Autoimmune Disease of Neuro-Ophthalmic Significance: Myasthenia Gravis & Thyroid Eye Disease

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ILLINOIS COLLEGE OF OPTOMETRY

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Disclosures

- Heidelberg Engineering (scientific advisory board)
- King Devick Technology (scientific advisory board)
- Horizon Therapeutics (scientific advisory board)

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Myasthenia Gravis

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Key Points

- Ptosis*
- Facial weakness
- Mixed EOM's
- Thymoma
- Progression from OMG to GMG

Variable course

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Thomas Willis

Circa 1672

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"for some time (she) can speak freely and readily enough, but after she has spoke long, or hastily, or eagerly, she is not able to speak a word, but becomes as mute as a fish, nor can she recover the use of her voice under an hour or two."

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Background

- Chronic disease of neuromuscular transmission
- Destruction of post-synaptic motor endplates
- Weakness & fatigue of voluntary muscles that improves with rest
- Variable presentation

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Epidemiology

- MAI = 4-5/100,000
- Autoimmune disorder
  - Young women (ave. age = 28 yrs.)
  - Older men (ave. age = 42 yrs.)

} Increasing trend among older women

- Potential involvement of antibiotics, statins, etc.

Parmar B, et al. *Lancet* 2002
Shin J, et al. *Muscle Nerve* 2008

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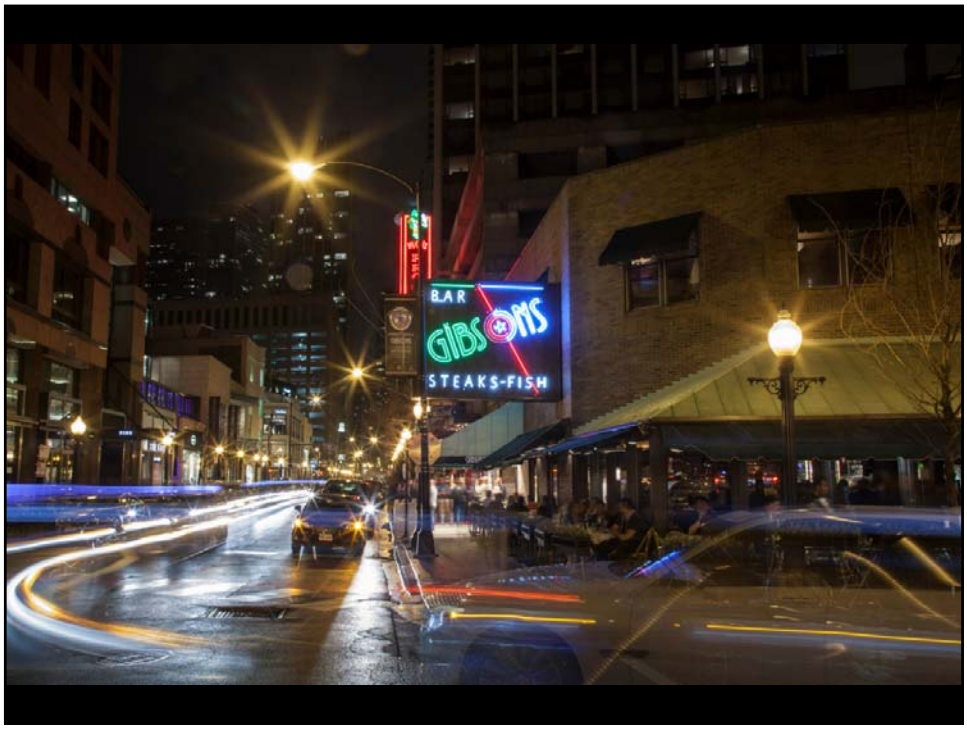

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Epidemiology (cont)

- Genetic predisposition
  - HLA - DRB1, A1, B8 &C7
- Racial predisposition
  - Early onset MG linked to Asian ethnicity
- Thymic hyperplasia / thymoma
  - "paraneoplastic syndrome"

Robertson NP, et al. *England J Neurol* 1998

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What is a paraneoplastic syndrome?

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- Tumor-induced antigen
- Immune/antibody response against <u>cross-reacting neural antigens</u>
  - *Myasthenia: Anti-AChR (thymoma)*
  - Optic neuropathy: Anti-CRMP-5 (small cell lung)
  - Retinal degeneration (CAR): Anti-recoverin (small cell lung)
  - Retinal degeneration (MAR): Anti-bipolar cell (cutaneaous melanoma)
  - Lambert-Eaton syndrome: Anti-voltage-gated-calcium channel (small cell lung, breast, lymphoma)

Jacobsen DA. *NANOS* 2003

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Pathophysiology of MG

- Autoimmune destruction of ACh receptors
- Anti-ACh receptor antibodies
  - IgG competitive blockade of ACh receptors
  - Receptor degradation

