Early Primary Open-Angle Glaucoma

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Introduction

Glaucoma is the leading cause of irreversible blindness worldwide and is projected to affect more than 79.6 million people by 2020, over 10% of whom will be bilaterally blind.[1]

This multifactorial progressive optic neuropathy causes characteristic retinal nerve fiber layer damage that will eventually lead to associated glaucomatous visual field defects if left untreated. Unfortunately, these visual field defects are difficult for the patient to detect until more advanced stages and, as a result, early glaucoma is usually asymptomatic.[2]

This paper presents a case that is consistent with population studies that suggest that as many as half of people with glaucoma are *unaware* that they have the disease.[3]

CASE REVIEW

A healthy 71-year-old Caucasian male reported to our office as a new patient with complaints of mild blurry vision, OD=OS, at both distance and near.

The patient reported that he had had an eye exam "6-7 years" prior to our exam and was told that he had "symptoms of glaucoma"; however, he was not diagnosed with glaucoma and did not receive additional treatment. He denied any family history of glaucoma, was in good general health, and reported no other difficulties involving either eye.

The patient was self-medicating with 81mg aspirin, multi-vitamins, fish oil capsules, vitamin B complex, and red yeast rice capsules, all taken once daily.

His most recent blood pressure was 150/67 at 14:05 in the seated position, while his A1C was 5.8% and his blood glucose level was 116 mg/dL at 14:37. His body mass index was 28. No allergies to any medications were reported.

The patient's unaided entering distance visual acuities and pinhole acuities (PH) were:
OD: 20/60-1 PH: 20/25
OS: 20/40+2 PH: 20/25+2
Subjective refraction and best-corrected visual acuities were:
OD: -0.75 -1.50 x070 20/20
OS: -0.25 -1.50 x062 20/25+1

Preliminary testing showed that the pupils were equally round and reactive to light with no relative afferent pupillary defect. Confrontation visual fields were full to finger count OD, OS. Motility testing was full without restriction or pain OD, OS.

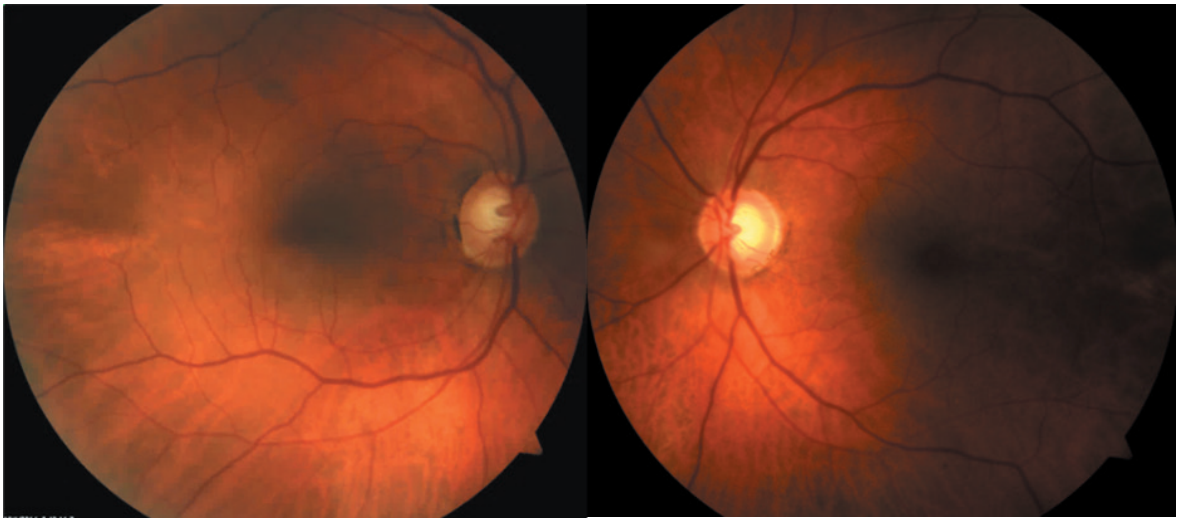
Slit lamp examination showed mild bilateral blepharitis, clear conjunctiva, and clear cornea without endothelial pigment or keratic precipitates. The anterior chamber was deep and quiet by Van Herick angle estimation and the iris was normal without signs of atrophy, obvious posterior synechiae, or trans-illumination defects. Intraocular pressures (IOP) were 17 OD, 15 OS at 08:01 by Goldmann applanation tonometry.

