Ocular Manifestations of Systemic Pathologies:
Diagnosis and Management
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Herpes Zoster Ophthalmicus

Case Presentation - Initial Exam
- 57YO female presented to our emergency service on Friday PM.
- CC: photophobia, “dull pain” OS, onset 2 days ago, gradually getting worse. Associated with left frontal HA.
- Systemic Hx: HTN, controlled with diet
- Ocular Hx: unremarkable

Case Presentation - Initial Exam
- Appearance: Patient had a few small skin lesions on the left forehead. When questioned, she indicated, “those are pimples I often get with stress”.
- Clinical Findings: - Grade 2+ anterior uveitis OS - IOP 14/16 OD, OS
- Treatment:
  - PF 1% Q2h x 2 days;
  - Homatropine 5% TID;
  - Blood work ordered to R/O systemic association.
- Asked pt to RTC on Monday AM for follow-up.

Case Presentation - FU Exam
3 days post initial examination
- Pt indicated on Friday night, she started to experience severe HA on the left forehead.
- On Sunday morning, she started to have “break outs” in the same region. Pt feels the condition continues to progress.

Varicella
Zoster
Virus (VZV)
Varicella Zoster Virus (VZV)

Primary infection: Chicken Pox

Route of infection:
1. direct contact with varicella or zoster lesions
2. air-borne droplet infection
3. vertical transmission during pregnancy

* incubation period: 14 - 16 days
* contagious: 1 - 2 days before onset of rash until all lesions are crusted (5 days)

Varicella Zoster Virus (VZV)

Reactivation: Herpes Zoster/Shingles

Herpes Zoster occurrence site:
- 50-60% - Thoracic dermatomes, especially T5-T12.
- 20-25% - Lumbosacral dermatomes.
- 20-25% - Cranial nerves: trigeminal nerve and facial nerve

Varicella Zoster Virus (VZV)

Reactivation - Trigeminal Nerve Involvement

Herpes Zoster Ophthalmicus

Dynamic Faces of HZO
Ocular Manifestations

- Anterior Segment:
  - Common Keratitis
  - Pseudodendrites
  - Decreased corneal sensitivity
  - Scarred lid retraction
  - Conjunctivitis
  - Episcleritis
  - Scleritis
  - Uveitis

- Posterior Segment:
  - Less Common
  - Retinitis
  - Acute retinal necrosis
  - Choroiditis
  - Papillitis
  - Retrolubar neuritis
  - Optic atrophy
  - Nerve palsies (3,4,6)

Significance of Hutchinson’s sign

Corneal Manifestations

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Punctate keratitis</td>
<td>50%</td>
</tr>
<tr>
<td>Neurotrophic Keratitis</td>
<td>25%</td>
</tr>
<tr>
<td>Pseudodendrites</td>
<td>50%</td>
</tr>
<tr>
<td>Exposure Keratitis</td>
<td>11%</td>
</tr>
<tr>
<td>Anterior stromal infiltrates</td>
<td>41%</td>
</tr>
<tr>
<td>Disciform Keratitis</td>
<td>10%</td>
</tr>
<tr>
<td>Keratouveitis</td>
<td>34%</td>
</tr>
<tr>
<td>Ulcerative Keratitis</td>
<td>7%</td>
</tr>
</tbody>
</table>


Non-ocular Complications

- Postherpetic Neuralgia
  - With resolution of the eruption, pain that continues for 3 months or more.
  - Patients appear to have abnormal function of unmyelinated nociceptors and sensory loss.
  - Pain and temperature detection systems are hypersensitive to light mechanical stimulation.
  - An imbalance involving loss of large inhibitory fibers and an intact or increased number of small excitatory fibers has been suggested.

Postherpetic Neuralgia

Risk factors:
- Advancing age.
  - 60 years old = 60% develop PHN
  - 70 years old = 75% develop PHN
- Site of HZ involvement:
  - Highest risk - Trigeminal;
  - Moderate risk - Thoracic;
  - Lower risk - Jaw, neck, sacral, and lumbar
- Severe prodromal pain/acute neuralgia
- Severe rash

Herpes Zoster vs Herpes Simplex

- Skin lesion
- Corneal lesion
Treatment of HZO

- **Systemic Treatments:**
  - Antivirals: Valacyclovir 1000mg TID x 7 days; Famciclovir 500mg TID x 7 days; Acyclovir 800mg 5x/day x 7-10 days.
  - Timing administration: start within 72 hours of the first herpes zoster lesion.
  - Accelerate skin lesion healing time, decrease incidences, severity and duration of ocular manifestation, and decrease duration and severity of acute pain.
  - Inclusive on impact of post-herpetic neuralgia
  - Special consideration: kidney function; pediatric usage; immunocompromised patients.

