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Disclosure Statement:
Speakers include disclosures in each presentation. I have none.
TAKING CONTROL: IS PHYSICAL EXERCISE BENEFICIAL OR A RISK FOR GLAUCOMA?

Mahsa Salehi OD, FAAO
Wilmer Eye Institute at Johns Hopkins Hospital
American Academy of Optometry
San Antonio, 2018
• No Financial Disclosures.
HISTORY

- 31 yo female; 1st seen by Wilmer glaucoma service in 10/2008
- Referred by uveitis specialist with blurry vision from uveitis flare OD
- PSH: Omphalocele repair (1st year of life)
  - Bilateral inguinal hernia repairs (age 1)
- POH: Panuveitis OU since age 10, OD > OS (negative work up)
  - Uveitic glaucoma
  - Suspected steroid responder (IOPs better with cyclosporine)
- DH: Methotrexate 25mg daily (since age 13), PF QID OU
  - Cosopt; Brimonidine
- SH: Artist assistant; Smoker
- FH: Positive for glaucoma (Maternal grand-mother)
## OPHTHALMOLOGY EXAM

<table>
<thead>
<tr>
<th></th>
<th>OD</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>VA</td>
<td>20/30-1</td>
<td>20/25</td>
</tr>
<tr>
<td>Pupils</td>
<td>Irregular limited constriction</td>
<td>Irregular limited constriction</td>
</tr>
<tr>
<td>IOP</td>
<td>21</td>
<td>20</td>
</tr>
<tr>
<td>Description</td>
<td>OD</td>
<td>OS</td>
</tr>
<tr>
<td>-------------------------</td>
<td>---------------------------------</td>
<td>---------------------------------</td>
</tr>
<tr>
<td>Lids, Conj</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Cornea</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>AC</td>
<td>Deep; Rare Cell</td>
<td>Deep; Rare Cell</td>
</tr>
<tr>
<td>Iris</td>
<td>Posterior synechiae 5pm</td>
<td>Posterior synechiae 4pm</td>
</tr>
<tr>
<td>Lens</td>
<td>Anterior cortical opacities 1+ PSC</td>
<td>Anterior cortical opacities Tr PSC; pigment on capsule</td>
</tr>
<tr>
<td>Vitreous</td>
<td>Rare vitreous cell</td>
<td>Rare vitreous cell</td>
</tr>
<tr>
<td>Disc</td>
<td>Large excavated cup, thin inferior rim</td>
<td>Large cup but no thinning</td>
</tr>
<tr>
<td>C:D ratio</td>
<td>0.8</td>
<td>0.5</td>
</tr>
<tr>
<td>Macula</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Vessels</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Periphery</td>
<td>CR scar nasal to macula</td>
<td>Normal</td>
</tr>
</tbody>
</table>
GLAUCOMA WORK UP

- CCT  OD 500, OS 527
- Gonio  OD Single inferior PAS
  OS Open to Scleral Spur for 360 degrees
- HRT  OD diffuse severe loss; OS within normal limits
- HVF  OD dense superior defect; OS within normal limits
- Target set to 17 OD, 21 OS
- Already on Cosopt BID & Brimonidine BID
- Xalatan qhs added
2008 ONWARDS

• 02/2009  IOP 27 OD, 13 OS despite meds. AGI OD
• 05/2009  IOP OD 11, OS 14
• 01/2010  IOP OD 15, OS 32 despite meds. HVF worse OS. AGI OS
• 04/2010  IOP 13, 11 on Cosopt and Xalatan qHS OU
• 05/2012  IOP 16, 14. S/p CE OU
• 05/2013  S/p Yag OU and macular hole repair OD
            IOP 11, 10; Acuity 20/40, 20/20
• 03/2015  IOP 10, 12 on Cosopt and Latanoprost qHS OU
• 06/2015  IOP 12, 10. VF improved since start exercise
• 09/2015  IOP 12, 11. Fields still improving on exercise
• 12/2015  IOP 12, 13. Fields little worse; less exercise in winter
• 10/2016  IOP 11, 13 on Latanoprost & Timolol. Fields improving
CORRELATION OF VFI WITH EXERCISE 2008-2016