Dilated examination showed trace nuclear sclerosis and cortical opacities without evidence of pseudoexfoliation or pigment. The macula, vessels, and periphery were all normal OD, OS. There was a posterior vitreous detachment OD, OS with no evidence of peripheral retinal abnormality.

The optic nerve head was average to large size OD>OS based on the vertical disc height using the adjusted slit lamp graticule and a Volk 78 D lens with a correction factor of 1.2x. The optic cup was of moderate depth, with early visible laminar dots OU. There was mild alpha zone parapapillary atrophy, but no signs of pallor or disc hemorrhages OU. There was a subtle inferior retinal nerve fiber layer wedge defect with associated inferior rim thinning, inferior vessel baring, and inferior arteriole narrowing OU. Additionally, the superior rim was suspicious for glaucomatous optic neuropathy OU with evidence of early vessel baring OD>OS and relative thinning compared to other optic nerve sectors. Cup-to-disc ratios were estimated to be 0.7 v/0.7 h OD and 0.75 v/0.7 h OS.

Baseline photos and optical coherence tomography (OCT) Optic Nerve Head (ONH) and Retinal Nerve Fiber Layer (RNFL) Analysis were acquired. Both subjective and objective imaging confirmed the findings in the clinical exam, as shown in Figures 1 and 2.

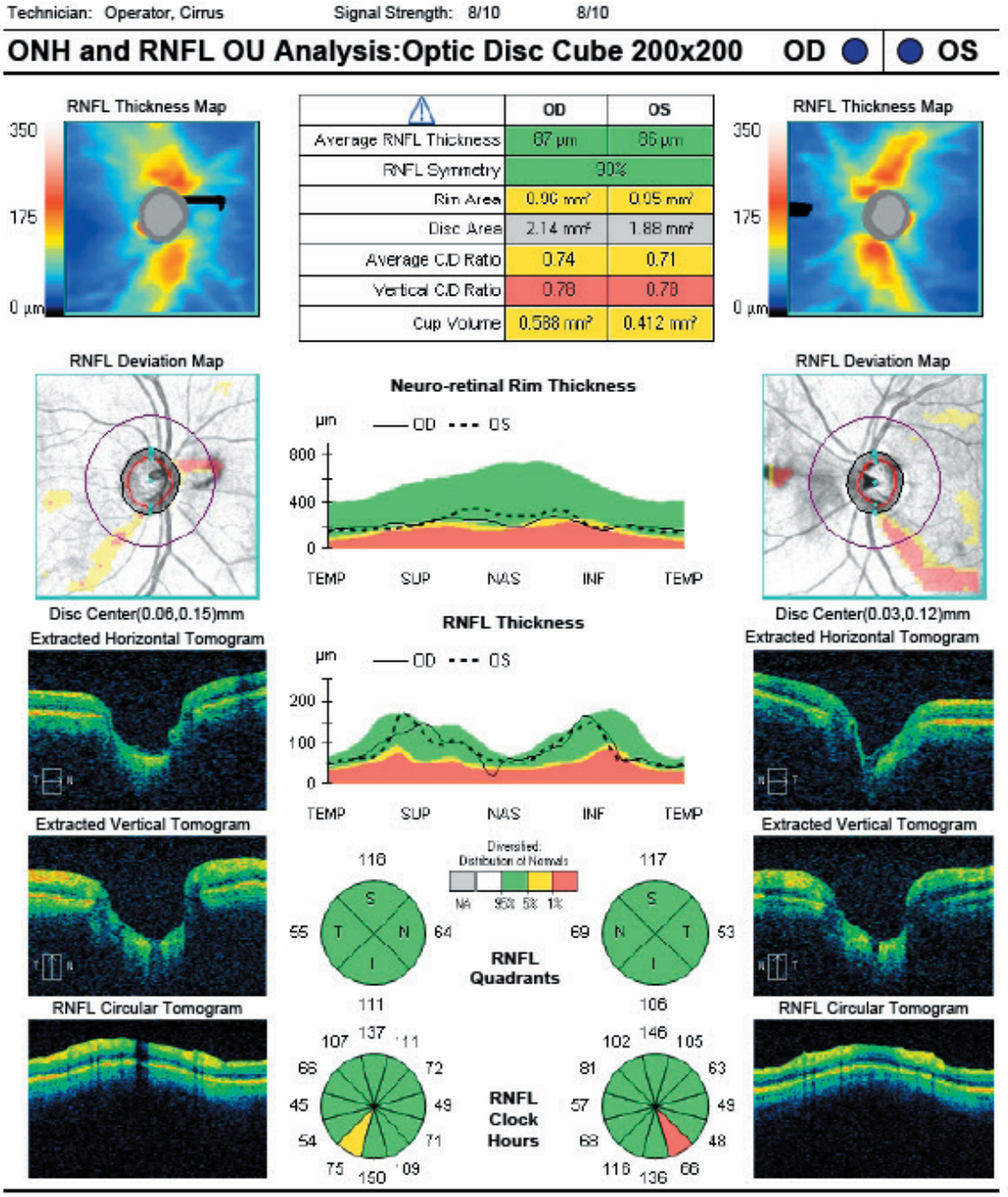
Figure 1: *Retinal images showing inferior-temporal localized retinal nerve fiber layer defects with associated inferior-temporal neuroretinal rim thinning. Note the early relative superior neuroretinal rim thinning OU.*