Postherpetic neuralgia management:

- **Systemic:**
  - Tricyclic antidepressant (e.g., nortriptyline, desipramine)
  - Gabapentin (neurontin)
  - Slow-release opioids (e.g., oxycodone)
- **Topical agents:**
  - Capsaicin cream
  - Lidocaine skin patch/cream
- **Injection:**
  - Purpose: frontal and nasal nerve blocks
  - Medication: bupivacaine, epinephrine and clonidine

HIV, HAART and Herpes zoster

- Incidence of herpes zoster is >15 fold higher for HIV pt.
- Highly Active Antiretroviral Therapy (HAART) induced immune recovery.
- Immune reconstitution inflammatory syndrome (IRIS): immune system recovers from an anergic state with reconstitution of T-cell antigen-specific immunity.
- 15-25% of patients on HAART develops IRIS with most cases occurring in the first three months of therapy.
- Many opportunistic pathogens may provoke IRIS, mycobacteria and herpes viruses are the most common.
- Treatment involves infectious specialist.

Topical Treatments

Case Presentation Continues...

- **FU Clinical Findings:** Grade 1 anterior uveitis OS; IOP 14/13 OD/OS
- **Diagnose:** HZO induced Anterior Uveitis
- **Treatments:**
  - Initiated Valacyclovir 1000 mg TID x 7 days
  - Continue uveitis management
  - Erythromycin oint. for vesicles to prevent infection
  - Regular FU to monitor for uveitis and IOP elevation.
- After 1 month duration, 6 follow up visits, patient’s vesicles were mostly healed and her uveitis were resolved. (-) neuralgia reported

Branch Retinal Artery Occlusion
Case Presentation

- **CC:** 51 year old man presented to the office with a chief complaint of sudden field loss OS of 8 hours duration.
- **Systemic History:**
  - Myocardial infarction (MI) one year ago.
  - Hypertension x 10 yrs.
  - Hyperlipidemia x 10 years.
  - Poor medical care.
- **Remarkable clinical findings:** pupil, CVF, DFE.

Etiology

- **Embollic**
  - Cholesterol
  - Calcific
  - Platelet-Fibrin
  - Leukocemboli
  - Fat
  - Amniotic Fluid
  - Tumors
  - Talc
  - Corticosteroid
  - Air
- **Nonembollic**
  - Thrombosis
  - Inflammatory
  - Vasospasm
  - Coagulopathies
  - Compression

Management

- **In-office procedure:**
  - Asscilation of the carotid artery.
  - Cranial nerve testing and motor and sensory assessment.
- **Immediate systemic workup referral:**
  - CBC, lipid panel, ESR, C-reactive protein, sickle prep, echo cardogram, transesophageal echocardiogram and Doppler.
- **Acute treatments for CRAO are not indicated for BRAO.**
- **Follow up:** 1 month, NV rare.
BRAO Prognosis

<table>
<thead>
<tr>
<th></th>
<th>CRAO Initial</th>
<th>CRAO Final</th>
<th>BRAO Initial</th>
<th>BRAO Final</th>
</tr>
</thead>
<tbody>
<tr>
<td>NLP, LP, HM, CF</td>
<td>16 - 70%</td>
<td>11 - 48%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>20/40 or better</td>
<td>2 - 9%</td>
<td>5 - 22%</td>
<td>11 - 37%</td>
<td>24 - 80%</td>
</tr>
<tr>
<td>Total pts</td>
<td>23</td>
<td>23</td>
<td>30</td>
<td>30</td>
</tr>
</tbody>
</table>


Central Retinal Vein Occlusion

Clinical Pearls

- BRAO tend to have good visual prognosis.
- Acute management for CRAO are not indicated for BRAO.
- Follow up 1 month. Monitor for NV.
- Systemic implications are common and severe.
- Immediate systemic evaluation and systemic management are critical for BRAO patients.