Rate of Progression:  
OD: +0.7 ± 1.3% / year (95% confidence)  
OS: -4.0 ± 1.7% / year (95% confidence)

Began - Stopped - Resumed - Stopped again

5 years
OD: ACTUAL 24-2 FIELDS: 2003-2016
OD: ACTUAL 24-2 FIELDS: 2003-2016

Began exercise

Stopped exercise

Began exercise
OD: ACTUAL 24-2 FIELDS: 2003-2016

Stopped exercise
OS: ACTUAL 24-2 FIELDS: 2003-2016
OS: ACTUAL 24-2 FIELDS: 2003-2016

Began exercise

Stopped exercise

Began exercise
OS: ACTUAL 24-2 FIELDS: 2003-2016

Stopped exercise
EXERCISE & GLAUCOMA: ASSOCIATION VS CAUSALITY

- Glaucoma affects mobility, balance and increases risk of falling due to visual field (VF) loss
- Correlation of glaucomatous VF loss & physical activity (PA) level
  - Severity of VF loss associated with:
    - Fewer daily steps (12% less / 5dB reduction in better eye VF)
    - Less time spent in MV (moderately vigorous) PA (21% less)
    - Runners with faster 10 km race time and longer running distances have lower risk for participant-reported physician-diagnosed glaucoma
  - VF damage remains associated with PA even after inclusion of fear of falling (activity restriction not due to fear of falling; vs AMD)
  - Could VF damage actually be a product of activity restriction?
EVIDENCE: NEURO-PROTECTIVE MECHANISM?

• PA is neuroprotective in Alzheimer’s & vascular dementia

• Chrysostomou et al, 2014: Exercise in old mice protects against IOP-induced nerve damage
  • 12mo BL6 mice swam for 60 min/day, 5 day/wk for 6 weeks
  • Wk 5: 50mmHg for 30mins in 1 eye (injury), 12mmHg control eye
  • 12mo exercised mice responded similarly as 3mo sedentary mice
  • Exercise abrogated injury-induced astrocytic gliosis and macrophage activation in aged retina
MECHANISM OF NEURO-PROTECTION?

• Reduction in IOP
  • MVPA leads to modest IOP elevation during exercise
  • Leads to IOP lower shortly after exercise & at baseline
• Ocular perfusion pressure (BP - IOP)
  • May create relative ischemia or poor nutritional supply to RGCs
  • RF for higher prevalence, incidence and progression of OAG
  • Tielsch et al: Lower OPP (<40mmHg): 6x in pts with lowest OPP
• BDNF (brain-derived neurotrophic factor)
  • Glaucoma correlates with down-regulated BDNF mRNA in rats
    • Overexpression of BDNF led to RGC protection
  • PA increases BDNF levels in brains of both rats and humans
Greater physical activity is associated with slower visual field loss in glaucoma.

Lee MJ1, Wang J2, Friedman DS1, Boland MV1, De Moraes CG3, Ramulu PY4. J of Ophthalmology Oct 2018

OBJECTIVE: To determine the association between physical activity levels and the rate of visual field (VF) loss in glaucoma.

DESIGN: Longitudinal, observational study.

PARTICIPANTS:
Older adults with suspect or manifest glaucoma.
141 participants (mean age 64.9 ± 5.8 years) were enrolled.

METHODS: Participants wore accelerometers for 1 week to define average steps per day, minutes of moderate-to-vigorous activity (MVPA) and minutes of non-sedentary activity. All available VF measurements before and after physical activity assessment were retrospectively analyzed to measure rates of VF loss.

