DEADLY DIPLOPIA: MYASTHENIA GRAVIS

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June 2020
Northwest Resident's Conference

DISCLOSURES

The Presenter and Organizers for DEADLY DIPLOPIA: MYASTHENIA GRAVIS
By Dr. Christina Kim, OD has no financial relationship with any company or products mentioned in this presentation.

OVERVIEW

• Review myasthenia gravis and pathophysiology
• Recognize systemic and ocular signs and symptoms
• Review diagnostic tests
• Inform on current and potential new biomarker antibodies
• Improve quality of care to patients

INTRODUCTION

• What is myasthenia gravis?
• Neuromuscular disease that leads to varying degrees of skeletal muscle weakness
• Two clinical forms:
  • General myasthenia gravis (GMG)
  • Ocular myasthenia gravis (OMG)
• Severe (potentially fatal) cases
• Myasthenia gravis crisis

GENERALIZED MYASTHENIA GRAVIS (GMG)

• Most common neuromuscular junction disorder
• Prevalence: 10-20 cases per 100,000 population
• Higher prevalence in African Americans and those close to equator
• Complex mix of heredity and environmental factors
• Bimodal distribution
  • Peak age at 30 years and 50 years
  • Steady rise in incidence after age 50
• Female predilection when younger; male predilection when older
OCULAR MYASTHENIA GRAVIS (OMG)

- Extraocular muscles and levator palpebrae superioris (LPS) involved
- 50% have ocular muscle weakness as first manifestation before generalized weakness
- 15-49% will have only ocular clinical form

MYASTHENIA GRAVIS CRISIS

- Respiratory failure due to worsening muscle weakness
- Requires intubation and mechanical ventilation to protect airway until strength improves
- 15-20% of patients experience usually early in disease course (within 1-2 years)
- Mortality <5%

ANATOMY/PATHOPHYSIOLOGY

NON-ACHR ANTIBODY MG


GENERAL MG

- Variable weakness of skeletal muscles
- Muscles affecting breathing, swallowing, and facial muscles
- Difficulty holding head upright
- Gait instability

OCULAR MG

- Weakness of levator palpebrae superioris (LPS), orbicularis oculi, and/or EOMs
- Initial presentation in 50% of patients: ptosis and diplopia
- Painless fluctuating, unilateral/bilateral or alternating ptosis
- Hyper-retraction of fellow eyelid

OCULAR CLINICAL SIGNS

- Lid fatigue
- Enhancement of ptosis
- Sustained in upgaze
- Repeated lid closure and opening
- Cogan’s lid twitch
- Peak sign – orbicularis oculi weakness
- Variable strabismus
- Ophthalmoplegia
- No pupil abnormalities

CLINICAL SYMPTOMS


OCULAR CLINICAL SIGNS

### DIAGNOSTIC TESTS

<table>
<thead>
<tr>
<th>Category</th>
<th>Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-pharmacological</td>
<td>Ice pack test, Sleep test</td>
</tr>
<tr>
<td>Tension (Edrophonium) testing</td>
<td>Not commonly used but performed by neuro</td>
</tr>
<tr>
<td>Auto-antibody bloodwork</td>
<td>AChR antibodies, MuSK antibodies, LRP4 antibodies</td>
</tr>
<tr>
<td>Electrophysiological studies</td>
<td>Repetitive nerve stimulation (RNS), Single fiber electromyography (SF-EMG)</td>
</tr>
</tbody>
</table>

### NON PHARMACOLOGIC TESTS

**ICE PACK TEST**
- Ice pack placed on eye for ~2-5 minutes
- Patient's ptosis should improve/resolve

**SLEEP (REST) TEST**
- Patient sleeps/rests in dark/quiet room for ~30 minutes
- Ptosis and diplopia should resolve/improve

### EDROPHONIUM TEST
- Edrophonium = short acting AChE inhibitor w/ onset 10-30 seconds after IV administration
- Improved muscle function within 5 minutes
- Potential severe adverse effects → used less often