Systemic Implication

Morbidity and Survivorship

<table>
<thead>
<tr>
<th>Years after observation of retinal embolus</th>
<th>Death Rate %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15%</td>
</tr>
<tr>
<td>3</td>
<td>29%</td>
</tr>
<tr>
<td>7</td>
<td>54%</td>
</tr>
</tbody>
</table>

Systemic Prognosis of patients with retinal infarction: a 4 year follow up

<table>
<thead>
<tr>
<th>Complications</th>
<th>Patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death - vascular</td>
<td>21</td>
<td>21%</td>
</tr>
<tr>
<td>Death - nonvascular</td>
<td>8</td>
<td>8%</td>
</tr>
<tr>
<td>CVA (1st episode)</td>
<td>10</td>
<td>10%</td>
</tr>
<tr>
<td>Coronary event</td>
<td>19</td>
<td>19%</td>
</tr>
<tr>
<td>Contralateral Retinal AO</td>
<td>1</td>
<td>1%</td>
</tr>
<tr>
<td>Without complication</td>
<td>40</td>
<td>40%</td>
</tr>
<tr>
<td>Total Patients</td>
<td>99</td>
<td>100%</td>
</tr>
</tbody>
</table>


Systemic Implication

Concomitant Medical Findings in patient’s with Retinal Infarcts


Initial examination

- CC: 49YO black male reported with sudden decrease of vision, OU; started 2 days ago.
- Systemic Hx:
  - Diabetes Mellitus x 15 yrs; LFBS: 107mg/Dl; HbA1c
  - Hyperlipidemia x 3 yrs
  - Hypertension x 1 yr
- Active Medications:
  - Insulin, Lisinopril, Atorvastatin
- Remarkable exam findings: BCVA 20/100 OD/OS, DFE

Differential diagnosis consideration

- Diabetic Retinopathy is characterized by microaneurysms, hemorrhages, other microvascular anomalies, hard exudates, and retinal ischemia localized to the posterior pole.
- Papillophlebitis, also referred to as Big Blind Spot Syndrome, is characterized by dilated and tortuous retinal veins, hemorrhages, exudates throughout retina and disc edema.
- Ocular Ischemic Syndrome is characterized by mild hemorrhages that are localized to the midperiphery, dilated but non-tortuous retinal veins, and mild macular edema. Patient often reports ocular angina, amaurosis fugax or transient ischemic attacks which may imply significant carotid occlusive disease.
**CRVO**

- CRVO is the second most common retinal vascular disease.
- Ischemic and non-ischemic CRVO are the two categories that have profoundly different clinical courses in which the former carries the poorer prognosis.
- The average age of onset for CRVO is between 60-65 years old.
- Systemic and ocular associations include hypertension, diabetic mellitus, hyperlipidemias, atherosclerotic vascular disease, smoking history, increased body mass, abnormal rheological factors, elevated intraocular pressure and chronic open-angle glaucoma.

**Pathogenesis**

- Three Potential Mechanisms
  - External compressive force by structures of adjacent connective tissues, i.e., arteriosclerotic changes within the confined laminae space.
  - Primary degenerative or inflammatory diseases of the venous vessel walls, i.e., endophlebitis and phlebitis.
  - Flow/transport disturbances such as sudden reduction of perfusion pressure and blood dyscrasias.
- Each factor by itself or in combination can result in stagnation of vascular flow and encourage the formations of potential thrombi in the venous lumen.

**Bilateral CRVO and/or CRVO in young patients**

- CRVO in a younger patient or bilateral in nature is an uncommon finding; only 7.5% to 19.8% of CRVO cases have reported to occur in patients younger than 50 years old and approximately 10% of CRVO cases have bilateral involvement.
- A comprehensive work up is indicated to rule out additional systemic etiologies such as hypercoagulable state, hyperviscosity syndrome, autoimmune, inflammatory and infectious causes.

**Management of CRVO - Initial**

- Biweekly FU for ischemic CRVO and monthly FU for non-ischemic CRVO during the initial six months.
- The initial six months are the most critical time for the development of ischemic CRVO from non-ischemic CRVO.
  - The Central Vein Occlusion Study conversion rates:
    - 15% <= 4 months
    - 34% <= 3 years
  - Hayreh’s study concluded:
    - 9.4% of 500 eyes converted within 6 months
    - 12.6% converted in 18 months

**Ischemic CRVO complication**

- A maximum of 45% of ischemic CRVO patients develop NVG (neovascular glaucoma).
- NVG development is mainly during the first 7-8 months of onset of ischemic CRVO. After that time interval, the risk falls from 40% to 5%.
- 33% of the eyes with NVI and NVA do not develop NVG on follow up.

