PEER REVIEWED

Primary Open Angle Glaucoma

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Abstract

This teaching case report involves a newly diagnosed patient with primary open angle glaucoma (POAG) and subsequent challenges to adherence. While this case may be appropriate as a teaching guide for optometry students at all levels because it provides a review of anatomical structures related to the aqueous humor and optic nerve and a discussion regarding key findings, differential diagnoses, epidemiology, pathophysiology, risk factors, assessment strategies, and treatment and management options associated with POAG, it would best serve third- and fourth-year students given the more complex nature of non-optimal patient reliability and adherence challenges.

Keywords

adherence, POAG, primary open angle glaucoma

Background

This teaching case report features a newly diagnosed 71-year-old White male with primary open angle glaucoma and challenges to adherence. Key learning goals of this case, including listing differential diagnoses associated with bilateral elevated intraocular pressures in a patient without acute ocular symptoms, explaining common assessment and treatment and management options associated with primary open angle glaucoma (POAG), discussing methods to address challenges with adherence to ophthalmic medications, and identifying key components of a referral to a specialist, are covered. While this case may be appropriate as a teaching guide for optometry students at all levels because it provides a review of anatomical structures related to the aqueous humor and optic nerve and a discussion regarding key findings, differential diagnoses, epidemiology, pathophysiology, risk factors, assessment strategies, and treatment and management options associated with POAG, it would best serve third and fourth year students given the more complex nature of non-optimal patient reliability and adherence challenges. It is important for eye care providers caring for patients with POAG to recognize the clinical findings, understand assessment strategies and treatment and management options, and modify the treatment plan as necessary.

Case Description

Patient AB, a 71-year-old White male, presented to our clinic reporting long-standing eye watering and noted relief with the use of artificial tears as needed. The patient's ocular history was significant for dry eye disease in both eyes, a developing cataract in the right eye, pseudophakia in the left eye (unknown surgical date), and anisometropia.

His medical history was significant for hyperlipidemia, hypertension and rheumatoid arthritis for which he took Lipitor, Diovan, Tenormin and Zyloprim. He had no known drug allergies. His blood pressure was

140/80 mm Hg right arm sitting with a pulse of 65 beats per minute. The rest of the ocular and medical history was negative and non-contributory. The family ocular history was significant for glaucoma in his mother. The family medical history was significant for hypertension in his father. The patient denied smoking, drinking alcohol and using narcotics. He reported neither history of ocular trauma nor use of oral or ophthalmic steroids.

His best-corrected visual acuity with a manifest refraction of +0.75-0.25×128 in the right eye and -1.25-0.75×162 in the left eye and was 20/30 in each eye. Pupils were round and reactive to light, and no afferent pupil defect was noted. Extraocular muscles were unrestricted in all gazes. Confrontation visual fields were full to finger counting in each eye.

Anterior segment evaluation by slit lamp examination revealed clear lashes and a quiet bulbar and palpebral conjunctiva. Lagophthalmos was not noted in either eye. A reduced tear meniscus was noted and a tear break-up time of 4 seconds in both eyes. Grade 2+ inferior punctate epithelial erosions were present at the inferior one-third of his corneas. No corneal infiltrates or endothelial pigmentation were noted in either eye. His irises were flat without signs of transillumination defects in both eyes. The anterior chambers appeared clear without cells or flare. Intraocular pressures were 27 mmHg in the right eye and 28 mmHg in the left eye with Goldmann applanation tonometry at 8:43AM following the instillation of one drop of Fluress.

Based on the presence of bilateral elevated intraocular pressure reading in a patient without acute ocular symptoms such as pain, the following differential diagnoses were considered as listed in **Table 1**, ranked starting with more likely.

TABLE 1

Conditions	Clinical Findings [1]
Ocular hypertension	Patients with ocular hypertension demonstrate elevated intraocular pressure with a normal optic nerve and no visual field defects.
Primary open angle glaucoma	Signs associated with primary open angle glaucoma include an elevated intraocular pressure with normal-appearing open anterior chamber angles, loss of optic nerve rim tissue, loss of retinal nerve fiber layer (e.g. RNFL defects), signs such as a splinter hemorrhage, and associated visual field defects typically in Bjerrum's area
Secondary open-angle glaucoma	More common examples that are appropriate to this case include pseudoexfoliation (white, flaky material on the pupillary margin, exfoliative material on the anterior lens capsule, peri-pupillary iris transillumination defects) and pigmentary (mid-peripheral iris transillumination defects, corneal endothelial pigment arranged in a vertical band inferior to the visual axis, densely pigmented trabecular meshwork visualized during gonioscopy) glaucoma

Table 1: Differential diagnoses for bilateral elevated intraocular pressure readings in a patient without acute ocular symptoms Click to enlarge

The patient was dilated using 1 drop of 0.5% tetracaine, 1 drop 1% tropicamide and 1 drop 2.5% phenylephrine. Grade 1+ nuclear sclerosis in the right eye and a well-centered posterior chamber lens implant with mild posterior capsular opacification in the left eye were noted. These findings may explain why the best-corrected visual acuity was 20/30 for each eye.

A clear vitreous was noted in both eyes. An evaluation of the posterior segment was completed by slit lamp with a 90D lens and by Binocular Indirect Ophthalmoscopy with a 20D lens. Fundus assessment revealed asymmetric optic disc sizes with the right eye greater than the left eye and moderate optic nerve cupping with a cup-to-disc ratio of .70H x .85V in the right eye and .65H x .75V in the left eye. Focal rim thinning superiorly>inferiorly was noted in the right eye greater than in the left eye. The neuroretinal rims appeared pink without any splinter (Drance) hemorrhages and disc margins were distinct in both eyes. Stereo-disc photography was not available. No apparent nerve fiber layer dropout was observed. Retinal vessels appeared normal with an arteriole-venule ratio of 2/3 in both eyes. His maculae appeared flat and homogenous, and the peripheral retina was flat and intact with no pathology noted in either eye.

Primary open angle glaucoma was the highest on the list of differential diagnoses given the characteristic appearance of his optic nerve head with elevated intraocular pressures, open anterior chamber angle and normal anterior segment, including clear cornea without endothelial pigment, quiet anterior chamber, normal iris appearance without transillumination defects.