### ELECTRODIAGNOSTIC TESTS

**REPETITIVE NERVE STIMULATION**
- 50% of OMG patients have abnormalities
- Overestimates so does not exclude disease
- Performed on orbicularis oculi, extensor digitori communis or frontalis muscles
- Evaluates jitter
- Can predict severity of disease
- Con: instrument not easily accessible and requires skilled/trained clinician

**SINGLE-FIBER ELECTROMYOGRAPHY**
- Striational
- Agrin
- Kv1.4
- Rapsyn
- Cortactin
- ColQ

### CURRENT AUTOANTIBODY ASSESSMENT
- AChR antibody
- MuSK antibody
- LRP4 antibody

### OTHER ANTIBODIES
- Striational
- Agrin
- Kv1.4
- Rapsyn
- Cortactin
- ColQ
CHEST IMAGING FOR THYMOMA

- Thymus function: regulate T-cell reactivity
- Positive selection
- Negative selection
- Thymus gland triggers or maintains production of antibodies that block AChR
- Can have thymus hyperplasia or thymoma (10%)
- Early onset – hyperplastic thymus
- Late onset – thymoma

TREATMENT/MANAGEMENT

- Acetylcholinesterase inhibitors
- Mestinon (pyridostigmine)
- Immunosuppressive drugs
- Prednisone (EPITOME trial)
- Steroid sparing agents
- Azathioprine
- Mycophenolate Mofetil
- Thymectomy

MANAGING YOUR PATIENT

PTOSIS
- Ptosis crutches or tape
- Surgery only for chronic, stable lid droop

DIPLOPIA
- Patch
- Prisms
- Strabismus surgery; poor outcome

SUMMARY – A CASE

- 70 year old white male
- Chief complaint:
  - Intermittent horizontal and vertical diplopia at distance and near by end of day
- Droopy upper eyelid OD
- POHx:
  - H/o prism for decompensating phoria but no longer useful
  - H/o variable cover test results
- PMHx: unremarkable
SUMMARY – A CASE

- **VA:**
  - OD: 20/20-2 holding upper lid
  - OS: 20/20
- **Pupils:** ERRL; (-) RAPD
- **Versions:** full and unrestricted
- **Cover test:** orthotropic

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SUMMARY – A CASE

- **Order lab tests**
  - AChR antibody and thyroid panel
  - Past MRI from Roseburg VA normal
- **Plan**
  - Refer to neurology and order chest CT

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CLINICAL PEARLS

- Consider OMG in patient with:
  - Fluctuating unilateral or bilateral ptosis and diplopia
  - Any pattern of painless pupil sparing ophthalmoplegia
  - Normal AChR-Ab lab results does not rule out MG
  - Refer to neurology or neuromuscular clinic for a full work-up
  - Patients may be on long-term corticosteroid
  - Consider visual treatment options for symptomatic relief

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Neurology visit

- AChR antibody ELEVATED at 24nmol/L  (positive if >0.4 nmol/L)
- TSH/free T4 normal
- Chest CT: no evidence of thymoma
- **Plan**
  - Start 60 mg pyridostigmine po TID
  - Continue to monitor with neurology and neuro-ophthalmology q6mos
REFERENCES


THANK YOU!

MENTORS
- Dr. Weon Jun
- Dr. Mark Williams
- Dr. Kimberly Winges
- Dr. Amara Callahan
- Dr. Kirk Halvorson
- Dr. Rebecca Kline
- Dr. Shannon Lutz
- Dr. Molly Phan
- Dr. Jonathon Thomas
- Dr. Grace Tsan

LOW VISION STAFF
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- Dr. Michelle Liang
DEADLY DIPLOPIA:
How To Diagnose & Manage Intracranial Aneurysms

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June 5-6 2020
Northwest Residents Conference
The presenter and organizers for Deadly Diplopia: How To Diagnose & Manage Intracranial Aneurysms

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My GASP...