**Management of CRVO - Long-term**

- The follow up regimen can be modified to every 3 months after the initial 6 months until complete resolution of CRVO retinopathy and/or macular edema or up to 3 years from the initial onset of CRVO.

**Blood work results**

**Autoimmune-Inflammatory-Infectious**

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
<th>Reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESR</td>
<td>48</td>
<td>&lt;90 mm/h</td>
</tr>
<tr>
<td>C-Reactive Protein</td>
<td>0.24</td>
<td>&lt;0.30 mg/dL</td>
</tr>
<tr>
<td>B2-Glucosuria</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>ANA (IgG)</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>ACE (Sarcoïd)</td>
<td>54</td>
<td>0-67 IU/L</td>
</tr>
</tbody>
</table>

**Results discussion**

**Autoimmune-Inflammatory-Infectious**

- The elevated erythrocyte sedimentation rate (ESR) and C-reactive protein can be associated to patient’s long history of diabetic mellitus.
- ESR is a non-specific screening test for various conditions. The amount of fibrinogen in the blood directly correlates with the ESR. And conditions that alter the fibrinogen levels, such as diabetic mellitus, may elevate ESR.
- The increased fibrinogen can enhance the tendency to form thrombi.

**Blood work results**

**Hemodynamic**

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
<th>Reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol</td>
<td>214</td>
<td>1.05 - 2.00 g/dl</td>
</tr>
<tr>
<td>Glucose</td>
<td>140</td>
<td>65-104 mg/dL</td>
</tr>
<tr>
<td>HbA1c</td>
<td>6.2</td>
<td>4.3-6.0%</td>
</tr>
<tr>
<td>Urea Nitrogen (BN)</td>
<td>16</td>
<td>1.5-4.5 mg/dL</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.56</td>
<td>0.50 - 1.30 mg/dL</td>
</tr>
</tbody>
</table>

**Results discussion**

**Hemodynamic**

- As expected from the initial case history, the patient has elevated cholesterol, blood glucose, and hemoglobin A1c level.
- The patient’s abnormal BUN and creatinine findings may imply decreased renal function, which is most likely secondary to diabetic nephropathy.

**Blood work results**

**Hypercoagulable-Hyperviscosity**

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
<th>Reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antithrombin III activity</td>
<td>2.8</td>
<td>0.5 - 1.2 0.3% normal</td>
</tr>
<tr>
<td>Antithrombin III antigen</td>
<td>2.0</td>
<td>16.33 mg/dL</td>
</tr>
<tr>
<td>Protein C</td>
<td>81</td>
<td>70-180s</td>
</tr>
<tr>
<td>Protein S</td>
<td>80</td>
<td>70-150s</td>
</tr>
<tr>
<td>Carboxyhemoglobin (a1A, a1B, a2M AB)</td>
<td>7.0</td>
<td>11.1 Normal</td>
</tr>
<tr>
<td>Prothrombin Time</td>
<td>10.4</td>
<td>9.0-11.5 sec</td>
</tr>
<tr>
<td>Partial Thromboplastin Time</td>
<td>29</td>
<td>27-36 sec</td>
</tr>
<tr>
<td>Homocysteine</td>
<td>10.6</td>
<td>-11.4 umol/L</td>
</tr>
</tbody>
</table>

**Results discussion**

**Hypercoagulable-Hyperviscosity**

- Homocysteine is a sulfur amino acid formed during the metabolism of methionine.
- Hyperhomocysteinemia has a positive association with atherosclerosis; although, the exact mechanism is currently under investigation.
- Hyperhomocysteinemia produces functional abnormalities of blood vessels and enhances thrombus formation.
Results discussion
Hypercoagulable-Hyperviscosity

- Hyperhomocysteinemia is associated with higher risk of coronary heart disease, stroke, peripheral vascular disease and retinal venous occlusive disease.
- High serum homocysteine level may result from a hereditary disorder or a deficiency of vitamin B6, B12, or folic acid, or from chronic kidney failure.

Etiology

- The etiology of the bilateral CRVO in this patient is multi-factorial. The elevated glucose, cholesterol, and blood pressure can lead to atherosclerosis of the central retinal artery at the lamina cribrosa. Subsequent compression on the central retinal vein can lead to decreased blood flow, increased pressure, turbulence, endothelial damage and thrombus formation.
- Hyperhomocysteinemia also is a significant contributing factor.