Given the patient's eagerness to further evaluate for primary open angle glaucoma, a Humphrey visual field 24-2 SITA-FAST was completed, demonstrating borderline reliability with a possible moderate incomplete superior and inferior arcuate (versus a possible cloverleaf defect due to challenges with patient attention) in the right eye (MD -11.02dB) and non-optimal reliability but no pattern defects in the left eye (MD -6.56dB). Results are available below in **Figure 1**.

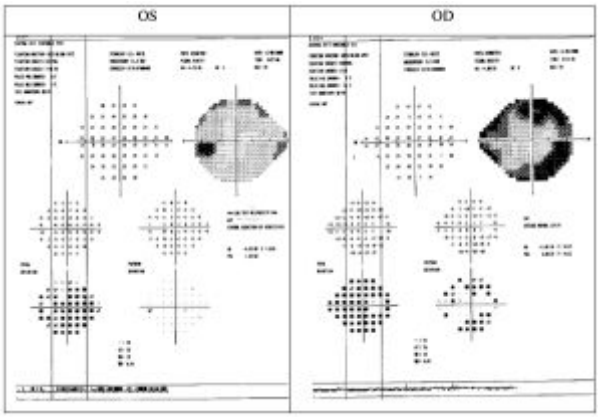


Figure 1: First Humphrey visual field 24-2 SITA-FAST Click to enlarge

The patient was educated thoroughly about the asymptomatic nature of the disease, importance of routine follow-up and future possibility of medical and/or surgical intervention. An appointment was scheduled for follow-up in 2 weeks to repeat threshold visual field testing, obtain optical coherence tomography scans of the retinal nerve fiber layer and optic nerve, re-check intraocular pressure and complete pachymetry and gonioscopy.

Dry eye disease likely secondary to the patient's rheumatoid arthritis and related to his long-standing eye watering and anterior segment findings was also discussed. Patient AB was encouraged to continue use of artificial tears at least 4 times per day in both eyes, with no mention regarding non-preserved versus preserved. The possibility of further intervention was discussed if his dry eye symptoms and/or signs persist or worsen.

Follow-up #1

Patient AB returned 2 weeks later for a repeat threshold visual field examination, optical coherence tomography of the retinal nerve fiber layer and optic nerve, intraocular pressure check, pachymetry and gonioscopy. He reported no changes in vision or ocular discomfort. His corrected visual acuity remained stable at 20/30 in the right eye, with no improvement with pinhole acuities in the left eye. Pupils were round and reactive to light and no afferent pupil defect was noted in both eyes. Extraocular muscles were unrestricted in all gazes.

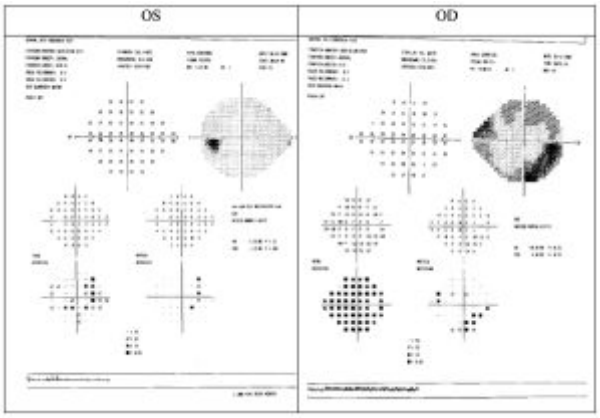


Figure 2: Repeat Humphrey visual field 24-2 SITA-FAST
Click to enlarge

The patient's second Humphrey visual field 24-2 SITA FAST results demonstrated improved reliability with a remaining incomplete inferior arcuate and superior nasal step in the right eye (MD -10.22dB) and improved reliability but again no pattern defects consistent with his optic nerve head appearance in the left eye (MD -3.75dB). Visual field results are in **Figure 2**.

Optical coherence tomography (OCT) was performed at this visit. As viewed in **Figure 3** from the RTVue Fourier-Domain OCT System, imaging of Patient AB's retinal nerve fiber layer was completed.

Relative retinal nerve fiber layer rim thinning was noted inferiorly and superiorly in the right eye and possibly inferiorly in the left eye with average retinal nerve fiber layer (RNFL) thicknesses of 68.59 µm in the right eye and 78.81 µm in the left eye. Asymmetric optic disc sizes in the right eye are greater than in the left eye were quantified, and the ganglion cell complex maps demonstrated thinning inferiorly and superiorly in the right eye and inferiorly in the left eye with average thicknesses of 65.61 µm in the right eye and 74.48 µm in the left eye. These findings were consistent with his optic nerve head appearance and visual field defects. **Figure 3** provides the retinal nerve fiber layer, optic disc scan and both the thickness of the ganglion cell complex maps and significance map.

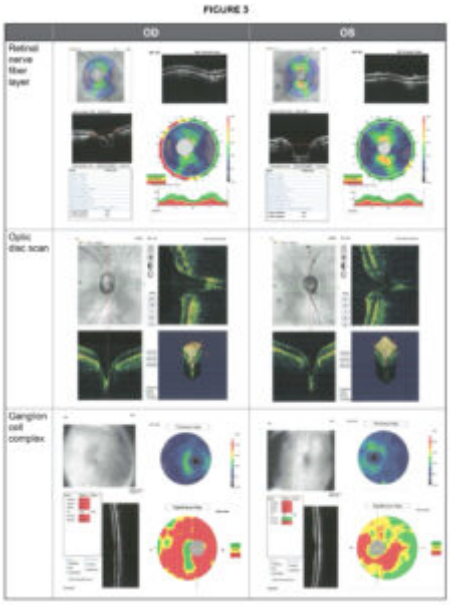


Figure 3: Optical coherence tomography
Click to enlarge

Slit lamp findings were unchanged and no Drance hemorrhages were seen in both eyes at this undilated visit. Intraocular pressures were 30 mmHg in each eye with Goldmann Applanation Tonometry (GAT) following the instillation of 1 drop of Fluress. Pachymetry revealed a central corneal thickness of 500 microns in the right eye and 510 microns in the left eye. Gonioscopy was also performed, and his anterior chamber angles demonstrated a flat approach and were open to the ciliary body in all views of both eyes. Moderate pigment and no peripheral anterior synechiae or angle recession were visualized during gonioscopy.