CONCLUSIONS:
Increased walking, greater time spent doing MVPA and more time spent in non-sedentary activity were associated with slower rates of VF loss in a treated population of glaucoma patients, with an additional 5,000 daily steps or 2.6 hours of non-sedentary physical activity decreasing the average rate of VF loss by roughly 10%.
Prospective observational study

10,000 American adults, aged 40 to 81 years old, enrolled in the Aerobics Center Longitudinal Study between 1987 & 2005.

Participants' physical activity and cardiovascular fitness were recorded weekly via a treadmill test with an average nearly six-year follow up period. Of those participants, 128 new cases of glaucoma were diagnosed.

Researchers found participants who met physical activity guidelines-150 minutes activity per week had a 50% lower risk of glaucoma than those considered completely sedentary.

Moreover, people with the highest cardiovascular fitness had a 40% lower glaucoma risk than those at the lowest fitness levels.

Those who both met the fitness guidelines and were in the highest fitness category had the lowest risk for developing glaucoma.
Another Reason to Exercise: Protecting Your Sight

People who are physically active appear to have a 73 percent lower risk of developing glaucoma.

New Orleans — People who engage in moderate to vigorous physical activity may be able to significantly lower their risk of glaucoma, according to research presented today at AAO 2017, the 121st Annual Meeting of the American Academy of Ophthalmology. Researchers from the University of California, Los Angeles reported a 73 percent decline in the risk of developing the disease among the most physically active study participants, compared with those who were the least active.
CONCLUSION

- Although the mainstay of glaucoma therapy remains lowering IOP with medication, laser treatment, or surgery, other controllable risk factors such as physical exercise may have a significant impact on the course of the disease.

- Eye care providers should emphasize the benefits of regular exercise for patients’ general and ocular health.

- Regular moderate exercise of various types can have a positive influence on glaucoma and ocular hypertension.

- This awareness is important to help patients avoid adverse outcomes and take an active role in the management of their disease.
REFERENCES


CN6 palsy and nystagmus in a young male

Caroline Ooley, O.D., F.A.A.O
Assistant Professor
Pacific University College of Optometry
Portland VA Optometry
No disclosure
30 year old Caucasian male

- Presents for a comprehensive exam
- No concerns
- After further questioning, reported mild headaches and new double vision that began 2 weeks prior
- The diplopia was described as horizontal and disappeared after closing one eye. The patient also reported twitching and drooping of the left eyelid beginning about a year ago. The lid drooping was variable and worse at various times of the day
30 year old Caucasian male

- Ocular history: unremarkable except for a recent concern for myasthenia gravis at his last eye exam due to mild ptosis of the left eyelid.
- LEE: 9 months prior
  - MUSK antibodies and Acetylcholine receptor antibody testing was ordered after that appointment. Results were unremarkable. No other pertinent ocular findings were reported at the time to suggest myasthenia gravis.
- Personal medical history: hypothyroidism, hyperlipidemia, acid reflux
- Medications: cholecalciferol (Vitamin D3), levothyroxine, omeprazole, ranitidine
- Smoking status: lifetime non-smoker
- Family ocular history: unremarkable
30 year old Caucasian male

- VA OD: 20/20     OS: 20/20
- Pupils: PERRL (-)APD
- IOP OD: 13mmHg     OS: 14mmHg
- Anterior segment exam was unremarkable
- Mild upper lid ptosis OS (see measurements)

Glasses Rx:
OD: -0.25 -0.50 x 110
OS: Plano -0.50 x 038
Mild upper lid ptosis OS

OD: MRD 1: 4mm  MRD 2: 6mm  Total IPF: 10mm
OS: MRD 1: 3mm  MRD 2: 6mm  Total IPF: 9mm
Cover Test

++Nystagmus  12 RET  8 RET  2 RET  +Nystagmus
EOMs

-1 0 0 0 0 0
-1 0 0 0 0
-1 0 0 0 0
-1 0 0 0 0 0
30 year old Caucasian male

- Dilated exam was unremarkable.
- C/D was 0.30 OU with no disc edema or pallor

- Cranial nerve testing
  - Intact cranial nerves 2-12 (olfactory not tested)