Follow up examination summary

<table>
<thead>
<tr>
<th>DATE</th>
<th>BCVA OD</th>
<th>OCT OD</th>
<th>BCVA OS</th>
<th>OCT OS</th>
<th>RAPD</th>
<th>NV*</th>
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</thead>
<tbody>
<tr>
<td>Apr, 09</td>
<td>20/100</td>
<td>851</td>
<td>20/100</td>
<td>1100</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>May, 09</td>
<td>20/70</td>
<td>740</td>
<td>20/100+</td>
<td>915</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>Jun, 09</td>
<td>20/40</td>
<td>367</td>
<td>20/60+</td>
<td>522</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>Jul, 09</td>
<td>20/25</td>
<td>192</td>
<td>20/20</td>
<td>282</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>Aug, 09</td>
<td>20/20</td>
<td>175</td>
<td>20/20</td>
<td>254</td>
<td>Absent</td>
<td>Absent</td>
</tr>
</tbody>
</table>

*NV = neovascularization of the iris, angle, disc or retina.

Visual acuity progression in younger patients

- Recent retrospective study conducted by Dr. Recchia and colleagues, focused on visual recovery in younger patients with CRVO. It concluded the baseline VA doesn’t appear to be predictive of final VA or clinical course.
- 1/3 of patients with entry VA of 20/40 or better had final VA of 20/400 or worse.
- 1/4 of patients with entry VA of 20/200 or worse had final VA of 20/40 or better.
- The progression of visual decline was most prominent within 3 to 6 months of the initial CRVO onset and visual improvement was uncommon after 12 months.

Central vein occlusion induced macular edema treatment update:

- SCORE
- CRUISE
- Ozurdex™
- Bevacizumab


CRUISE Study: Lucentis™ treatment for macular edema 2 to CRVO.

- Randomized selection
- VA improvement: >15 letters vs mean gain
- OCT macular thickness reduction
- Primary endpoint at 6 months


Ozurdex™ Dexamethasone Implant - DI

- Invented by Allergan, approved by FDA July 2009.
- Patients with BRVO and/or CRVO.
- N = 1300
- 0.7 mg intravitreal DI vs placebo
- DI achieved the 3-line (15 letters) improvement significantly faster
- 20% to 30% within 2 months of therapy
- Adverse events: IOP elevation, conjunctival hemorrhage


Bevacizumab (Avastin™)

- Case series. (no randomized clinical trials available)
- N = 21 (14 CRVO, 7 BRVO)
- Intravitreal injection of 1.25mg
- Injection improved visual acuity by 2 lines or better (10 letters) in all patients
- Peak gains in VA were achieved 3-6 weeks after injection


Case management

- The patient did not develop ischemic CRVO during the initial follow up period. His VA fully recovered and macular edema was resolved.
- The patient will continue to be monitored every 3 months until complete resolution.
- The blood work results, specifically hyperhomocysteinemia, were communicated to the patient’s PCP for systemic management.
- The initiated treatment included the supplement intake of folate in combination with vitamins B6 and B12.
Clinical pearls
• CRVO occurs mostly in the older population and it is strongly associated with systemic vascular diseases.
• The occurrence in younger patients, whether unilateral or bilateral, is less common and mandates a complete medical evaluation to rule out any coagulopathies, hyperviscosity, autoimmune, inflammatory and/or infectious etiology.
• Acute treatments are available for CRVO induced macular edema.
• Stringent follow up examinations are required after CRVO, and the use of OCT can be a valuable tool to monitor for anatomical resolution of macular edema.

Ocular complications of Marfan’s syndrome

Initial examination
• CC: 44YO black male reported to clinic on 8/15/08 with sudden decreased vision, OS.
  • Patient indicated he had a history of subluxated lenses, OU. His feeling was that his left lens had moved additionally “since this morning.”
• Ocular Hx:
  • Strabismic Amblyopia OD; BCVA 20/400.
  • Subluxated lenses OU, of 20 years duration.
  • Rhegmatogenous retinal detachment (RD) OD, 10 years ago.
  • Retinal repair surgery, OD, 10 years ago.
  • Lensectomy, OD, 10 years ago, along with retinal repair surgery.