As intraocular pressure readings remained elevated with repeatable visual field defects that corresponded to his optic nerve head appearance and optic coherence tomography results, Patient AB was diagnosed with primary open angle glaucoma which was greater in the right eye than in the left eye.

Primary open angle glaucoma, the importance of treatment, adherence and regular follow-up was re-discussed with the patient. The benefits and side effects of medical treatment were also discussed, and Travatan-Z was initiated before bedtime in both eyes. Instillation procedures including punctual occlusion were reviewed. A target intraocular pressure of a 30% reduction was set at 20 mmHg for each eye. Patient AB was instructed to return in 6 to 8 weeks for an intraocular pressure check. Patient AB was encouraged to continue use of artificial tears 4 times per day in both eyes and the patient was given personal contact information if he ran into any questions or concerns.

Follow-up #2

Patient AB returned 8 weeks later for an intraocular pressure check and presented with a chief concern of continued long-standing ocular irritation and tearing relieved by artificial tears 4 times per day in both eyes. The patient suspected that the irritation and tearing may have been exacerbated using Travatan-Z. He reported good adherence with the Travatan-Z before bedtime in both eyes and reported that his last dose was at 10:00PM. He was able to demonstrate competency in proper drop instillation technique with a bottle of artificial tears but noted difficulties with punctual occlusion. Notably, he was unable to describe both the color and size of the medication bottle and brought up concerns over the cost of Travatan-Z.

His corrected visual acuity remained stable at 20/30 in each eye with no improvement with pinhole acuities. Pupils were round and reactive to light and no afferent pupil defect was noted in both eyes. Extraocular muscles were unrestricted in all gazes and confrontation visual fields were full to finger counting in both eyes. Slit lamp findings were unchanged. His intraocular pressures were 26 mmHg in the right and left eyes with GAT. Optic nerve findings remained stable with no Drance hemorrhages seen in both eyes at this undilated visit.

Based on the patient’s dry eye symptoms and signs despite his reported continued use of artificial tears, collagen punctal plugs were inserted in both his right and left lower lid punctum. The potential for punctal plugs to also maximize the amount of Travatan-Z that stayed in his eye and thus increasing the effectiveness of his glaucoma medication was also considered.

Because Patient AB was unable to recall either the color or size of the medication bottle and he expressed concerns regarding the cost of medications, there were concerns regarding adherence. Because generic intraocular pressure-lowering medications with a once a day dosing were not yet available at the patient’s visit and given concerns relating to exacerbating dry eye symptoms and signs with the introduction of preservatives, Patient AB was kept on the Travatan-Z before bedtime in both eyes, counseled extensively on the importance of adherence, consequences of untreated glaucoma, and the possibility of additional intervention if intraocular pressure readings continued to remain above target levels. An appointment was scheduled in 2 to 4 weeks for an intraocular pressure check and dry eye

disease follow-up. If the patient reported relief from symptoms with collagen punctal plugs, silicone punctual plugs would be considered. Patient AB was encouraged to continue use of artificial tears at least 4 times per day in both eyes and was requested to bring the bottle of Travatan-Z he was using at the next follow-up visit.

Follow-up #3

Patient AB returned a month later for an intraocular pressure check and dry eye follow-up. He Patient AB returned a month later for an intraocular pressure check and dry eye follow-up. He reported no relief of ocular irritation or tearing following the insertion of the punctal plugs. He reported good adherence with Travatan-Z at bedtime in both eyes (last dose 10:00PM) and artificial tears at least 4 times per day in both eyes. However, he failed to bring his bottle of Travatan-Z to the visit. His corrected visual acuity remained stable at 20/30 in each eye with no improvement with pinhole acuities.

Pupils were round and reactive to light and no afferent pupil defect was noted in both eyes. Extraocular muscles were unrestricted in all gazes and confrontation visual fields were full to finger counting in both eyes. Intraocular pressures were 26 mmHg and 25 mmHg with GAT following the instillation of 1 drop of Fluress. Slit lamp findings were unchanged and no Drance hemorrhages were seen in both eyes at this undilated visit.

Because Patient AB's intraocular pressure remained above the target intraocular pressure despite his reported adherence with Travatan-Z, the addition of a topical beta-blocker, such as Timolol 2 times per day in both eyes, to the patient's medication regimen was also considered. However, the patient was on an oral beta-blocker so Alphagan-P 2 times per day in both eyes was added to the patient's regimen. The importance of treatment, adherence and regular follow-up were emphasized. The benefits and side effects of both medications were reviewed, and follow-up was scheduled in 1 to 2 months for an intraocular pressure check. The patient was encouraged to use his artificial tears at least 4 times per day in both eyes for relief of his symptoms from dry eye disease. Patient AB was also given the dosing schedule for each of his three eye drops on the back of a business card.

Follow-up #4

Two months later, Patient AB returned for an intraocular pressure check. He reported no change in vision but presented with a chief concern about the inconvenience in using multiple eye drops throughout the day. He continued to report use of Refresh Tears®, Alphagan-P and Travatan-Z but was unable to recall the dosing schedule for each medication. Intraocular pressures remained above target at 25 mmHg in each eye with GAT following the instillation of 1 drop of Fluress. His corrected visual acuity remained stable at 20/30 for each eye with no improvement with pinhole acuities.

Pupils were round and reactive to light and no afferent pupil defect was noted in both eyes. Extraocular muscles were unrestricted in all gazes and confrontation visual fields were full to finger counting in both eyes. Slit lamp findings were unchanged including at the optic nerve and no Drance hemorrhages were seen with 90D in both eyes at this undilated visit.

Because the 30% target reduction in intraocular pressure was not achieved with two topical medications (and use of his oral beta blocker) and questionable patient adherence was noted, surgical and laser intervention were considered. The benefits and risks of surgical and laser interventions were reviewed with Patient AB. Specifically, selective laser trabeculoplasty was briefly reviewed with mention of argon laser trabeculoplasty and trabeculectomy.

While Patient AB was cautious about the prospect of surgical and/or laser intervention, he was agreeable to a referral to a local glaucoma specialist. A referral letter was written and mailed to the glaucoma specialist along with the patient's contact information and a request for their office to contact

the patient for scheduling.

