Evidence Based Management of Secondary Glaucoma
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8:00 – 10:00 AM
Mile High 4

Abstract:
This course presents an evidence-based literature review for the primary care practitioner regarding the diagnosis, treatment, and management of secondary glaucoma. The most common secondary glaucomas including pseudoexfoliation, pigmentary dispersion, uveitic, traumatic, steroid induced, and neovascular glaucoma will be discussed. Recent studies on ocular perfusion pressure and other vascular risk factors for glaucoma will also be reviewed.

Learning Objectives:
1. Identification of ocular signs associated with the most common secondary glaucomas
2. Understanding the pathophysiology and natural history of these risk factors for glaucoma.
3. Review perfusion pressure and its link to glaucoma through an evidence-based review of studies
4. Review nocturnal changes to IOP and blood pressure and how this influences glaucoma management
5. Review current literature on most effective medical and surgical management in the case of each disease

I. Pseudoexfoliation Syndrome and Glaucoma
   A. Background
      a. Disorder of extracellular matrix where fibrillar basement membrane material is produced by anterior segment structures (endothelium of iris, cornea, trabecular meshwork and epithelium of lens/ciliary body)
      b. Scandinavian (93% of glaucoma in region) and European populations
   B. Pathophysiology and ocular manifestations
      a. Pseudoexfoliative material blocks or restricts aqueous flow at trabecular meshwork and results in an increase in IOP
      b. Pseudoexfoliative deposits on anterior capsule of lens – Bull’s Eye Pattern
      c. Pupillary ruff atrophy
      d. Poor Mydriasis
      e. Corneal endothelial dysfunction
      f. Spontaneous iris hemorrhages
      g. Gonioscopy: patchy pigmentation of TM often greater in eye with more glaucomatous damage.
   C. Natural History and differences compared to Primary Open Angle Glaucoma
a. Conversion rate from pseudoexfoliation syndrome to glaucoma – approximately 30-40%, ALL initially ocular hypertensive PEX eyes converted to glaucoma (Puska, J Glaucoma 2002)
b. Diurnal fluctuations, higher mean IOP, pressure spikes, higher frequency/severity of ONH damage, worse VF loss, poorer response to medications, more frequent necessity for surgery
c. Amount of pseudoexfoliative material does not correlate with severity of glaucoma or IOP measurements
d. Association with angle closure—zonular weakness leads to forward lens movement, pupillary block from posterior synechiae formation

D. Clinical Management
   a. Suspects vs. Pseudoexfoliative Glaucoma
   b. Only secondary glaucoma found to increase risk for VF progression (EMGT)
   c. IOP lowering medications
   d. Glaucoma surgeries and effectiveness
   e. Increased complication rates for cataract surgery (phacodenesis, poor mydriasis, lens subluxation, harder lens nuclei) – consider surgery sooner
   f. Post cataract surgery management and risks

II. Pigmentary Dispersion Syndrome (PDS) and Glaucoma
   A. Background
      a. Backward bowing of iris causing rubbing of pigmented iris epithelium against lens zonules, leading to the liberation of iris pigment, trabecular meshwork changes and subsequent potential increase in IOP.
      b. Young male myopes (78-93% male)
      c. Caucasians
      d. Accounts for 1-1.5% of glaucoma in the United States
   B. Pathophysiology and ocular manifestations
      a. Pigment liberation causing blockage of aqueous outflow at trabecular meshwork
      b. Reverse Pupillary Block- pressure in anterior chamber great than posterior chamber and closes iris-lens flap valve
      c. Triad: Krukenberg spindle on corneal endothelium, transillumination defects or iris, pigment in anterior trabecular meshwork – only 42% show all 3 signs
      d. Anterior chamber: very deep with pigment showers
      e. Iris: heterochromia, anisocoria
      f. Lens: subtle pigment on anterior capsule, pigment at junction of zonules and posterior capsule (Scheie’s line)
      g. Gonioscopy: increased pigmentation, of TM, tends to be homogenous but can be greater inferiorly due to gravity; can also have pigmented Schwalbe’s line
      h. Influence of Exercise – increases pigment dispersion, IOP, decrease aqueous outflow
   C. Natural history and differences compared to Primary Open Angle Glaucoma
a. Conversion rate from PDS to pigmentary glaucoma – approximately 10-15%
   i. exercise, blinking, accommodation
b. Burned out phase
   i. Reduced pigment dispersion and normalized IOP
   ii. Pigment reversal sign
   iii. Zonules rubbed the entire posterior pigment epithelium off iris
   iv. Age related increase in lens axial length, decreased pupil size
c. Unlike pseudoexfoliation, degree of pigment dispersion tends to correspond to severity of glaucoma
d. Other cause of pigment dispersion (cataract surgery)