The patient was given a provisional diagnosis of early glaucoma, OS>OD, and asked to return within 1 month for repeat IOP measurements with baseline gonioscopy, pachymetry, and threshold visual field testing.

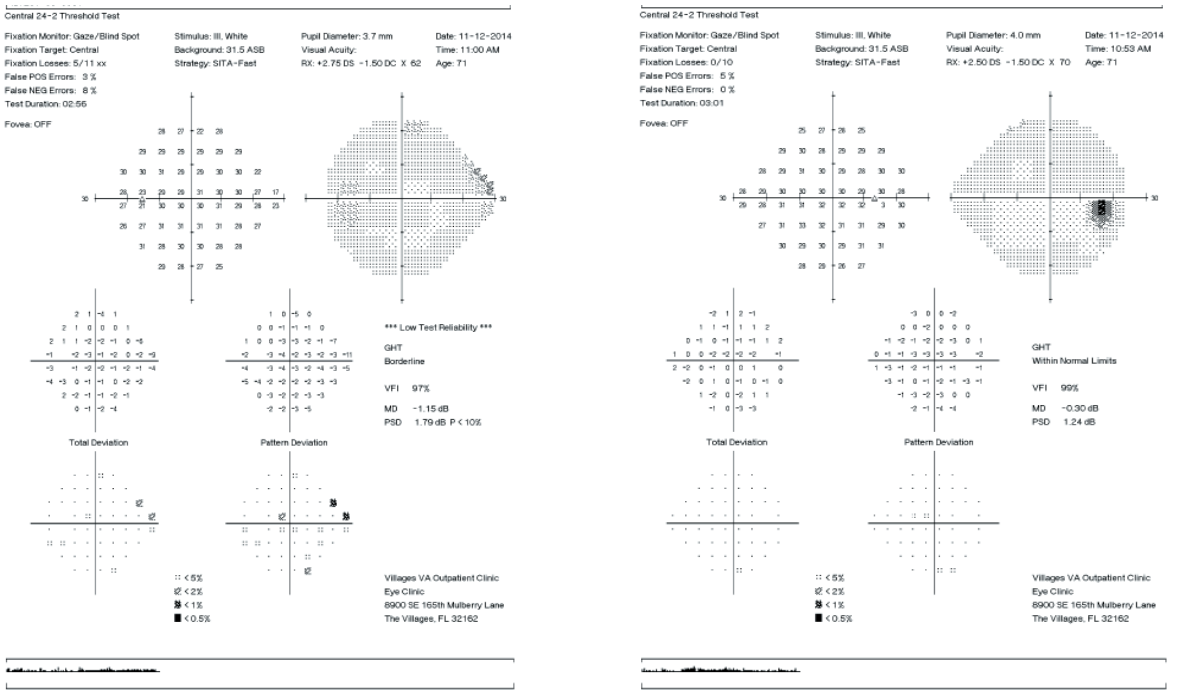
At the one-month follow-up appointment, the patient was found to have stable acuities without any additional ocular complaints. His intraocular pressures were slightly higher than baseline, at 21 OD, 19 OS at 10:42 am by Goldmann applanation tonometry. Pachymetry yielded central corneal thickness measurements that were slightly thinner than average, at 524u OD, 525u OS. Gonioscopy showed that the ciliary body was visible in all four quadrants with flat iris insertion, light trabecular meshwork pigmentation, and no evidence of peripheral anterior synechiae or angle recession OD, OS.