Educators' Guide

Learning Objectives

At the end of this case discussion, readers should be able to:

1. Identify the anatomical structures related to:
    1. Aqueous humor production and outflow
    2. The optic nerve
2. List appropriate differential diagnoses for bilateral elevated intraocular pressures in a patient without acute ocular symptoms
3. Describe the definition, epidemiology, pathophysiology and risk factors associated with POAG
4. Describe common assessment strategies for diagnosing POAG
5. Explain common treatment and management options for POAG
6. Discuss methods to address challenges with adherence to ophthalmic medications
7. Identify key components of a referral to a specialist

Key Concepts

1. Describe an abnormal optic nerve in a systematic manner.
2. Recognize clinical findings seen in POAG.
3. List common assessment strategies for diagnosing POAG.
4. Identify treatment and management options for POAG.

Discussion Questions

1. Knowledge and concepts required for critical review of the case
    1. What anatomical structures are within the anterior chamber angle and optic nerve?
    2. Describe the epidemiology, pathophysiology and risk factors associated with POAG.
    3. Explain key clinical findings that are found in patients with POAG.
2. Differential diagnoses
    1. List appropriate differential diagnoses for elevated intraocular pressure and/or abnormal optic nerve appearance.
    2. What assessment strategies are helpful in formulating a definitive diagnosis?
3. Disease treatment and management
    1. What are common initial treatment options for POAG?
    2. List alternative/additional treatment options and discuss the rationale behind each one of them.
    3. What are potential complications associated with anti-glaucoma therapies?
    4. When should laser and surgical procedures be considered in POAG?
4. Critical thinking
    1. How would you have managed this case? Justify your answer based on the findings.
    2. What are indications of poor adherence to a treatment regimen? How can these be addressed?

Learning Activity

1. Assign the case with selected discussion questions as a homework assignment during a didactic course featuring glaucoma or as part of a clinical assignment.

2. Require students to provide at least 2-4 recent, peer-reviewed articles to support their answers.
3. Block off 1-2 hours during class or clinic time to allow students to present their answers and learn from each other; encourage questions from other students by providing participation credit incentives.

Learning Assessment

1. Assess knowledge regarding POAG and differential diagnoses by use of multiple choice and/or short answer questions.
2. Facilitate demonstration of clinical skills associated with a glaucoma evaluation including slit lamp examination with optic nerve assessment, gonioscopy and pachymetry, and systematically describing abnormal clinical findings and relationships to ancillary testing such as threshold visual fields and optical coherence tomography.
3. Incorporate the case into clinical or didactic discussions.

Discussion

Identify anatomical structures

Related to aqueous humor

A transparent fluid located in the anterior and posterior chambers of the eye, the aqueous humor facilitates circulation of nutrition, removes excretory products and maintains pressure within the eye. Aqueous humor is produced at the ciliary body, which is located at the anterior portion of the scleral spur. The aqueous humor travels through the ciliary body, around the lens, through the pupils, into the anterior chamber, and passively leaves the eye through either the trabecular meshwork (conventional) or the uveoscleral pathway (non-conventional).[2] When aqueous humor travels through the trabecular meshwork, it crosses the inner wall of Schlemm's canal and drains through the aqueous and episcleral veins.[3] When aqueous humor travels through the uveoscleral pathway, it enters the connective tissue between the ciliary muscle bundles, goes through the suprachoroidal space, and leaves through the sclera.[4] The uveoscleral pathway accounts for around 10% of aqueous outflow.[5]

The average intraocular pressure is approximately 15mmHg in a healthy eye[2]; a dis-equilibrium between the production and drainage of aqueous humor, which results in an increase in intraocular pressure, is a major risk factor for glaucoma progression.[6] As such, current pharmacological and surgical therapies to lower intraocular pressure and thus reduce the risk of vision loss from glaucoma are mainly focused on reducing aqueous production or increasing aqueous humor outflow.

Related to the optic nerve

The optic nerve is the only tract in the central nervous that can be clinically visualized and is where the axons of retinal ganglion cells convergence.[7] These axons form the retinal nerve fiber layer and intrapapillary neuroretinal rim.[8] In normal eyes, the neuroretinal rim is broadest inferiorly, followed by superiorly, nasally and lastly temporally[9], which forms the basis of the ISNT rule.[10]

Changes to the nerve fibers lead to visual field defects. Specifically, damage to the macular fibers that enter the disc temporally can lead to central, centrocecal, and paracentral scotomas. Alterations to the fibers from the temporal retina that enter the disc superiorly and inferiorly cause arcuate and nasal step scotomas, while changes to the fibers that enter the disc nasally can lead to wedge-shaped temporal scotomas. Defects in the thickness of nerve fibers can also be appreciated through optical coherence tomography and scanning laser polarimetry.[7] Because there are no photoreceptors at the optic nerve, it

represents a blind spot in vision.

List differential diagnoses for bilateral elevated intraocular pressures in a patient without acute ocular symptoms

Normal intraocular pressure ranges from 12-21 mmHg; a reading of 22 mmHg or higher is considered elevated.[11] The top three differential diagnoses for bilateral elevated intraocular pressures in a patient without acute ocular symptoms are: ocular hypertension, primary open angle glaucoma and secondary open-angle glaucoma. Chronic narrow angle could also be a possibility for increased IOP without symptoms.

A diagnosis of ocular hypertension is applied in a patient that presents with elevated intraocular pressures without acute ocular symptoms and no optic nerve head damage and no visual field defects.[1]

Clinical findings that support the diagnosis of primary open angle glaucoma include elevated intraocular pressures with characteristic optic nerve head changes, nerve fiber layer defects, and visual field loss despite a normal-appearing open angle as viewed by gonioscopy. Optic nerve head changes can include cup: disc enlargement and/or asymmetry, the presence of thinning and/or notching of the neurosensory rim of the optic nerve, splinter (Drance) hemorrhages and nerve fiber layer defects.[1]

Bilateral elevated intraocular pressures in a patient without acute ocular symptoms can also be due to secondary open-angle glaucoma, such as pseudoexfoliation (or exfoliation) and pigmentary glaucoma. Signs of pseudoexfoliation glaucoma include: iris transillumination defects, exfoliative material on the lens capsule and/or on the iris, anterior hyaloid, or zonules, and increased, oftentimes patchy, pigment deposit on the trabecular meshwork and at Schwalbe line with gonioscopy.[12] Signs of pigmentary dispersion glaucoma include: pigment on the corneal endothelium (Krukenberg spindle), mid-peripheral iris transillumination defects, and significant gonioscopy findings including increased homogenous pigment in the trabecular meshwork and/or irregular pigment deposit on the trabecular meshwork, particularly inferiorly, anterior to Schwalbe line (Sampaolesi line).[13] It is important to mention that patients with dark irides may occasionally have pigment on or slightly above Schwalbe's line and not have glaucoma. Furthermore, patients with either pigmentary dispersion or pseudoexfoliation glaucoma must demonstrate a characteristic optic nerve head appearance and corresponding visual field defects consistent with glaucoma. If such findings are not found, the patient is considered not to have glaucoma but may remain a glaucoma suspect.

