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Ganglion Cell Complex Measurement in Compressive Optic Neuropathy

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Occasionally, I'm asked by a patient right before surgery, "will my vision recover after my tumor is removed"? The crucial predictor is the appearance of the optic discs. Recovery of function correlates with the amount of optic atrophy (1–4). This can be gauged so easily by fundus examination that I seldom bother with optical coherence tomography (OCT). Yet, OCT examination of the inner retina seems to fascinate neuro-ophthalmologists. No less than 27 studies have shown that reduction of the retinal nerve fiber layer (RNFL) is correlated with visual field loss and augers a worse outcome following chiasm decompression (5). Given that ganglion cell axons convey the output of the retina to the brain, such observations are hardly surprising.

The study by Tieger et al (6) addresses a different but related issue. It examines the reduction of the ganglion cell complex (GCC), rather than the RNFL, using the Cirrus OCT instrument (Carl Zeiss, Dublin, CA). The manufacturer of this device defines the GCC as the ganglion cell layer combined with the inner plexiform layer. These retinal layers contain ganglion cells and their dendrites but leave out the axons. Confusingly, not all manufacturers agree on the meaning of the term "ganglion cell complex." For example, the RTVue device (Optovue, Fremont, CA) includes the nerve fiber layer along with the ganglion cell layer and inner plexiform layer. To interpret data, one must be careful to note what brand of OCT instrument is being used and what layers of the retina are being measured.

The relative thickness of the RNFL and the GCC vary in a complicated fashion as a function of location in the fundus because the nerve fiber layer contains axons that sweep across the retinal surface from the periphery. As a result, RNFL thickness often does not correspond to local ganglion cell density. This fact has led to the idea that the measurement of the GCC might be more informative than the analysis of the RNFL for the detection of certain optic neuropathies. Tieger et al report that in patients with chiasmal compression, the mean deviation assessed by 30° Humphrey perimetry correlates more strongly with the thickness of the GCC than with the RNFL. I leave arbitration of this point to OCT aficionados, but note that others have come to a similar conclusion (7). To me, the most striking finding is that data for both GCC and RNFL are quite noisy (Tieger et al, Fig. 1). While the trends are significant, the coefficient of determination is low for both parameters. For example, patients with a GCC or RNFL thickness of 60 μm can have either a normal visual field or a mean deviation of −25 dB. When it comes to making predictions about individual patients, this variability sharply limits the value of OCT measurements.

In the discussion section of their article, Tieger et al report an observation (Tieger et al, Fig. 3) that raises several provocative questions about the relationship between visual field loss and retinal ganglion cell function. They cite the case of a 61-year-old man with a bitemporal hemianopia and binasal thinning of the GCC. A year later, his visual fields improved essentially to normal, but the deficit in the GCC remained unchanged. In 7 of 8 patients, surgical decompression led to an improvement in the visual fields despite persistent thinning of the GCC. Should one expect improvement in visual function to be accompanied by some recovery in the thickness of the GCC?

Changes in RNFL after tumor decompression have been analyzed by 4 different research groups. The data are conflicting, with reports of a slight increase in thickness (8), no change (9), and a small decrease in thickness (10,11). The latter would be expected if axons destroyed at the optic chiasm were still undergoing retrograde degeneration at the time of surgery. In any event, the bottom line from these studies is that scant change occurs in the RNFL after tumor removal. This conclusion is consistent with clinical experience based on fundus observation: an atrophic optic disc and a decimated RNFL do not recover a normal appearance after the relief of compression. Pale discs don't turn pink.

This fact begs the question: why does function improve without recovery in RNFL or GCC thickness? The crucial point is that a compressive lesion can block the transmission of nervous impulses without causing the actual destruction of axons. Seddon (12), who studied soldiers after peripheral nerve injury during World War II, coined the term "neurapraxia" to describe this phenomenon. Virtually, all laboratory research has concerned the peripheral nervous

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system, but likely the same principles hold for the central nervous system. Presumably, after decompression of the optic chiasm, physiological conduction block is reversed in axons that remain intact. These axons comprise the surviving fibers in the RNFL. Consequently, visual function improves after chiasmal decompression, even without any concomitant increase in the thickness of the RNFL. The improvement can occur incredibly fast (13).

In the case of the 61-year-old man highlighted in their article, Tieger et al reported that the bitemporal field defects evaporated despite persistent thinning of the GCC. How could the visual fields return to normal in a patient with badly damaged optic nerves? The authors explained this result by invoking the lack of sensitivity of standard automated perimetry. This conclusion is supported by a 57-year-old patient whom I cared for recently in my clinic. Acuity loss in the left eye led to discovery of a bitemporal hemianopia from a pituitary adenoma (Fig. 1). Both optic discs were pale. After decompression, Humphrey visual fields returned essentially to normal, when tested using a conventional stimulus size III target (4 mm^2). However, when the patient was tested the same day using a stimulus size I target (0.25 mm^2), the visual fields appeared far from normal. This case underscores the fact that Humphrey perimetry can miss visual field defects when a stimulus size III is used. A considerable fraction of the ganglion cell population at any given site in the retina must be lost before such a large stimulus can detect a visual field deficit. Unfortunately, the problem with the routine use of smaller stimuli is that false scotomas occur more frequently.