D. Clinical Management
   a. IOP lowering medication
   b. Surgery: Peripheral Laser Iridotomy
      i. When is it most appropriate to recommend surgery? Most useful during active stage of disease
      ii. Equalizes pressure between AC and PC, relieves posteriorly bowed iris
      iii. Relieves reverse papillary block
      iv. Most beneficial prior to development of glaucoma
   c. Glaucoma surgeries and effectiveness
      i. ALT vs SLT – proposed mechanisms
      ii. Research on monocyte modulation of aqueous outflow and recruitment to the trabecular meshwork following SLT

III. Uveitic Glaucoma
   A. Background
      a. Intraocular inflammation causes rise in IOP
      b. Inflammation treated with corticosteroids → Steroid Responders can also experience a rise in IOP
      c. Trabecular meshwork blocked by inflammatory cells
   B. Pathophysiology and ocular manifestations
      a. Peripheral Anterior Synechiae (PAS) can develop and block TM → secondary angle closure glaucoma
      b. Cells
      c. Flare
      d. Keratic Precipitates (stellate vs mutton fat)
      e. Hypopyon
      f. Iris Nodules (Koepe, Busacca)
      g. Iris Posterior Synechiae
      h. Iris Atrophy
      i. Iris Heterochromia
      j. Band Keratopathy
   C. Natural History
      a. Rate of glaucoma development in children versus adults
b. Risk factors for elevated IOP
   i. Types of uveitis (Posner Schlossman, Fuch’s, HSV highest risk)
   ii. Chronic/recurrent vs. Acute Uveitis – Chronic more likely to have increase in IOP (Herbert et al, J Glaucoma 2004)
   iii. Steroid usage – More likely to have raised IOP
   iv. Active vs Inactive Uveitis – active inflammation more likely to have higher IOP (Takahashi et al, Japan J Ophthalmology 2002)

D. Clinical Management
   a. Treat systemic condition
   b. Treat ocular inflammation
      i. Mydriatic
      ii. Corticosteroids (steroid responders) - 18 to 30%, occurs 2-6 weeks after starting (oral, IV, inhaled, topical, periocular, intravitreal)
   c. Treat glaucoma
      i. Role of prostaglandin analogs (Markomichelakis et al, Graefes Arch Clin Exp Oph 2009) – reports Xalatan greater efficacy and lower rates of recurrence of uveitis compared to Cosopt
      ii. LPI

IV. Angle Recession (AR) and Traumatic Glaucoma
   A. Background
      a. Recession of anterior chamber following non-penetrating ocular trauma, cleft forms between circular and longitudinal muscles of ciliary body
      b. Patient history: common causes of injury inducing angle recession
         i. Sports, recreational activities, assault
   B. Pathophysiology and ocular manifestations
      a. Blunt trauma forces aqueous laterally and posteriorly against iris, hydrodynamic force exerts traction on iris root → tear between longitudinal and circular muscles of ciliary body
         i. Obliteration of intertrabecular spaces and Schlemm’s canal
         ii. Direct damage to trabecular meshwork can cause early rise in IOP
         iii. Scarring/fibrosis/atrophy of TM over time leads to gradual decrease in outflow facility with increasing age
      b. Correlation between hyphema and angle recession
         i. 56 to 100% patients with hyphema have some degree of angle recession
      c. Signs of Trauma
         i. Corneal scars, pigment deposits, pupillary sphincter tear (dilated pupil), Vossius ring, hyphema, iridodialysis, torn iris processes, phacodenesis, retinal/choroidal atrophy or hyperpigmentation, tears
         ii. With orbital fracture, watch for orbital emphysema
      d. Gonioscopy appearance
         i. Broad ciliary body band
ii. Disruption of regular pattern of insertion of iris fibers into the ciliary body or scleral spur
iii. Localized deepening, change in color/texture of angle