Deadly Diplopia

- Myasthenia Gravis
- Giant Cell Arteritis
- Aneurysm
- Syphilis
- Papilledema
Overview

• Definitions & epidemiology
• Clinical presentation, neuro-anatomy, and physiology
• Management
Intracranial Aneurysms

• A cerebrovascular disorder in which there is a pathological outward bulging or ballooning due to a weakened artery wall

• Rupture of the weakened wall can lead to a subarachnoid hemorrhage
  • When an aneurysm ruptures, the mortality rates are as high as 50% and considerable neurologic morbidity

• May present with diplopia

• One of the *true emergencies* of eye care
Demographics

- 3-5% of the population
- Rupture rate of 1-2% per year; 6% if symptomatic
- 500,000 annual deaths due to ruptured aneurysms
- 10-30% can have multiple aneurysms
- Peaks in the 4th-6th decade
- More common in females

<table>
<thead>
<tr>
<th>Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Female sex</td>
</tr>
<tr>
<td>Positive family history</td>
</tr>
<tr>
<td>Hypertension, especially uncontrolled</td>
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<tr>
<td>Genetic conditions (i.e. connective tissue disorders)</td>
</tr>
<tr>
<td>Cigarette smoking</td>
</tr>
<tr>
<td>Alcohol abuse</td>
</tr>
<tr>
<td>Japanese and Finnish populations</td>
</tr>
<tr>
<td>Estrogen deficiency? Hormone replacement therapy?</td>
</tr>
</tbody>
</table>
Pathophysiology & Etiology of Symptoms

• Acquired degenerative changes (impaired vessel wall integrity)
• Hemodynamic stress
  • Aneurysms occur most often at arterial bifurcations and the Circle of Willis (flow pattern changes)
  • Perpendicular and parallel forces against the vessel wall

1. Mass effect
   • Dependent on adjacent neural tissue

2. Alteration of distal circulation of their parent vessel
   • Vascular compromise
   • Transient or permanent

3. Rupture (90%)
   • Increased intracranial pressure
   • Later on: intracranial vessel spasm
The interval from presenting signs to rupture varies from 1 day to 4 months.

Higher risk of rupture if:
- Previous history of a subarachnoid hemorrhage
- In posterior circulation
- Presence of a daughter sac
- Patient is a smoker or has concurrent hypertension
- Rupture is associated with ~70-80% mortality and morbidity
## Classification

### Shape or type
- Berry or saccular (90%)
- Fusiform
- Dissecting
- Other

### Size
- Sac
- Small: <10 mm
- Large: 10-25 mm
- Giant: >25 mm
- Neck
- Small: <4 mm
- Large: >4 mm

### Location
- Intradural vs. extradural
- Which arterial branch

![Saccular aneurysm with narrow neck](saccular.png)
![Saccular aneurysm with broad base](saccular.png)

![Brain with vessels](brain.png)

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Reference:
- [Neurooperations](http://www.neurooperations.com/index.php?page=facilities_detail&category_id=149&subcategory_id=183&article_id=256)
- [Circle of Willis Anatomy Diagram and Functions](https://www.scienceabc.com/humans/circle-of-willis-anatomy-diagram-and-functions.html)
Clinical Presentation

**General**
- Headache: 23.7%
- Ischemic cerebrovascular disease or transient ischemic attack: 10.6% and 10.5% respectively
- Cranial nerve palsy: 8%
- Undefined “spells”: 7.1%
- Other

**Ocular**
- Ophthalmoplegia
- Vision or visual field loss
- Horner’s Syndrome
- Cortical blindness
- Specifically, when ruptured:
  - Papilledema
  - Terson’s Syndrome
Diplopia

- Cranial nerve 3 palsy
- Cranial nerve 4 palsy
- Cranial nerve 6 palsy
- Multiple nerve palsies