Initial examination
• Systemic Hx: Marfan syndrome.
• Ocular medication: Atropine 1% QHS, OS.
  • Patient indicated atropine was prescribed by his cataract surgeon to improve vision, OS until cataract extraction (CE) surgery which was scheduled for 9/1/08.
  • BCVA: 20/400 OD, 20/40 OS.
  • EOM: full and smooth, OU.
  • Pupils: pharmacologically dilated OS; (-) APD
  • CVF: FTFD OD/OS.

Initial examination
• Anterior Segment:
  • OD - Aphakic; otherwise unremarkable.
  • OS - Subluxed lens.

Initial examination
• Dilated fundus examination
  • OD: scleral buckle superior temporal; otherwise, unremarkable.
  • OS: vitreous traction in the peripheral retina 360, (-) holes or tears.
• Diagnosis:
  • Subluxated lens OS; possible recent progression in subluxation per patient history.
Initial examination

- Management:
  - Patient’s cataract surgeon was consulted. The surgeon indicated the patient had minimal risk of retinal detachment or other complications occurring before the scheduled surgical date; therefore, the original surgical date was retained.
  - Patient was educated on signs and symptoms of retinal detachment and the need to return if changes were noted.

Second examination

- CC: Patient returned to clinic on 9/2/08, complaining of “seeing a floating spot OS,” since “this morning.” It appears to look like a dark bubble.” The patient noticed flashes of light upon eye movements.
- BCVA: 20/400 OD, 20/40, OS.
- EOM: full and smooth, OU.
- Pupils: pharmacologically dilated, OS; (-) APD.
- CVF: FTPC OD; inferior constriction, OS.

Second examination

- Anterior segment: unchanged, OU.
  - OD – Aphakic.
  - OS - Subluxed lens.
- Dilated fundus examination:
  - OD: Scleral buckle superior temporal.
  - OS: Rhegmatogenous retinal detachment with the macula attached.

OS retinal detachment (RD)

- Marfan syndrome

  - Marfan syndrome (MFS) was first recognized by Antonine Marfan in 1896. A complete description was given by an ophthalmologist named Whilliams in 1876.
  - MFS is a variable, autosomal dominant disorder of the connective tissue. The condition affects the cardiovascular system, eyes and skeleton.

Second examination

- Management:
  - Retinal surgeon was contacted and the patient was referred immediately for a combination procedure to remove the subluxed lens and to repair the retina.
  - The surgery preserved the central vision.
Marfan syndrome

- The minimal birth incidence is 1 in 9800.
- It affects both sexes equally and is prevalent in all races.
- Abnormalities with fibrillin (FBN1), a main component of extracellular microfibrils found in a wide range of tissues are responsible for the characteristic changes.

Diagnosis criteria

- The most up-to-date criteria were revised in 1996 and are referred to as the Ghent criteria.
- The Ghent criteria are divided into seven different categories: ocular, cardiovascular, skeletal, dura mater, pulmonary system, skin and integumentary and family or genetic history.
- The diagnosis requires criteria findings in two different areas as well as involvement of a third area.

Diagnosis criteria

- The major ocular criteria is ectopia lentis.
- The minor ocular criteria includes flat cornea, long axial length, hypoplastic iris and hypoplastic ciliary muscle causing miotic.

Systemic manifestations

- The musculoskeletal abnormalities are the most striking characteristics of MFS.
  - Individuals have long extremities with tall stature.
  - They have dolichoostenomelia: their arm span is greater than their total height.
  - They have achromachia: their fingers are disproportionately long and thin.

Systemic manifestations

- The cardiovascular manifestations can be life threatening.
  - Patients have aortic and pulmonary artery dilatation.
  - They can have mitral and tricuspid valve prolapse with or without regurgitation.
  - The principle cause of mortality is progressive aortic dilatation, associated with aortic valve incompetence leading to aortic dissection or rupture.

Marfan patient compared to normal (right)
Ocular manifestations

- Lens abnormalities.
- Cornea.
- Glaucoma.
- Retinal abnormalities.
- Myopia.
- Strabismus.
- Amblyopia.

Lens abnormalities: Ectopia lentis

- The condition is usually bilateral, symmetric and stable from early childhood. The condition occurs in 50% of the patients.
- The dislocation is typically supero-temporal.
- Fibrillin abnormalities cause fewer abnormal ciliary processes. This causes defective zonular fiber production, leading to dislocation of the lens.

