perimetric modalities, it has been found that there is a fairly good correlation between the RNFL and the mean visual field indices. Flicker data perimetry are the best correlated results, but this is perhaps because flicker threshold are more resistant to optical image degradation by factors like media opacities or refractive defocus. (12) Some claim that standard perimetry techniques often fail to show deficits associated with localized changes in the NFL. (15) In the opinion of other researchers, automated visual field testing appears to be more sensitive in detecting damage than manual perimetry. (2)

Cup-to-disc ratio is the risk factor that has classically been used to detect neuronal damage and to help predict eventual field loss. Most clinicians continue to depend strictly upon disc features to detect physiological changes. Yet studies show that prediction of visual field loss by using disc features is 82-86% accurate, while using NFL evaluation yielded 84% sensitivity. (7) NFL evaluation was equal in sensitivity and specifitiy to cup-to-disc ratio as a baseline criteria for prediction of future field loss. In addition, the position of NFL defects often correspond to the hemifield in which the field defect eventually develops. This is not possible to discover by examining disc data. Other parameters, such as asymmetry, disc changes, hemorrhages, vertical elongation, and peripapillary crescents have been found to have much less predictive value. (8) There is an ongoing effort to improve the accuracy of using disc data in the management of glaucoma, such as the measurement of the neuroretinal rim or topography measurements. Although these procedures show promise, studies are not completed and each requires specialized equipment and substantial computation time. (8) The opinion remains for many the optic disc measurements even with the most high-tech equipment are far less sensitive than NFL evaluation, particularly in early glaucoma. (4,15)

It has already been proven that optic nerve damage usually preceded visual field defects, now others have proven that NFL defects precede optic nerve damage. Various studies suggest strongly that RNFL damage may even be a good predictor of subsequent optic disc changes. (15) Tuulonen found, on the other hand that the most accurate way to detect neuronal damage and to predict eventual field loss was to look for RNFL changes in combination with disc anomolies. (17) However, NFL evaluation alone can evaluate eyes with considerable accuracy. In a study of 1400 eyes, RNFL photography correctly confirmed the diagnosis of glaucoma in almost 90% of cases. (4) Airaksinen and Drance also found a correlation between localized RNFL and rim tissue and also between NFL and neuroretinal rim area. Certainly the results of these studies suggest that further efforts in the development of automated analysis of morphological glaucomatous changes should be directed toward the assessment of retinal nerve fiber layer. (12)

## IX. Advantages of NFL Evaluation

When one considers the many advantages of NFL evaluation, it is difficult to understand why the simple examination procedure is not used more often in clinical practice. Perhaps the most important advantage to consider is the fact that proper NFL evaluation allows for the detection of glaucoma before the beginning of any significant field loss. (4) Another great advantage of using NFL evaluation is that only one photo or view is required to demonstrate the presence of glaucomatous damage. (2,4) On the other hand, a whole series of photos or examinations are required to track optic nerve damage over time. This becomes a more important factor in the present, commercialized eye-care world where patients tend to jump from optometrist to optometrist and there is less continuity of care.

Even though many consider the evaluation of NFL an unnecessary procedure, it is important to remember that there are patients who are not good visual field candidates. (4,7) To participate in visual field testing, the patient must be attentive, answer reliably, and be mentally and physically capable. In addition, visual field testing requires a trained person, expensive equipment, and valuable clinic time. (4) In other patients it might not be possible to get an adequate view of the optic nerve. (7,20) It is sometimes difficult to evaluate tilted discs or other disc anomalies. Also, high amounts of astigmatism can distort the view and make it difficult to correctly estimate the cup-to-disc ratio. (20)

Something that might tend to occur even more often is the need to differentiate glaucomatous cupping from physiological large cups. The condition of the NFL may be used to help make a diagnostic decision in that situation. A good clinician is already going to be examining the fundus of the posterior pole. Nerve fiber layer evaluation is quick and causes little patient discomfort. A good clinician is already going to be examining the fundus of the posterior pole anyway. But perhaps most importantly, NFL evaluation can be used with a high degree of sensitivity and specificity to detect glaucoma very early in its course. (2)

## X. Disadvantages of NFL Evaluation

Although NFL evaluation can be very useful, it has limitations like any other diagnostic procedure. Any opacities in the media, primarily cataracts, can significantly degrade the view or the photograph of the NFL. (4,11) It is well known that the elderly often have processes affecting their lens, cornea, or even the vitreous which might affect the ability to get the sharp focus that is necessary to view the NFL. (4) Even though the well-trained NFL evaluator can use the appearance of the underlying vessels to overcome this obstacle, visibility of the NFL can also be a problem in people who have very lightly pigmented fundi. (8) An optimal dilation of the patient is required for photography and this is sometimes difficult with the elderly or those on certain medications. Also for photography, a high quality fundus camera, sharp focus, and lots of practice at the interpretation of photo are required. (2,4)

Individual variations can prove to make the evaluation of the NFL difficult. The NFL thickness and the position of fibers from various retinal locations can prove to be unique in any given patient. Also,

the development and distribution of NFL losses can significantly vary among individuals. (7) Even though those with dark fundi are easier to examine, sometimes slit-like defects that are visible in their eyes are just a normal variation. Also in very dark fundi, the striations may appear to be very coarse, especially the fiber coming out of the 6 and 12 o'clock positions of the nerve head and arching toward the macula. These coarse streaks could possibly be misinterpreted as abnormal NFL. (4) Two other possible cases of pseudo-NFL defects exist. Sometimes Meuller cells which are inserted into the posterior internal limiting membrane give the appearance of a slit defect. Fortunately these are usually <1 arteriole width in size so there should be no confusion if one is using the >1 vein width guideline. Another physiological variant that can sometimes be confused with a NFL defect is a vitreal adhesion to the anterior surface of the internal limiting membrane. (2) Another important fact to keep in mind is that many other conditions besides glaucoma can alter the appearance of the NFL. (4)

## XI. Conclusion

None of the authors of this literature proposed that NFL evaluation should replace disc evaluation or any other diagnostic technique. Rather the suggestion is that the use of NFL could substantially contribute to the overall diagnostic picture in some cases. When looking for better modes of diagnosis of glaucoma damage, it seems logical to look for direct signs of damage in preference to other factors that may be more indirectly correlated with optic nerve atrophy. If optometry wants to play in the glaucoma game, we should be using all of our tricks so that we can get to be effective at diagnosing and managing the disease. After all, NFL evaluation with equivalent amounts of instruction and practice is not any more difficult than optic disc evaluation and has been proven to be equally effective. (7)

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