e. Gonioscopy technique
   i. Compare appearance between angles within eye to detect differences in appearance
   ii. Compare same angle between 2 eyes - important especially for 360 degree angle recession
   iii. May need to switch lens from eye to eye several times

C. Natural History
   a. 6-7% of eyes with recession of iridocorneal angle will eventually develop glaucoma
   b. Correlation between extent of angle recession and decrease in outflow
      i. Eyes with less than 180 degrees recession unlikely to develop glaucoma
      ii. 180 to 360 degrees of angle recession greater risk of developing late-occurring glaucoma
   c. Two peak incidences of glaucoma
      i. 1st peak - first few weeks to years after trauma, easier to treat with medications alone
      ii. 2nd peak - 10 or more years after injury, more difficult to treat and may require surgical intervention
   d. Other signs of trauma – subconjunctival hemorrhage, corneal scars, hyphema, iris sphincter damage, iritis, vossius ring, rosette cataract, phacodenesis, commotion retinae, choroidal rupture, macular hole, retinal tear
   e. Glaucoma in fellow eye – is angle recession a risk factor or merely a trigger for glaucoma development in somebody who is already going to develop the disease?

D. Clinical management
   a. IOP lowering medications
   b. Argon laser trabeculoplasty unsatisfactory
   c. Trabeculectomy (43% in AR vs 74% POAG success rate)
      i. Bleb fibrosis earlier, increased tendency for fibroblast proliferation, change in aqueous humor properties

V. Steroid Induced Glaucoma
A. Background
   a. Oral, IV, inhaled, topical, perioocular or intravitreal corticosteroid therapy can cause ocular hypertension
   b. If ocular hypertension not recognized and treated, subsequent glaucomatous optic neuropathy can develop.
B. Pathophysiology
   a. Steroid Response: physical/mechanical changes in microstructure of TM, increased deposition in TM, decreased capacity for phagocytosis by endothelial cells in TM
C. Natural History
a. Ocular hypertension can develop within 2-6 weeks following steroid use
b. Approximately 18-30% exhibit a steroid response or increase in IOP
c. Armaly study, 90% of POAG patients responded with IOP elevation greater than 6 mm Hg
d. IOP returned to baseline approximately 1 week after discontinuation of medication
e. Bimodal distribution of increased risk: Older patients and children
f. Pre-existing POAG, glaucoma suspect, and first degree relative with POAG are important risk factors for steroid-induced ocular hypertension
g. Most patients successfully managed with topical glaucoma medications
h. Surgical techniques required in less than 2% of cases

D. Clinical Management
   a. Increased popularity of intravitreal triamcinolone for subretinal fluid, macular edema and adjunctive therapy in treatment of CNVM has led to increase in steroid induced ocular hypertension