- Color vision testing
  - Ishihara plates were all correctly identified OD and OS

- Blood pressure: 117/80mmHg RAS
Assessment & Plan

- CN6 palsy with gaze-evoked nystagmus

- Plan
  - MRI with and without contrast
  - Fresnel Prism 8pd BO OD
  - RTC 1 month

http://www.fresnel-prism.com/what-is-a-fresnel-prism-lens
MRI results
30 year old Caucasian male

- The patient’s ocular symptoms decreased over time with a reduction in cover test measurements and improvement of EOMs
- Fresnel was decreased over time

- The patient is now followed by Neurology for suspected **Multiple Sclerosis**
  - Oligoclonal bands and an MRI of the spine were ordered for further testing
Discussion – MS

- What is MS?
  - An immune-mediated inflammatory **demyelinating** disease
  - More common in **women** (2-3:1)
  - Average age of onset: **20-40 years old**
  - More common in Caucasians of **N. European** descent

- What are the symptoms of MS?
  - Fatigue and muscle weakness or spasms
  - Paresthesia
  - Bladder, bowel, sexual dysfunction

Signs and symptoms separated in time and space
Discussion – MS

- What are the ocular findings in MS?
  - Optic neuritis, Internuclear ophthalmoplegia (INO)

- CN palsy (~10%)*
  - CN5, CN7, CN6, CN3, CN8

- Nystagmus (2-3%)

Pathway of CN6

https://webeye.ophth.uiowa.edu/eyeforum/cases/252-internuclear-ophthalmoplegia.htm
# Common types of MS

<table>
<thead>
<tr>
<th>Name</th>
<th>Characteristic symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapsing-Remitting (RRMS)</td>
<td>• Short duration (days to months)</td>
</tr>
<tr>
<td></td>
<td>• May remain symptom-free for months or years</td>
</tr>
<tr>
<td>Secondary-Progressive (SPMS)</td>
<td>• Slow, steady progression – with or without relapses</td>
</tr>
<tr>
<td></td>
<td>• Relapses do not fully remit</td>
</tr>
<tr>
<td>Primary-Progressive (PPMS)</td>
<td>• Steady worsening from the start</td>
</tr>
<tr>
<td></td>
<td>• Do not have periodic relapses and remissions</td>
</tr>
<tr>
<td>Progressive-Relapsing (PRMS)</td>
<td>• Steadily worsen from the onset</td>
</tr>
<tr>
<td></td>
<td>• Flare-ups – with or without remissions – are also present</td>
</tr>
</tbody>
</table>

Discussion – MS

How is MS diagnosed?
- MRI w/ and w/o contrast
- Lumbar puncture (oligoclonal bands of IgG in 95%)
- VEP (increased latency)

How is MS treated?
- Injections: Interferon Beta, glatiramer acetate (Copaxone)
- Orals: dimethyl fumarate (Tecfidera), terflunomide, fingolimod
- Infusions: natalizumab (Tysabri), alemtuzumab, ocrelizumab

For severe relapses or if vision loss is involved: **IV methylprednisolone**
Other causes of a CN6 palsy

- Aneurysm
- Diabetes
- Hypertension
- Trauma
- IIH
- Tumor
- Infection
- Vasculitis
Take Home Message

- Know that a CN palsy can be caused by MS
- Know that nystagmus can be caused by MS

- Know the ocular and systemic manifestations of MS
- Know other causes of CN6 palsy
References

- Ramagopalan, Sadovnick. Epidemiology of Multiple Sclerosis. Neurol Clin 2011; 29: 207
- Simpson, Blizzard, Otahal. Latitude is significantly associated with the prevalence of multiple sclerosis: a meta-analysis. J Neurol Neurosurg Psychiatry 201; 82:1132
- Websites: American Academy of Neurology (www.aan.com)
Disclosures