Describe the definition, epidemiology, pathophysiology and risk factors associated with POAG

POAG is a "chronic, progressive disease that most often presents with characteristic optic nerve (ON) damage, retinal nerve fiber layer (NFL) defects and subsequent visual field (VF) loss" that primarily occurs bilaterally but asymmetrically and mostly in adults that have elevated intraocular pressure (IOP).[14]

Glaucoma has been reported to affect 2.2 million Americans and is the third most common cause of blindness in the United State**s**.[15] Primary open angle glaucoma (POAG) is the most common type of glaucoma. Primary open angle glaucoma is an adult-onset, typically bilateral disorder that produces characteristic optic nerve head and visual field changes.

While the etiology of primary open angle glaucoma is constantly undergoing further investigation, there is strong evidence that suggests glaucoma is caused by damage to the retinal ganglion cell axons within the lamina cribrosa of the optic nerve head[16,17] leading to gradual vision loss. Two main theories have emerged to explain the mechanism of ganglion cell dysfunction: mechanical and vasogenic. According to the mechanical theory, pressure-induced deformation of the lamina cribrosa structure leads to blockage of axon transport and subsequent axon damage.[18] According to the vasogenic theory, vascular

insufficiency at the optic nerve head results in hypoxia and decreased nutrition to optic nerve axons ultimately with ganglion cell death.[19]

According to the Ocular Hypertension Treatment Study, risk factors for primary open angle glaucoma include: increased age, African-American heritage, increased intraocular pressure, decreased corneal thickness, larger vertical cup-to-disc ratio, larger horizontal cup-to-disc ratio, heart disease and greater Humphrey visual field pattern standard deviation.[20] The Los Angeles Latino Eye Study suggests a similar prevalence of open angle glaucoma among Latinos as for those with African American heritage.[21] **Table 2** briefly summarizes these risk factors for primary open angle glaucoma. The primary modifiable risk factor is reducing intraocular pressure[22,23], which is most addressed with prescription ophthalmic medications. Because patients with primary open angle glaucoma are typically asymptomatic until later stages of the disease[24], adherence is oftentimes a challenge.

TABLE 2

Increased age
African American and/or Latino heritage
Increased intraocular pressure
Decreased corneal thickness
Larger vertical cup-to-disc ratio
Larger horizontal cup-to-disc ratio
Heart disease
Greater Humphrey visual field pattern standard deviation

Table 2: Risk factors for primary open angle glaucoma
Click to enlarge

Describe common assessment strategies for diagnosing POAG

Intraocular pressure

Intraocular pressure is determined by the balance between the rate of aqueous secretion and the rate of outflow. A common method to measure intraocular pressure is via Goldmann applanation tonometry, which has been shown to have excellent test-retest repeatability.[25] Short-term variations are associated with factors such as diurnal variation and posture.

Specifically, a maximum intraocular pressure value is usually detected in the early morning and the lowest value in the early afternoon.[26] Head position is also a concern since an erect sleeping position lowers perfusion pressure, which could jeopardize perfusion to the nerve. Another factor that has been evaluated closely is the association between intraocular pressure and corneal thickness. Corneal thickness measurement is important to obtain a more accurate understanding of the intraocular pressure and risk for the development of glaucoma.[27] While there are various factors that may alter our assessment of intraocular pressure, decreasing intraocular pressure early and consistently is the only reported means of reducing progressive visual field loss. In particular, the Collaborative Normal Tension Glaucoma Study found a slower rate of visual field loss with a 30% or more reduction of intraocular pressure.[22]

Anterior chamber angle

The main four structures that are seen in normal angles include, from anterior to posterior, are:[28]

- Schwalbe’s line, which appears as a thin, translucent line and represents collagen condensation of Descemet’s membrane. The presence of pigmentation at Schwalbe’s line can be suggestive of pigmentary dispersion or pseudo-exfoliative syndrome and is known as Sampaolesi’s line;

pigmentation can also be found in angle-closure glaucoma, due to the lens moving forward and zonule involvement, and in previous trauma, which is typically accompanied by other signs such as angle recession, dis-inserted or ruptured iris processes and/or pupillary sphincter ruptures. Pigmentation is not expected in patients with primary open angle glaucoma
- Trabecular meshwork, which has a dull grey appearance at the top half and a pigmented lower half
- Scleral spur, which is appreciated as a thin white line and represents where Schlemm's canal rests and the longitudinal ciliary muscle inserts
- Ciliary body, which is a pale grey to brown appearance

Angle assessment not only includes visualization of structures and thus determination of the level of iris insertion, but also an evaluation of the width of the angle, approach of the peripheral iris, amount of pigment, and any signs not consistent with primary open angle glaucoma, such as pseudo-exfoliative material, peripheral anterior synechiae, neovascularization, or signs of angle recession.