VI. Neovascular Glaucoma
   A. Background
      a. Severely blinding, intractable disease
      b. Need to have high index of suspicion for development
   B. Pathophysiology
      a. Retina starved for oxygen → VEGF released, moves anteriorly through pupil → NVI develops → VEGF travels to angle → NVA develops → fibrovascular membrane → PAS and Angle Zipped Up → Increased IOP
      b. Most common diseases associated with NVG
         i. Ischemic CRVO – 45% develop NVG, highest risk first 7-8 months, primary factor for blindness is NVG not ischemic CRVO
         ii. Ocular Ischemic Syndrome
         iii. Proliferative Diabetic Retinopathy
      c. Other causes: BRVO, BRAO, CRAO, Radiation Retinopathy, Tumor, Chronic Uveitis, Chronic RD, Retinopathy of Prematurity, Sickle Cell Retinopathy, Eales Disease
   C. Natural History
      a. Once NVA develops, fibrovascular membrane is sticky and leads to peripheral anterior synechiae, angle becomes “zipped up” and IOP spikes.
   D. Clinical Management
      a. Do not let it develop!
      b. Have high index of suspicion for which conditions can lead to neovascular glaucoma and treat underlying condition early
      c. Topical Steroids - evidence that they inhibit angiogenesis and NV, but be aware of steroid responders masking as NVG, perform gonioscopy
      d. Cycloplegics
      e. Cyclodestruction
      f. Alcohol Injection
      g. Evisceration, Enucleation, Exenteration
VII. Ocular Perfusion Pressure
A. Difference between arterial BP and the intraocular pressure (IOP)
   a. Diastolic PP (DPP) = DBP - IOP
B. Alterations can cause ischemia and poor irrigation of tissues in optic nerve
   a. Can be due to low BP or relatively high IOP
   b. During nocturnal period, potential for both low BP and high IOP
C. Ocular Perfusion Pressure: risk factor for development of new glaucoma and progression of established glaucoma
   a. Barbados Eye Study- low OPP (< 55 mm Hg) associated with 3 times increased risk of glaucoma
   b. Baltimore Eye Survey – low DPP (<30 mm Hg) associated with 6 times higher risk than DPP > 50 mm Hg
   c. Egna-Neumarket Study – low DPP (< 68 mm Hg) associated with marked, progressive increase in frequency of glaucoma
   d. Early Manifest Glaucoma Trial – low SP, lower SPP, and cardiovascular disease at baseline progressed faster than counterparts
   e. Los Angeles Latino Eye Study – both low diastolic and high systolic BP associated with increased prevalence of open-angle glaucoma
   f. Rotterdam Study – only patients on antihypertensive medications, 4.68 times greater chance of developing glaucoma in patients with low DPP < 50 mm Hg compared to DPP > 65 mm Hg
   g. Thessaloniki Eye Study – cup area, C/D ratio were increased and rim area decreased in subjects with lower DBP resulting from treatment compared to high DBP and untreated normal DBP groups

VIII. Ocular Perfusion Pressure: Nocturnal influences on IOP
A. Management Dilemma
   a. Glaucoma patients with advanced disease and/or progression in spite of low pressures during office visits
   b. Compliance
   c. Diurnal curve
      i. Serial Tonometry, IOP checks in AM or PM
B. Nocturnal IOP
   a. 24 hour IOP monitoring
      i. Highest IOPs often measured during period where patient is not in office.
      ii. Greater fluctuation of IOPs
   b. Both healthy and glaucoma patients experience increase in IOP overnight
   c. Office readings may not give accurate clinical picture
      i. Exercise caution when extrapolating results of in-office IOP measurements when making glaucoma treatment decisions
   d. Sleeping on back- Supine position
      i. IOP increases – due to increased episcleral venous pressure?
ii. Nocturnal IOP increase still seen even when all IOP measurements performed around the clock in supine position; more than just supine position involved
e. Glaucoma patients greater IOP rise when change from upright to horizontal vs. normals
   i. Greater IOP variation with more advanced disease
   ii. Worsening of visual field in NTG associated with IOP in supine position and magnitude of IOP elevation with postural change
f. Sleeping on side
   i. Larger C/D ratio on preferred side for sleeping
g. Sleeping on stomach – Prone position
   i. Significantly higher IOP than supine position
   ii. Angle closure risk
h. Management Pearls
   i. Elevating head by using pillow neutralized IOP increase
   ii. Supine position better for IOP than prone position, especially in patients with potential for angle closure