Figure 2: *Optical coherence tomography (OCT) Optic Nerve Head (ONH) and Retinal Nerve Fiber Layer (RNFL) Analysis OU. Note the bilateral nasal posterior vitreous detachments with associated artifacts observed on the RNFL Thickness and Deviation Maps. Furthermore, the RNFL thinning is localized and, as such, is only noted on the RNFL Clock Hours Map while appearing as "normal" on the RNFL Quadrant Map.*



Baseline threshold visual field testing (Humphrey 24-2 SITA Fast) showed normal-sensitivity OD with good reliability (0/10 fixation losses, 5% false positives, and 0% false negatives) and several focally depressed superior nasal defects OS with lower reliability (5/11 fixation losses, 3% false positives, and 8% false negatives).

Figure 3: *Baseline Humphrey 24-2 SITA Fast visual field plots show focally depressed defects OS only.*



Due to the normal gonioscopic appearance of the angle, the patient was given a more specific diagnosis of early primary open angle glaucoma OS>OD with questionable early perimetric defects OS based on the SITA Fast testing algorithm. Bengtsson and Heijl[4] found that SITA Fast test times (avg 5.0 min) were significantly shorter than Full Threshold (avg 14.6 min) and Fastpac (avg 9.4 min) test times, but were essentially equal in terms of reproducibility. However, as expected, the sensitivity for detecting shallow (subtle) defects was greater with Full Threshold testing. In other words, shallow defects noted in Full Threshold testing were progressively less visible (perhaps even absent) with Fastpac and SITA Fast, while the detection of deeper focal defects was essentially identical with all three strategies.

Through collaboration with the patient, we decided to monitor the condition closely at that time *without* treatment until repeat structural and functional testing confirmed the suspected defects (and/or suggested progression) and to further establish baseline intraocular pressures at various diurnal time points. However, based on the case findings thus far, and based on the Early Manifest Glaucoma Trial (EMGT) and the Collaborative Normal Tension Glaucoma Study (CNTGS), treatment will likely be initiated to help reduce the risk of disease progression. Furthermore, and perhaps more specific to our patient, Kim et al. found that sufficient IOP reduction slowed disease progression even in patients with suspected preperimetric glaucoma.[5]