The oldest and most common method to evaluate characteristics of an anterior chamber angle is gonioscopy, which is either direct, because it involves the use of a contact gonio lens and provides a direct, magnified view, or indirect, because it involves the use of a contact gonio lens and provides an inverted view of the anterior chamber angle.[29]

While the Van Herrick grading system, which involves placing a slit lamp beam of light obliquely and comparing the width of the light beam and space between the corneal endothelium and anterior iris surface[28], can be used as an initial screening tool to detect for possible narrow angles and devices such as ultra-biomicroscopy, anterior segment optical coherence tomography and Pentacam can be used, gonioscopy is essential. Gonioscopy allows for the differentiation between both open angle and closed angle glaucoma and primary from secondary glaucomas.[15]

Visual field

Various test strategies exist for evaluating visual field changes in patients with primary open angle glaucoma. A commonly used instrument is the Humphrey Field Analyzer, an automated computer-driven perimeter that offers various threshold strategies; the 24-2 testing strategy is more commonly used for patients with glaucoma.[30] Visual field defects typically associated with primary open angle glaucoma are those that correspond to optic nerve fiber bundle defects: arcuate defects, nasal steps and paracentral defects.[31] Visual field severity classification systems for glaucoma have been established and are often used in clinical practice; the most common criteria to stage glaucoma is that of Hodapp, Parish and Anderson (H-P-A).[32] The H-P-A classification system considers the overall extend of the damage using the MD value, the number of defective points, and the proximity of the defect(s) to fixation.[33]

Other non-specific visual field defects seen in patients with glaucoma may include a generalized depression in sensitivity or increased diffuse variability. Cataracts and other age-related changes in the retina can cause a generalized depression in visual field sensitivity. Increased diffuse variability as seen in early glaucomatous visual fields makes determining the diagnosis and judging progression particularly difficult. Variability necessitates keeping a consistent test strategy for a patient and, most importantly, evaluating visual field defects and their correspondence to the optic nerve head appearance.

Optic nerve head appearance

Abnormality in the appearance of the optic nerve is oftentimes the earliest sign of glaucoma.[34] It is important to look for cup: disc enlargement and/or asymmetry and the presence of thinning and/or notching of the neurosensory rim of the optic nerve. While deviations from the ISNT rule, which refers to the inferior neuroretinal rim typically being the broadest, followed by the superior, nasal and then

temporal, has increased clinicians' suspicions of glaucoma, a more recent variant, the IST and IS rule, has been championed as more valid.[35] Other signs of glaucomatous damage include Drance hemorrhages,[36] nerve fiber layer defects, changes to the circumlinear vessels and peripapillary atrophy.[37] A stereoscopic evaluation of the optic nerve head appearance in a fully dilated patient, typically using an indirect technique with a 60D, 78D, or 90D lens with the slit lamp, continues to be the gold standard to evaluate for signs of glaucomatous progression.

Another technique to assess for changes to the structure of the optic nerve head is the use of optical coherence tomography. OCT provides cross-sectional images of the optic nerve and retinal nerve fiber layer (RNFL).[38] Studies have demonstrated a correlation between retinal nerve fiber layer thickness and visual field defects with Time Domain OCT. Recent research has indicated that Fourier Domain OCT measurements of cross-sectional peri-papillary RNFL thicknesses have similar diagnostic performance as Time Domain OCT measurements with respect to glaucoma detection.[39] Practitioners commonly focus on the RNFL thickness average analysis report, which displays the results of the RNFL circumpapillary scans (NFL thickness versus position around the optic nerve head) taken at a diameter of 3.45 mm. This diameter is used because it intercepts all of the nerve fibers from the optic disc while avoiding inaccuracies from peripapillary atrophy.[40] Scans are displayed on a graph broken up into the superior, inferior, temporal and nasal quadrants. The thickest RNFL corresponds to the superotemporal and inferotemporal nerve fiber bundles. Each region is color-coded based on a comparison to normative data. Green indicates the 5th to 95th percentile, or statistically "normal" thickness within the population. Yellow specifies 1st to 5th percentile while red indicates the 0 to 1st percentile, indicating borderline and abnormal RNFL thickness, respectively. Values are calculated in the four quadrants around the disc as well as an average NFL thickness around the entire disc. Optic disc scans including cross-sectional images of the optic disc and 3D view assist in demonstrating disc boundaries and the optic disc contour.

Thickness of the ganglion cell complex (GCC) thickness maps and significance maps that illustrate the percent loss value at each location from an age-matched normative database may also be useful to detecting early changes from glaucoma. More research is needed to compare the ganglion cell complex (GCC) values with visual field defects in glaucoma and the normative database is limited but expanding. Research to date has indicated that the retinal ganglion cells, encompassing the retinal nerve fiber layer, ganglion cell layer and inner plexiform layer, become thinner in glaucoma.[41]

Explain common treatment and management options for POAG

Lowering intraocular pressure, either by decreasing aqueous humor production and/ or increasing aqueous humor outflow, is associated with a reduced progression of visual field defects[42,43,44] and is the standard treatment for POAG. Currently intraocular pressure is the only risk factor for glaucoma that is currently amenable to therapy. The main categories of medications used to treat primary open angle glaucoma are: prostaglandin analogs, beta-blockers, adrenergic agonists, carbonic anhydrase inhibitors, rho kinase inhibitors, miotic agents, epinephrine compounds and osmotic diuretics. Laser and surgical intervention are also available. **Table 3** features common drug classes with select examples and dosages for open angle glaucoma. While pharmacologic intervention has traditionally been considered the first line of treatment,[45] laser therapy and surgical intervention may also be considered.[15]

TABLE 3

Drug class	Class examples and dosages
Prostaglandin analogs	Latanoprost 1 gtt qhs Bimatoprost 1 gtt qhs
Nitric oxide (NO) Donors	Latanoprostene bunod 1 gtt qhs
Beta blockers	Bexaolol 1 gtt bid Carteolol 1 gtt bid Levobunolol 1 gtt bid Timolol 1 gtt bid
Adrenergic agonists	Apraclonidine 1 gtt tid Brimonidine 1 gtt tid
Carbonic anhydrase inhibitors	Metazolamide 50-100 mg po bid-tid Acetazolamide 125-250 mg po q4h Dorzolamide 1 gtt tid
Rho kinase inhibitors	Netarsudil 1 gtt qhs
Musicarinic receptor agonists	Pilocarpine 1 gtt tid-qid

Table 3: Common drug classes with select examples and dosages for open angle glaucoma Click to enlarge

Prostaglandin analogs

Because this category is typically effective, well-tolerated and requires only a once daily dosing for 24-hour efficacy, prostaglandin analogs, such as latanoprost, are currently the most common first line medications prescribed to reduce intraocular pressure for treatment of primary open angle glaucoma.[46,47] This group of drugs lowers intraocular pressure by enhancing uveoscleral outflow[48] and is also suspected to increase the ocular perfusion pressure.[49] Studies indicate the prostaglandins lower intraocular pressure by around 30 percent when dosed once a day.[50] Additionally, the once-a-day dosing regimen is better-tolerated by patients and encourages adherence. Ocular side effects can include hypertrichosis[51], which is seen in 50% of patients within 12 months[46], increased peri-ocular skin pigmentation[5], deepening of the upper eyelid sulcus[52], cystoid macular edema[53], and hyperemia[15]; contraindications include a history of uveitis, cystoid macular edema and herpes simplex keratitis.