- No disclosures

Acknowledgements
- Guide Dogs NSW/ACT
- Thank you to the Centre for Eye Health Staff
“Rare can still turn up in your chair”
Background
Case History: 25M Asian

- **Sx:** none
- **Medical History:** Gaucher Type 3
- **Family Hx:** Brother has Gaucher Type 3

<table>
<thead>
<tr>
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<th>OD</th>
<th>OS</th>
</tr>
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<tbody>
<tr>
<td>VA (Rx)</td>
<td>-0.75/-1.00x80</td>
<td>20/16</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-1.00/-1.00x110</td>
</tr>
<tr>
<td>Pupils</td>
<td></td>
<td>No afferent pupillary defect</td>
</tr>
<tr>
<td>Motilities</td>
<td></td>
<td>SAFE</td>
</tr>
<tr>
<td>Anterior segment</td>
<td>Iris mamillations</td>
<td>Iris mamillations</td>
</tr>
<tr>
<td>IOP</td>
<td>15 mmHg</td>
<td>16 mmHg</td>
</tr>
</tbody>
</table>
Clinical Examination
Fundus Autofluorescence
Macular OCT
RNFL and GC Analysis
Differential Diagnosis

- **Asteroid hyalosis**
  - Vitreous degeneration
  - Unilateral disease
  - >55 years of age
  - Calcium deposits

- **Synchisis Scintillans**
  - Yellow cholesterol crystals
  - Unilateral
  - Not suspended in the vitreous
Differential Diagnosis

- Posterior uveitis
  - Choroidal inflammation
  - Cells/exudates
  - Disc oedema
  - Retinal haemorrhages
  - Vitritis
Gaucher Disease (pronounced go-shay)

- Autosomal Recessive
- Mutation on 1q22
- Lipids affected
  - Glucocerebrosidase (GC) deficiency causes Glucocerebroside (sphingolipid) accumulation

https://www.bioexplorer.net/autosomal-recessive-inheritance.html/
What and how?

Metabolic Product

Glucocerebroside

Glucocerebrosidase

Ceramide

Glucose

Adapted from Sidransky E. Mol Gen Metab. 2004;83:6–15.
What and how?

Normal macrophage

- Lysosomes
- Nucleus
- Cellular debris, such as worn-out red blood cells

Gaucher disease macrophage

- Lysosome without glucocerebrosidase
  - unable to digest lipid in red blood cells
- Lysosomes swell and cause whole cell to swell
- Gaucher cell swollen with undigested lipid
- Nucleus is displaced

## Gaucher Disease

<table>
<thead>
<tr>
<th></th>
<th>Non-neuropathic</th>
<th>Neuropathic</th>
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<tbody>
<tr>
<td></td>
<td>Type 1</td>
<td>Type 2</td>
</tr>
<tr>
<td>Prevalence</td>
<td>1 in 40000-60000</td>
<td>&lt;1 in 100000</td>
</tr>
<tr>
<td></td>
<td>Ashkenazi Jews: 1 in 850</td>
<td></td>
</tr>
<tr>
<td>CNS involvement</td>
<td>None</td>
<td>Severe</td>
</tr>
<tr>
<td>Symptom Onset</td>
<td>Any age</td>
<td>First year of life</td>
</tr>
</tbody>
</table>
Systemic effects

- Pulmonary involvement
- Hepatosplenomegaly
- Skeletal involvement
- Progressive neurologic symptoms*
- Thrombocytopenia and anemia

* In neuronopathic subtypes only.