The patient was asked to return to our office in 3-4 months for repeat tonometry, pachymetry, and 24-2 threshold visual field testing, as well as baseline optical coherence tomography Ganglion Cell Analysis and 10-2 visual field testing. As a brief review, the importance (and benefits) of central 10-degree visual field analysis cannot be overstated: approximately 50% of eyes with mild-moderate glaucoma were found to have defects within the central 3 degrees,[6] 11 eyes with *normal* 24-2 visual fields outside the central 10 degrees showed arcuate defects within the central 10 degrees with 10-2 testing,[7] nine percent of *normal* 30-2 threshold visual fields in glaucoma

suspect or early glaucoma patients were actually classified as abnormal with 10-2 testing[8] and approximately 50% of eyes will show macular glaucomatous damage on 10-2 testing while being classified as normal with just 24-2 testing.[9]

DISCUSSION

Weinreb et al. proposed a glaucoma continuum - a spectrum of structural and functional stages in glaucoma in which the patient generally progresses from "normal" and asymptomatic disease to functional blindness – with structural glaucomatous changes usually preceding functional symptoms.[10] The World Glaucoma Association also described this temporal relationship between structural and functional changes throughout the course of the disease[11] and both representations suggest that structural changes are usually detected prior to functional changes. However, and as an important reminder from Alasil et al.'s retrospective study and their findings of a structural and functional "tipping point", *both* structural and functional tests are still necessary to assess early glaucomatous damage.[12]

The American Academy of Ophthalmology Preferred Practice Pattern (AAO PPP) for Primary Open-Angle Glaucoma states that mild (early) glaucoma is characterized by "optic nerve abnormalities consistent with glaucoma [such as] ... diffuse thinning, focal narrowing, or notching of the optic disc rim, especially at the inferior or superior poles; progressive narrowing of the neuroretinal rim with an associated increase in cupping of the optic disc; diffuse or localized abnormalities of the parapapillary RNFL [retinal nerve fiber layer], especially at the inferior or superior poles; disc rim, parapapillary RNFL, or lamina cribrosa hemorrhages; [and/or] optic disc neural rim asymmetry of the two eyes consistent with loss of neural tissue" in the presence of "a normal visual field as tested with standard automated perimetry."[13]

In the American Optometric Association Optometric Clinical Practice Guidelines (AOA CPG), mild glaucoma is defined as an optic nerve with "mild concentric narrowing or partial localized narrowing of the neuroretinal rim; disc hemorrhage; [and/or] cup/disc asymmetry". Furthermore, the nerve fiber layer shows a "less bright reflex; fine striations to texture; [and/or] large retinal blood vessels [that appear relatively] clear [whereas] medium retinal blood vessels [are] less blurred [and] small retinal blood vessels [are] blurred". However, unlike the AAO PPP, the AOA CPG says that early glaucoma may show "isolated paracentral scotomas, partial arcuate or nasal step [defects]; [and that the] damage [is] limited to one hemifield with fewer than 25% of points involved, [with a] mean deviation (MD) less than -6dB".[14] A more succinct definition that seems to help bridge the two above definitions is given by Song and Caprioli: "a progressive optic neuropathy that is defined by characteristic structural changes of the optic nerve with *corresponding* functional changes of the visual field."[15]

Nonetheless, once functional loss is detectable, the severity of the glaucomatous optic neuropathy increases with the severity of the visual field loss, as shown by Ng et al.[16]

The present patient presented with several risk factors for open-angle glaucoma,[17,18] including his slightly elevated intraocular pressure *with* mild fluctuation[19] (albeit based on only two isolated readings) and his mid-advanced age.[20,21] However, additional risk factors that were not applicable to this case, but which should also be considered, include presence of lenticular exfoliation,[22,23] glaucomatous disc hemorrhages,[24-28] African-American ancestry,[29] a first-degree history of glaucoma,[30] and a general history of diabetes[31] or hypertension.[32-34]