Nitric Oxide (NO) donors

Nitric oxide donors such as latanoprostene bunod are suspected to increase outflow of aqueous humor through the uveoscleral pathway (by up-regulating matrix metalloproteinase expression and remodeling the extracellular matrix of the ciliary muscle) and via the trabecular meshwork (by inducing cytoskeletal relaxation via the soluble guanylyl cyclase-cyclic guanosine monophosphate signaling pathway).[54]

Beta-blockers

Second choice is typically the topical beta-blockers, such as timolol, which bind to beta-receptors in the ciliary body to decrease aqueous formation and thus lower intraocular pressure.[46] While twice a day dosing has been shown to be most effective[55], once a daily dosing in the morning has been proposed either as solo or adjunctive therapy[46] because of systemic concerns from absorption that may occur via the nasolacrimal mucosa.[56] In particular, studies have suggested that beta-adrenergic antagonists may induce bronchoconstriction, brady-arrhythmias and nocturnal systemic hypotension[57,58], the latter of which is concerning because systemic hypotension can lead to optic nerve hypo-perfusion and increased glaucoma progression.[59] Selective beta-blockers are available but may be less effective at reducing intraocular pressure.[60] Reduced efficacy and potential for more side-effects in prescribing topical beta blockers in patients who are also being treated with systemic beta blockers are also concerns[61] that may require either modification of treatment regimens or consideration for change in intervention.

Adrenergic agonists

Adrenergic agonists, such as brimonidine, cause both a reduction of aqueous humor production and

increase in uveoscleral outflow, thereby lowering intraocular pressure.[62] While effective as a short-term therapeutic means to reduce intraocular pressure, adrenergic agonists are less tolerated long-term due to high rates of conjunctival hyperemia, high frequency of allergic reactions and tachyphylaxis, and frequent dosing schedule (typically 3 times a day).[63,64] Use of brominidine purite 0.15%, which contains a more gentle preservative and decreased concentration, has shown to reduce rates of allergic reaction.[65]

Contraindications include patients that are on monoamine oxidase inhibitors and central nervous system depressants. Studies on brimonidine, an alpha-2 adrenergic agonist, have shown that brimonidine is one thousand times more selective for alpha-2 than alpha-1 adrenergic receptors[66] and thus better tolerated.[67] Studies have furthermore demonstrated possible neuroprotective properties;[68] however, it may not be as effective in monotherapy at lowering intraocular pressure when compared to latanoprost, a prostaglandin analog.[69] Brimonidine demonstrates an additive effect with prostaglandin analogs such as latanoprost[69] and is often used in combination therapy.

Carbonic anhydrase inhibitors

Carbonic anhydrase inhibitors (CAIs), which are available in both oral and topical forms, reduce intraocular pressure by reducing bicarbonate and thereby water within the aqueous humor. This decreases aqueous volume and lowers intraocular pressure.[70] Although this category of medications is effective at lowering intraocular pressure, CAIs are typically only used in for short-term control of acutely elevated intraocular pressure or as third- or fourth-line agents.[46] Concerns with CAIs include their multiple dosing schedules and poor safety profiles, particularly with oral preparations. For example, acetazolamide (Diamox) is usually given orally in doses of 125-250 mg every 4 hours and can cause rare but life-threatening issues such as electrolyte imbalances and Stevens-Johnson syndrome.[71] Side effects of the oral regimen include a metallic taste, malaise and kidney stones; patients using the topical formulations can also report a bitter taste, burning and present with secondary corneal edema.[72] Sulfonamide allergies are a relative contraindication for both the oral and topical formulations.

Rho kinase inhibitors

Rho kinase inhibitors, such as netarsudil, cause a relaxation of the trabecular meshwork, enhancing aqueous humor outflow and thus lowering intraocular pressure.[73] Netarsudil is also suspected to act as a norepinephrine transport inhibitor, which causes constriction of ocular vascular structures, including blood flow to the ciliary processes, thus inhibiting production of aqueous humor.[74] More than half of patients in clinical trial settings report conjunctival hyperemia and around 20% present with other side effects such as corneal verticillata.[75]

Muscarinic receptor agonists

While muscarinic receptor agonists, such as topical pilocarpine, can increase parasympathetic tone of the ciliary muscle, thereby increasing trabecular outflow[76] and reducing intraocular pressure, they are most commonly used as short-term preparatory agents before laser treatment for glaucoma or in cases of acute angle closure.[46] Significant ocular side effects (stinging, irritation and blurred vision), systemic side effects (headache, sweating, salivation and bradycardia), and difficult dosing schedule (up to 4 times per day) limit its use.

Methods to address challenges with adherence to anti-glaucoma medications

As glaucoma is typically an asymptomatic disease, adherence is an important issue in the prevention of visual consequences secondary to glaucoma.[77] In some patients there may be little motivation for a

lifelong therapeutic regimen.[78] In others, adherence can be related to difficulties with obtaining the medication, problems successfully instilling it into the eye and/or challenges in remember to use the medication at the appropriate time each and every day.[79] Rates of non-adherence have been cited ranging from 30-80%.[80,81] Barriers particularly associated with poor adherence include low self-efficacy, forgetfulness and difficulty with drop administration and the medication schedule.[82]

TABLE 4

Brand name and dosage	Components
Combigan 1 gtt q12h	Brimonidine Timolol
Simbrinza 1 gtt tid	Brimonidine Brinzolamide
Cosopt 1 gtt bid	Dorzolamide Timolol
Rocklatan 1 gtt qhs	Latanoprost Netarsudil

Table 4: Examples of fixed combination medications for open angle glaucoma Click to enlarge

Providers can work to address these barriers, such as simplifying the dosing schedule. Patients who used eye drops once a day were more likely to comply than those using eye drops twice a day or more.[83] Other examples of methods that practitioners can use to increase adherence to glaucoma medications include using eye drops with milder side effects, adding medication reminders and recommending drop assistance devices.[84] For patients that require the use multiple glaucoma medications to adequately reduce intraocular pressure, fixed combination medications can simply dosing schedules and improve adherence. **Table 4** shows examples of fixed combination medications for open angle glaucoma.