**TABLE 59.1** Etiology of Isolated Palsies of Cranial Nerves III, IV, and VI

<table>
<thead>
<tr>
<th></th>
<th>Oculomotor Nerve</th>
<th>Trochlear Nerve</th>
<th>Abducens Nerve</th>
<th>Mixed</th>
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</thead>
<tbody>
<tr>
<td><strong>PROPORTION (%)</strong>‡</td>
<td>31</td>
<td>11</td>
<td>45</td>
<td>13</td>
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<tr>
<td><strong>ETIOLOGY (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Head trauma</td>
<td>13</td>
<td>34</td>
<td>11</td>
<td>18</td>
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<tr>
<td>Neoplasm</td>
<td>11</td>
<td>5</td>
<td>19</td>
<td>29</td>
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<tr>
<td>Ischemic</td>
<td>25</td>
<td>22</td>
<td>20</td>
<td>7</td>
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<tr>
<td>Aneurysm</td>
<td>17</td>
<td>1</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>Other</td>
<td>14</td>
<td>8</td>
<td>21</td>
<td>19</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>20</td>
<td>30</td>
<td>26</td>
<td>16</td>
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</table>
Anatomy

- 85% of saccular aneurysms occur in the internal carotid artery or its branches
- About 1/3 within the main trunk of the internal carotid artery
- Less frequently, aneurysms may form on basilar and vertebral artery
Anatomy

- Most often presents as multiple cranial nerve involvement, including facial pain
- 6\textsuperscript{th} nerve runs closest to the internal carotid artery with the cavernous sinus
Pupil Sparing Rule

- 95% of aneurysmal palsies have a sluggish or fixed/dilated pupil
- 73% of ischemic palsies have pupil sparing
- 3 caveats
  1. Must be *complete* paralysis with *complete* pupil sparing
  2. Apply *sparingly* when <50 years old
  3. Only if neurologically isolated

https://blog.optoprep.com/pupil-involved-vs.-pupil-sparing-acquired-oculomotor-nerve-palsy
Ocular Clinical Presentation: CN III Palsy

- Sudden onset of binocular horizontal or vertical diplopia
- Down and out appearance with a dilated, non-reactive pupil, and ptosis
  - Paralysis of adduction, elevation, and depression
  - Anisocoria worse in bright light
- If a partial lesion:
  - The pupil may be either normal
  - Ptosis of varying degree
  - EOMs may be partially involved

https://jamanetwork.com/journals/jamaneurology/fullarticle/791333
CN III Palsy:
62 Year Old Male
With Internal Carotid Artery Aneurysm

Primary gaze
Right ptosis
Left gaze
ADDuction deficit

https://www.reviewofoptometry.com/article/double-trouble-ii
CN III Palsy:
49 Year Old Female
With Posterior Communicating Artery Aneurysm

Primary gaze
Left hypo- & exotropia
Supra-, infra-, & ADDuction deficit
CN III Palsy:
62 Year Old Female
With Posterior Communicating Artery Aneurysm
Partial CN III Palsy:
58 Year Old Female
With Subarachnoid Hemorrhage From Left Posterior Communicating Artery Aneurysm
Partial CN III Palsy:
58 Year Old Female
With Subarachnoid Hemorrhage From Left Posterior Communicating Artery Aneurysm
Partial CN III Palsy:
57 Year Old Male
With Left Posterior Communicating Artery Aneurysm
Work-up

Case History
- Onset
- Direction & gaze of maximal diplopia
- Constant, episodic, or fatigable?
- Other ocular, systemic, or neurological symptoms, especially headache

Mental status
- Make note during history
- Ask about changes in behavior
- Observe other features like gait, balance, and coordination

Visual Fields
- Rule out other possible neurological issues

Pupils
- Evaluate lids during this time as well
- Size in dark and light conditions
- Reactivity
- RAPD
Work-up Continued

- Extraocular Motility
  - Ductions
  - Versions

- Evaluation of Diplopia
  - Unilateral and alternating cover test or Maddox rod
  - 9 fields of gaze
  - Rule out involvement of 4th and 6th nerve (Park’s 3 step, etc.)