The primary clinical sign that was *most* convincing that this patient did indeed have glaucoma was the appearance of the optic nerve and retinal nerve fiber layer. Specifically, the inferior retinal nerve fiber layer defects with associated inferior rim thinning, inferior vessel baring, and inferior arteriole narrowing (and potential superior rim thinning) are all characteristic of early glaucoma. Because of this preferential pattern of neuroretinal rim loss, the ISNT Rule[35,36] mnemonic has been proven to be very effective in differentiating normal optic nerves from those with early glaucomatous damage. Furthermore, the absence of rim pallor helps rule out other optic neuropathies (ischemic, infiltrative, traumatic, toxic, metabolic, and compressive) that could also result in retinal nerve fiber layer defects and arteriole narrowing, and which would necessitate a more through systemic workup, possibly including blood work and neuroimaging.[37-39] Baseline photos were taken to assist in monitoring for future structural progression[40] that would manifest as widening of the nerve fiber layer defects (locations of future progression and correlating visual field defects[41]), increased rim thinning/vessel baring/arteriole narrowing, increased parapapillary atrophy, and/or further nasalization of the central retinal vessel trunk.

Subjective evaluation of serial photos and objective imaging (OCT) are complementary structural evaluations used in concert with regular functional (visual field) assessment to monitor for progression. All are necessary: the World Glaucoma Association notes that "(c)urrently, no specific test can be regarded as the perfect reference standard for detection of glaucomatous structural and/or functional progression".[41] Supporting this position, Banegas et al. reported that, in their observational study of 246 eyes, glaucomatous progression was detected in 6.9% of eyes by stereo photos, 15% of eyes by visual field testing, and 25.6% of eyes by OCT-guided progression analysis (GPA) software. Interestingly, of those cases that showed progression, most were only discovered by either stereophotos, perimetry, *or* OCT testing alone, suggesting a lower percentage of positive agreement among evaluation methods, and emphasizing the importance of using all three to monitor for change.[42,43] In this situation, the clinical appearance of the ONH correlated very well with the baseline RNFL OCT testing, establishing supporting subjective and objective structural baselines.

In support of making a diagnosis of glaucoma based solely on the appearance of the optic nerve and *not* waiting for the development of correlating glaucomatous visual field defects, Sommer et al. suggested in 1977 that glaucomatous nerve fiber layer defects (such as those observed in this patient) may develop several years prior to reliable glaucomatous visual field defects.[44] Furthermore, and more recently, Kuang et al. found that RNFL defects observed on OCT testing were noted up to 8 years prior to associated glaucomatous visual field defects.[45] Consistent with these findings, histological studies have found that as much as 50% of retinal ganglion cells are lost prior to *clinically detectable* visual field defects[46] - resulting in a "broken-stick" correlation model between retinal nerve fiber thickness and glaucomatous visual fields, as described previously by Alasil et al.[12]

As mentioned previously, despite the clinically correlating information suggesting early open-angle glaucoma, collaboration with the patient determined that we did not initiate treatment for the following 3 reasons:

1. To establish a baseline IOP range in light of potential fluctuation in initial IOP measurements,
2. To establish baseline visual field reproducibility and reliability,[47]
3. To establish rate of progression, in recognition of the fact that not all patients with glaucoma will progress to the point of visual symptoms affecting their activities of daily living.[48]

CONCLUSION

Elevated intraocular pressure is the primary (and currently the only readily modifiable) risk factor for the development of glaucoma and glaucoma progression.[49-53] Accordingly, if treatment is required in the future, we will work with the patient to establish a customized, unique target IOP range – the "upper limit of a range of IOP at which it is judged likely to retard further optic nerve damage"[54] and to minimize associated visual field loss.[55] It is very important to balance this dynamic IOP range with quality-of-life factors including the estimated lifetime risk of visual disability for the patient, the potential side-effects of treatment options (topical vs. laser vs. minimally-invasive glaucoma surgery), the financial burden of treatment, and the instillation technique/capability.

Primary open angle glaucoma can be missed in its early stages due to its asymptomatic nature, subtle optic nerve morphological changes, and often pre-perimetric presentation. For these reasons, vigilance is required, as we have the best success of preserving a lifetime of functional vision for the patient if we can diagnose glaucoma earlier and, if needed, treat glaucoma sooner. ●

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