Lens abnormalities

- Microspherophakia: The condition is typically bilateral. The crystalline lens is small and relatively spherical. The cortical fibers are thinner than normal by 20%.
- Premature opacities: Cataracts tend to present around 30-50 years old.
- Lens coloboma: Faulty fetal fissure closure is also associated with MFS.

Cornea

- Flat cornea: MFS patients have flatter corneas. In a study, a mean of 40.8 D was measured compared to mean of the control group of 42.9 D.
- Endothelial abnormalities: Gutta formation with cell pleomorphism is associated with MFS.
- Megalocornea: MFS patients often have megalocornea (nonprogressive enlargement of the cornea to 13mm or greater).

Patient topography

Glaucoma

- Glaucoma is more prevalent in MFS patients.
- Primary open-angle glaucoma is the most common form, but other forms can be caused by anterior lens dislocation and/or anterior chamber angle abnormalities.
- MFS patients can have displacement of Schlemm’s canal. This may explain the mechanism of elevated intraocular pressure in open angle cases.
- Treatment options include standard medical and surgical modalities.
Retinal abnormalities

- Retinal degeneration: Peripheral changes include lattice degeneration, atrophic holes, vitreous traction, myopic degeneration and chorioretinal pigment proliferation.
- Retinal detachment: The prevalence of RD in MFS patients is 5-11%. In patients with ectopia lentis, the incidence increases to 8-38%. The incidence of RD becoming bilateral can be as high as 69% within the population of patients with RD in one eye.

Myopia

- The second most common ocular manifestation in MFS is myopia. It has a prevalence of 34-44% compared to 4.8% in the normal population.
- In MFS, an increased axial length is commonly found. In patients with ectopia lentis and or RD, the ocular axial length is frequently significantly longer than the average axial length. This leads to axial myopia.

Strabismus/Amblyopia

- Strabismus occurs in 19-39% of individuals with MFS.
- In a study of 573 patients, 11.7% had exotropia, 2.1% had esotropia and 7.5% had amblyopia.
- MFS children are more likely to develop amblyopia secondary to strabismus, axial myopia, anisometropia, astigmatism, subluxated lens and/or microspherophakia.

Other Ocular Features

- Pupil: The iris sphincter and dilator muscles are poorly developed, leading to pupils that often dilate poorly when challenged by pharmacologic preparations.
- Sclera/choroid: Both structures are unusually thin in MFS patients.

Treatment of subluxated lens

- If the subluxation is mild, no treatment is required; patients can see through the phakic portion of the pupil.
- Significant subluxations require aphakic correction or therapeutic pupillary dilatation.
- Lens extraction is indicated when:
  - The lens obstructs the pupil making optical correction impossible.
  - The lens luxates into the vitreous cavity.
  - The lens anteriorly displaces leading to pupil block glaucoma.
  - The lens undergoes significant cataract formation.
Complications of lens extraction

- Greater frequency of cataract extraction complications occur in MFS patients compared to the general population.
- Complications include vitreous loss, incarceration of the wound, iris prolapse, corneal edema, hyphema, cystoid macular edema and persistent anterior uveitis.
- Surgical options include iris or scleral-fixation intraocular lenses and pars plana vitrectomy.

Treatment of retinal detachment

- Standard procedures include scleral-buckling surgery and/or 3-port-pars-plana vitrectomy.
- Depending on the detachment and lens status one or both procedures may be required.
- In severe lens subluxation cases, pars-planavitreolensectomy, internal drainage, chorioretinal adhesion and retinal tamponade via gas or silicone oil should be considered.

Patient 3 months status post RD treatment

Superior retina is re-attached following a combination of scleral buckle and vitrectomy surgery.

Patient 3 months status post RD treatment

The superior temporal retinal tear which induced the rhegmatogenous RD.

RPE hyperplasia post laser treatment surrounding the tear.

Patient 3 months status post RD treatment

Laser scars, demonstrating RPE hyperplasia surrounding the scleral buckle.

Clinical pearls

- 50% of the MFS patients are diagnosed by an eye physician due to multiple ocular manifestations.
- When MFS is suspected, the primary care physician must be notified for systemic confirmation and management.
- Eye examinations at an early age are recommended for MFS patients to detect any amblyopia, strabismus or other manifestations.
- At the minimum, annual eye care is indicated in all MFS patients to monitor for lens stability, lens opacification, intraocular pressure and retinal health.
For additional questions, comments and complete references, please email to:

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