C. IOP lowering treatment
   a. Beta blockers and alpha 2 agonists not as effective, natural 50% aqueous production decrease over night
   b. Prostaglandin analog have sustained 24-hour IOP lowering effect
   c. Carbonic anhydrase inhibitors shown to be better than beta blockers and alpha 2 agonists at controlling nocturnal IOP
   d. SLT showed benefit in nocturnal IOP measurements even if did not show response during the day
   e. Trabeculectomy controlled 24-hour IOP better than maximum medications

IX. Ocular Perfusion Pressure: Nocturnal Hypotension
   a. Hypertension
      i. One of most important risk factors for cardiovascular morbidity and mortality
      ii. Risk of cardiovascular mortality doubles with each 20 mm Hg rise in systolic BP and each 10 mm HG rise in diastolic BP
   b. Hypotension – not ideal either
      i. Stroke, heart attack, renal damage, end-organ damage
      ii. “White Coat Syndrome”
      iii. Orthostatic Hypotension: flashes and floaters with postural changes
      iv. During sleep, decrease in sympathetic nervous system – leads to nocturnal dip in blood pressure ~ 10-15%
   c. Glaucoma and Blood Pressure
      i. Systolic BP increase of 10 mm HG is equivalent to 0.23 – 0.32 mmHg higher IOP. Diastolic BP increase of 10 mm Hg equivalent to 0.19 to 0.60 increase in IOP
ii. Low BP and nocturnal over-dipping associated with increased probability of VF deterioration in glaucoma patients

iii. Rotterdam Study: increased risk of glaucoma with calcium channel blockers compared to beta blockers

iv. Hayreh Study: if diastolic BP decreased below critical level, beneficial effect is lost and mortality/morbidity rates increase again. Avoid excessive reduction of BP overnight

v. If not contraindicated, consider changing blood pressure medication dosage time to morning

X. Normal Tension Glaucoma

A. Collaborative Normal Tension Glaucoma Study Group
   a. 10 baseline IOP measurements, median IOP < 20 mmHg
   b. 30% IOP reduction decreased chance of VF progression
   c. Factors for progression of VF abnormalities: Women, Migraines, Disc Hemorrhages, Race (Black > White > Asians)

B. Women
   a. Estrogen stimulates and enhances blood flow
   b. Increased risk of POAG with early menopause (Rotterdam Study)
   c. Shorter estrogen exposure associated with POAG (Blue Mountains Eye Study)
   d. Oral contraceptive use > 5 years, age of first period > 13 years old associated with increased risk of POAG (Nurses’ Health Study)

C. Migraines
   a. Vasospasm, reduced or absent autoregulation of blood flow
   b. Decreased blood flow during aura

D. Optic Nerve Hemorrhages
   a. Splinter or flame shaped hemorrhages at optic nerve border
   b. Radially oriented and perpendicular to disk margin
   c. Most common in low tension glaucoma, but also seen in POAG, Ocular Hypertension
   d. Warning sign that eye at risk for developing glaucoma or having progression of glaucomatous damage
   e. Pathophysiology: vasculopathic event leading to NFL loss, degeneration of tissue from stress on microvasculature
   f. Natural History: Resolve in 2-3 months, Tend to recur in same region with corresponding visual field defect, common in early and moderate glaucoma
   g. Clinical Management: Ocular Hypertension Treatment Study, Collaborative Normal Tension Glaucoma Study, Visual field progression with heme vs without heme, recurrent heme vs single occurrence

E. Obstructive Sleep Apnea
   a. Pauses in breathing or abnormally low breathing during sleep
   b. Characterized by snoring, restless sleep, daytime drowsiness
   c. Continuous Positive Airway Pressure (CPAP)
i. Keeps airway open during sleep
ii. Also increases IOP, but believed that oxygen delivery more important to glaucoma than IOP increase

d. Glaucoma
i. Higher prevalence of glaucoma in OSA patients than general population
ii. Ischemic Mechanism: disrupted blood flow from either less blood reaching optic nerve or less oxygen in blood that does reach optic nerve
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