Spectrum of Gaucher Disease

Adapted from Sidransky E. Mol Gen Metab. 2004;83:6-15.
Diagnosis of Gaucher Disease

- **Enzyme Activity**
  - GC activity in peripheral blood leukocytes

- **Genetic testing**

- **Complete Blood Cell Count**
  - Platelet count to assess cytopenia

- **Liver function enzyme testing**
  - Elevation in the liver enzyme levels
Ocular findings in the literature

- Gaucher disease 1882
- Ocular findings 1975:
  - Petrohelos et al
    - Yellow conjunctiva
    - Pingueculae-like, granular mass at corneal-limbal junction
    - Pigmented lesion in fundus
Anterior Segment

- Possible increase in yellowing conjunctiva
  - Similar to spleen cells (East et al 1940)
  - No Gaucher cells in pinguecula (Chu et al 1984)

- Corneal manifestations
  - Hazy cornea with corneal opacities, abnormal keratocytes on confocal (Geens et al 2013)
Posterior Segment

- Most frequent ocular manifestation in GD patients
- Pre-retinal sphingolipids: 3% of cases  (Hsing et al 2014)
Sphingolipids in Vitreous

- Severe case in 20F
- Vitrectomy OU

*Shrier et al*
Vitreous analysis: What is it

- Shrier et al, Fujiyaki et al
How?

- Pathophysiologic mechanism is unclear
  1. Material a by-product of myelin, leukocytes, RBCs and endothelial cells; may be deposited when axonal cells migrate through lamina cribrosa.
  2. Leakage from vasculature

Possible recurrence even after vitrectomy?
Progression of lipids

- Risk of retinal detachment *(Zhao et al 2018, Watanabe et al)*
  
  - Liquefaction of vitreous body
  - Vitreoretinal traction

Zhao et al
Uveitis

- Gaucher Cells found in choroid (Petrohelos et al 1975)

- Only 2 of 527 patients detected with uveitis
  - Study found improvement when treated with enzyme replacement therapy (Dweck et al 2005)

- Sphingolipids associated with inflammation (Chen et al 2014)

- Be aware of masking of multiple myeloma and chronic lymphocytic leukemia if chronic uveitis
- Thinned RNFL observed in 29F with GD III (Matos et al 2017)
  - History of seizures
Ganglion Cell Thickness

- Retinal thinning in GD patients and carriers
  - 14 GD and carriers, 7 controls
    - no neurological disease
  - Thinner GCC
- Mechanism? Possible loss of GC enzyme activity » oxidative stress

McNeill et al 2013
Oculomotor abnormalities

- Oculomotor parameters correlating with neurological status? (Harris et al 1999, Bremova-Ertl 2018)
  - Gaze holding deficits
  - Upbeat nystagmus
  - Saccadic abnormalities
  - Bilateral abducens palsy

- Suggestive of neuronal dysfunction at brainstem and cerebellar levels
Electrophysiology

- Reduced scotopic and general response
- Mueller Cells vital for retinal neurons (ERG b-wave) are defective due to GC (sphingolipid) absorption

Seidova et al 2009
Evidence of progression

- GD Type III
- Patient followed over 5 years
- Neurological examination normal progressing to slowing of horizontal saccades
- Increase in white globular lesions
- ERG findings normal

Coussa et al
Patient’s brother

- Younger sibling (23M Asian)
- Less retinal lesions in peripheral retina
  - Progression of the disease over time
Patient’s brother
Patient’s brother
Treatment in Gaucher Disease

Metabolic Product

Glucocerebrosidase

Enzyme Replacement Therapy (ERT)

Glucocerebrosidase

Substrate Reduction Therapy (SRT)

Glucose

Ceramide

Adapted from Sidransky E. Mol Gen Metab. 2004;83:6–15.
Treatment of Ocular Manifestations

- Vitrectomy to remove lipids
- Controversial, lack of evidence
- Eye movements reportedly improved with SRT \(^{(\text{Accardo et al 2010})}\)
- No improvement of vitreous changes with ERT \(^{(\text{Wang et al 2005})}\)
Management

- Review scheduled for 12 months time
  - Monitor for changes in oculomotor activity, or progression in RNFL and GCA
- Likely increase in floaters over time
- Patient sees neurologist annually
Clinical Pearls

- Piecing together a patient’s systemic condition with reported findings in the literature can exclude other differential diagnoses.
- Gaucher disease may not affect vision or function in the early stages, but may over time.
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