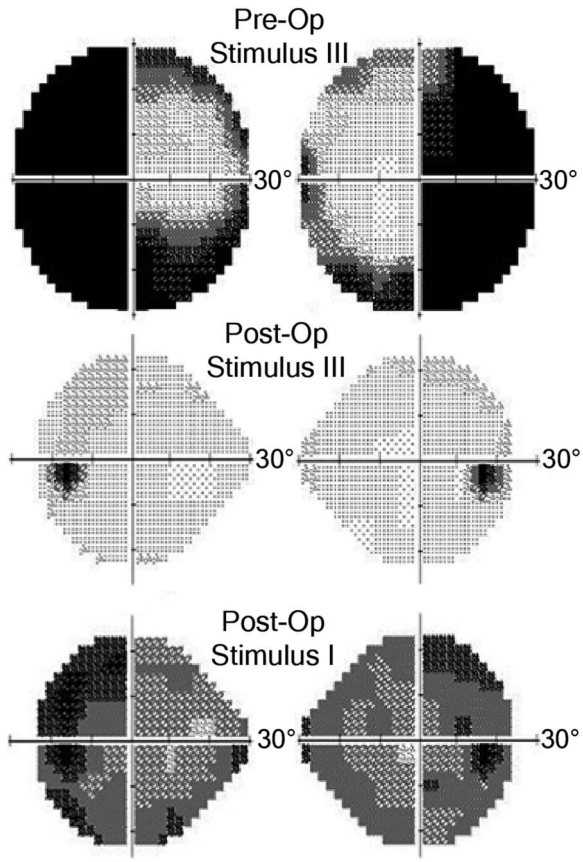

FIG. 1. Bitemporal hemianopia in a patient with a pituitary adenoma. A month following the surgery, the visual fields appeared nearly normal with a stimulus size III spot, but testing the same day with a stimulus size I spot showed persistence of relative bitemporal depression.

It remains to be determined which is superior for the early detection of chiasmal lesions: OCT or visual field testing. Tieger et al mention 6 patients who had significant reduction in RNFL and GCC, despite normal visual fields. A larger cohort must be tested to compare the sensitivity and specificity of OCT vs perimetry. In some respects, the issue has become moot. Many ophthalmologists use OCT to screen patients with visual symptoms and find it quicker and more efficient to rely on RNFL or GCC analysis than visual field testing to detect lesions of the anterior visual pathway. Some ophthalmologists are even using OCT as a surrogate for careful examination of the fundus with an ophthalmoscope.

As the authors point out, GCC thinning may sometimes become evident before visual field loss because of the relative insensitivity of perimetry. It is worth keeping in mind that in some situations, the reverse is true. A block in conduction of action potentials precedes actual loss of retinal ganglion cells and axons. When vision loss occurs suddenly, as in a patient with chiasmal compression from pituitary apoplexy, perimetry will show visual field loss before OCT can detect any thinning of the RNFL or GCC. Depending on the clinical situation, both OCT and perimetry have advantages and disadvantages for the detection of chiasmal compression.

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Form Versus Function: A State of Disunion?

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> "Form and function should be one, joined in a spiritual union." —Frank Lloyd Wright

Frank Lloyd Wright was referring to an architectural paradigm with this iconic quote, but the concept of interdependence between form and function is equally germane to our understanding of the afferent visual pathway (1). As a functionally eloquent and anatomically elegant region of the central nervous system (CNS), the afferent visual pathway has been aptly characterized as "a chain of hierarchically organized and synaptically linked neurons that maintain strong topographic connectivity" (2). As such, it represents an ideal model to study both the acute and chronic effects of lesions affecting any of its constituent parts, from retina to cortex. Because the afferent visual pathway is amenable to study with sensitive measures of function and structural integrity, this model potentially could allow us to elucidate mechanisms of neurologic injury and repair for a wide variety of CNS disorders (1).

Two publications in this issue of the *Journal of Neuro-Ophthalmology* have challenged the notion that form and function are synergistically linked in the afferent visual pathway. In a series of patients with chiasmal syndromes, Tieger et al (3) described patterns of ganglion layer loss that could be used to facilitate early detection of compressive lesions. These investigators also highlighted several cases in which visual field recovery manifested post-decompression, despite the persistent ganglion layer thinning as measured by optical coherence tomography (OCT). Similarly, Fraser and Klistorner (4) illustrated a pattern of ganglion cell loss corresponding to the homonymous visual field defect caused by a demyelinating optic tract lesion. Again, permanent structural deficits were noted with OCT despite recovery of the homonymous field loss.

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To better understand the apparent disconnect between form and function in these reports, we must carefully consider the accuracy of our measures of form and the sensitivity of our measures of function. To this end, consider the experience of our glaucoma colleagues who have long grappled with the clinical implications of this conundrum: namely, establishing a structural-functional paradigm that, early in the disease course, identifies patients at risk for vision loss. This approach seems apropos given that glaucoma is viewed by many as a neurodegenerative disorder associated with progressive loss of retinal ganglion cells and their axons within the optic nerve, with effects on afferent visual pathway structures that parallel those of primary CNS disorders (5).

While visual field testing with automated perimetry has become the mainstay in capturing visual deficits in patients with glaucoma and other optic neuropathies, patient-related factors including fatigue and reliability often hamper interpretation of results. Attempts to correlate form and function in glaucoma also have been encumbered by the fact that OCT and automated perimetry values tend to vary from day to day. This becomes problematic in cross-sectional studies when results from a single time point are analyzed (6). Furthermore, many studies, including the report by Tieger et al (3), have compared averaged automated perimetry data with mean OCT measures. However, a more sensitive approach would be to compare local visual field sensitivity to local retinal nerve fiber layer (RNFL) loss, so that regional relationships can be identified. Hood et al (6) have pointed out that reliance on automated perimetry values expressed as an average of decibel units is a potential confounder in defining structural-functional relationships in glaucoma. These values should be antilogged before averaging and then logged again after averaging to more accurately reflect the correlation between retinal ganglion cell integrity and visual field sensitivity. In general, structure-function correlations will be limited by any factor that negatively impacts the sensitivity and reliability of the psychophysical test being used to detect vision loss.