With respect to Patient AB, he was started on Travatan-Z, a prostaglandin analog, because of its simple dosing regimen and known efficacy. The target pressure was set to 20 mmHg in the right eye and in the left eye, a 30% reduction from Patient AB's maximum measured intraocular pressure. A 30% reduction was established based on lessons from the Ocular Hypertension Treatment,[43] Early Manifest Glaucoma Trial,[85] Collaboratively Initial Glaucoma Treatment Study,[86] and Collaborative Normal Tension Glaucoma Treatment Study, with the latter showing that 30% lowering reduced the risk of glaucoma progression to 12% in the study group compared to 35% in the control arm.[87]

Because his intraocular pressure was not at target levels after treatment initiation, the risks and benefits of additional medications were weighed and due to its additive effects with prostaglandin analogs, less frequent dosing regimen and lack of interaction with his other medications Alphagan-P, an adrenergic agonist, was added. The addition of a beta-blocker was avoided due to Patient AB's long-standing and successful use of an oral beta-blocker to control his hypertension. When Patient AB returned, he reported difficulty in remembering the dosing regimen for both drops despite extensive education and written dosing schedules. Furthermore, because an appropriate reduction in intraocular pressure was still not demonstrated a consultation for consideration for surgical or laser intervention was placed to reach an appropriate intraocular pressure level and thereby reducing the risk of glaucomatous progression.

Laser and surgical procedures

While medical intervention by means of prescription eye drops is typically considered first line of treatment[45] for patients with open angle glaucoma, if adherence to medication(s) becomes a problem or intraocular pressures are not adequately reduced and/or there is a rapid rate of destruction and advanced damage despite good patient adherence, laser and/or surgical intervention may be recommended to reduce intraocular pressure and thus decrease glaucomatous progression.[88,89]

Trabeculoplasty, which involves the application of laser spots to the trabecular meshwork leads to an increase in outflow facility of the aqueous humor and subsequent decrease in intraocular pressure.[90] There are two main forms that are used to treat open angle glaucoma: argon laser trabeculoplasty and selective laser trabeculoplasty. Argon laser trabeculoplasty (ALT) involves laser-induced thermal burns of the trabecular meshwork, causing contraction and thus increase in aqueous outflow.[91] Selective laser trabeculoplasty (SLT) involves selective photothermolysis of pigmented trabecular meshwork cells. Because SLT causes no histologic scarring or damage to the trabecular meshwork and because repeat treatments are possible, SLT is preferred over ALT.[92] According to the Laser in Glaucoma and Ocular Hypertension (LiGHT) Trial, more than 70% of SLT-treated eyes achieved adequate IOP control without the need for medical or surgical treatment after 6 years of treatment and monitoring and is the recommended first-line treatment in the United Kingdom and is considered first-line treatment alongside IOP-lowering eye drops in the European Union and the United States.[93]

Trabeculectomy is currently considered the gold standard surgical intervention[94] and involves the creation of an alternative drainage pathway for aqueous humor outflow through a drainage bleb in the conjunctiva. Blebs are commonly positioned superiorly because the upper eyelid can provide protection, thus reducing the risk of infection. While use of anti-metabolites such as mitomycin C can improve long-term bleb success, risks associated with trabeculectomy include hypotony, bleb leak and endophthalmitis.[95]

Tube shunt surgery is also a method to reduce intraocular pressure, however it is typically reserved for patients with refractory glaucoma. With tube shunt surgery, a tube is placed in the anterior chamber and is connected to a plate, which acts as a drainage reservoir and is anchored onto the sclera behind the superior and lateral recti. Concerns with tube shunt surgery include hypotony, particularly initially after surgery, and possible risk of bullous keratopathy.[96]

Minimally-invasive glaucoma surgeries (MIGS) have been increasing in popularity, particularly in patients with mild to moderate glaucoma and/or along with cataract surgery, because they are safer and less traumatic than other forms of glaucoma surgery.[97] There are three main types of MIGS devices:[98]

- Trabecular, which improve trabecular outflow through Schlemm's canal
- Suprachoroidal, which connect the anterior chamber and suprachoroidal space to improve uveoscleral outflow
- Subconjunctival, which offer an alternative pathway of aqueous outflow to the subconjunctival space

Additional but less commonly used treatment options for open angle glaucoma include laser cyclophotocoagulation of the ciliary body, cyclocryotherapy and cyclodialysis.

Key components of referral to a specialist

A referral is "a request from one physician to another to assume responsibility for management of one or more of a patient's specified problems"[99] and can be completed in person, electronically, or, most commonly, through written communication.[100] Regardless of the referral method, clear and well-organized communication is essential[101,102] and can be achieved by using structured referral sheets[102] or standardized communication methods such as the SBAR (Situation, Background, Assessment and Recommendation) technique.[103] Using the SBAR technique as a structure, key referral information includes:

- **Situation**: Patient demographics and specific reason for the referral
- **Background**: Patient history, medications and allergies, appropriate diagnostic studies
- **Assessment**: Referring provider's analysis of the patient

- **Recommendation**: Specific action that is requested or recommended by the referring provider

Educating the patient regarding their referral and scheduling a follow-up examination help to ensure that the patient's needs are being met.

Conclusion

This case demonstrates the importance of individualized care for patients with primary open angle glaucoma. This case emphasizes the importance of recognizing clinical findings and ruling out other possible causes, understanding the course of the disease and constantly evaluating the need for modification of treatment plans. Key learning goals of this case, including listing differential diagnoses associated with bilateral elevated intraocular pressures in a patient without acute ocular symptoms, explaining common assessment and treatment and management options associated with POAG, discussing methods to address challenges with adherence to ophthalmic medications, and identifying key components of a referral to a specialist, are covered.

In most cases of primary open angle glaucoma, intraocular pressure can be reduced with topical therapy alone to a target pressure, which studies demonstrate reduces glaucomatous progression. However, in some instances, particularly with patients who have difficulty with adherence or demonstrate progressive damage on pharmacological interventions, a referral to a glaucoma specialist for consideration of laser or surgical intervention may be necessary. It is important for clinicians to recognize clinical findings, understand the course of the disease, reinforce the need for adherence and modify the treatment plan as necessary.

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