- Evaluation of Other Cranial Nerves
  - CN I: normal olfaction
  - CN V: normal sensation V1, V2, V3
  - CN VII: no facial weakness
  - CN VIII: equal hearing
  - CN IX-X: symmetrical uvula/soft palate
  - CN XI: equal shoulder strength
  - CN XII: symmetrical tongue on protrusion

- Ocular Health
  - Dilate only after evaluation the pupil thoroughly
  - Possibly small pupil examination
  - Ancillary imaging as necessary

- Referral
  - Send to and consult with the emergency department
  - Neuro-imaging
  - Consult with neuro-ophthalmology/neurology and primary care

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Referral

Pupil involved or incomplete, other neurological symptoms, or <50 yo
- **Emergent CT/CTA (or MRI/MRA)**
- Order lab testing as necessary
  - Older than 50 yo: rule out GCA; order CBC with differential, ESR, and CRP
- Dispense patch for diplopia

Pupil sparing, complete, **and** isolated palsy
- Neuro-imaging controversial in the past
- Given recent updates, improved technology, and increased access, recommendation is to obtain emergent CT/CTA (or MRI/MRA)

In both cases, consult with neuro-ophthalmologist
Imaging

Ruptured Aneurysms
- Head Computed Tomography (CT): 98-100% for up to 12 hours
- Magnetic Resonance Imaging (MRI) with FLAIR sequence: superior for non-aneurysmal causes of cranial mononeuropathies
- Lumbar Puncture (LP): gold standard

Unruptured Aneurysms
- CT Angiography (CTA): 53%-95% sensitivity; overall 98.9% specificity
- MR Angiography (MRA): 95% pooled sensitivity; 89% pooled specificity
- Digital Subtraction Angiography (DSA): gold standard
Goal is to **exclude the aneurysm from circulation** in order to:

1. Prevent aneurysmal rupture
2. Restore neurologic and visual function

Achieved through:

a. Surgical aneurysm clipping*
b. Endovascular coiling
c. Flow diverter therapy
Optometric Management

- Patching
- Prism
- Fresnel
- Ground-in
- Referral for strabismus or ptosis surgery
- Binocular vision or low vision specialty exam or referral
Aberrant Regeneration

- Involuntary muscle movement that accompany voluntary movements
- May develop following a CN III palsy
- **Very rare** in ischemic cases
- 65% have persistent diplopia
Most commonly results in:

- Eyelid-gaze dyskinesis: upper eyelid elevation in infra- or adduction
  - Also called Pseudo Von-Graefe sign
- Pupil-gaze dyskinesis: pupil constricts on infra- or adduction
  - Also called Pseudo Argyll-Robertson pupil
- Limitation of vertical movement: with globe retraction or adduction
Aberrant Regeneration

Residual supra-deficit

Right anisocoria & ptosis

Residual infra-deficit

https://webeye.ophth.uiowa.edu/eyeforum/atlas/pages/aberrant-regeneration-3rd-nerve-palsy.htm
Aberrant Regeneration

Miosis & lid elevation when adducting

https://webeye.ophth.uiowa.edu/eyeforum/atlas/pages/aberrant-regeneration-3rd-nerve-palsy.htm
Summary

• As eye care practitioners, a common reason we may see patients are for complaints of acute onset diplopia

• Though rare, intracranial aneurysms should be considered in double vision cases as they may quickly become life threatening
  • There are many possible symptoms, but suspicion should rise with presentation of a pupil-involved CN III palsy with ipsilateral head or eye pain

• Emergent CT/CTA is recommended as first line imaging

• Follow-up with the patient to manage their diplopia symptoms
  • Watch for development of aberrant regeneration
References


THANK YOU!

Co-residents:
Bee Bui, OD
Vincent Chan, OD
Christina Kim, OD
Michelle Lising, OD

Low Vision Team:
Jodi Roth
Kara Hackney
Leif Johanson
Elena Thomas
Paul Thomas

Residency Mentors:
Weon Jun, OD
Russell Jew, OD
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Kirk Halvorson, OD
Rebecca Kline, OD
Shannon Lutz, OD
Molly Phan, OD
Jonathon Thomas, OD
Grace Tsan, OD
Kimberly Winges, MD

Dr. Robert Watzke 😊