Lindstrom JM, et al. *Neurology* 1976

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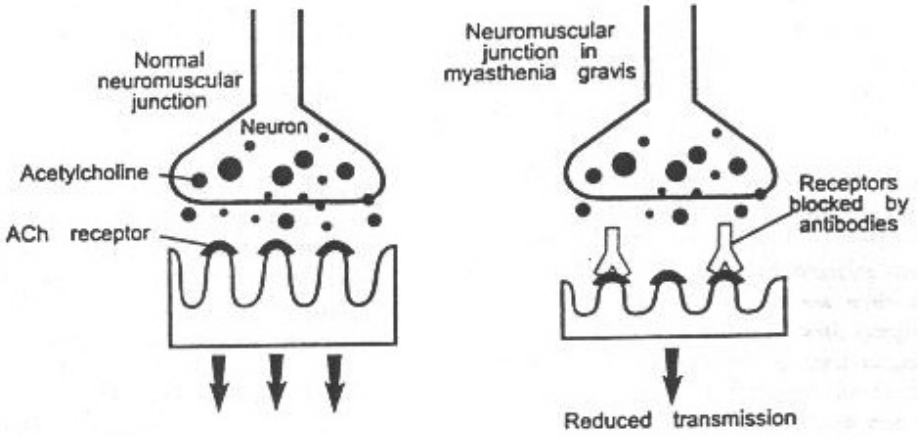

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Common Muscle Involvement

- Eyes (EOMs, levator)
- Face (orbicularis oculi / oris)
- Throat
- Neck
- Limbs

Simpson JA. *Disorders of Voluntary Muscle* 1981

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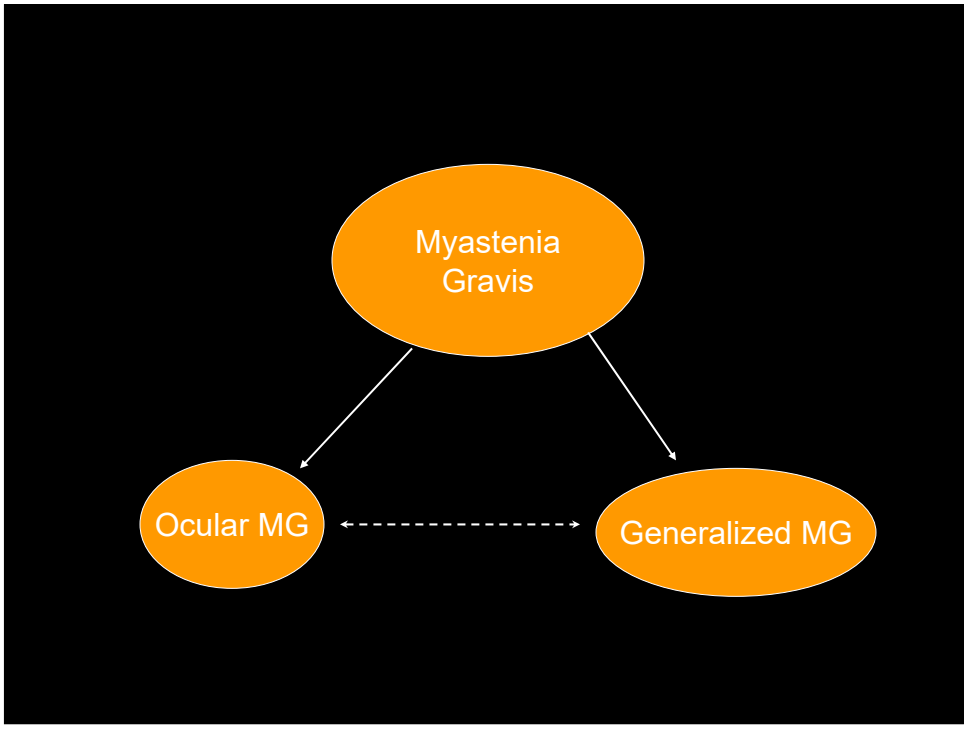

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Signs & Symptoms of Myasthenia (Generalized MG)

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Signs & Symptoms: Generalized MG

- Facial muscle weakness
  - "masked facies"
  - Orbicularis weakness
    - Reduced lid closure
    - Myasthenic "snarl"
- Abnormal speech and tone (oropharyngeal paralysis)
  - Nasal, tongue-tied speech pattern
- Hyperacousis
  - Stapedius
- Neck extensor weakness
  - "head ptosis"

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Signs & Symptoms: Generalized MG

- Difficulty swallowing
- Difficulty breathing

} *Myasthenic crisis!*

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Signs & Symptoms: Ocular MG

- Levator & EOM's
  - 70% initial presentation
  - 90% of all MG
  - Variable course
  - *Combined with orbicularis oculi weakness*

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Ptosis

- *Most common eye sign*
  - 10% ptosis only
  - 90% ptosis with other EOM's
  - 25% ptosis with orbicularis oculi weakness
- Unilateral with shift between eyes
- Spread to bilaterality
- Asymmetric

Evoli A, et al. *Acta Neurol Scand* 1988

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Ptosis (cont)

- Fatigability:
  - Repeated eyelid closures
  - Sustained up-gaze (Simpson Test)
    - Enhancement with manual elevation of fellow upper lid (Herring's law)
      - "see-saw" ptosis

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16 y/o AA Male with Progressive Ptosis and Diplopia

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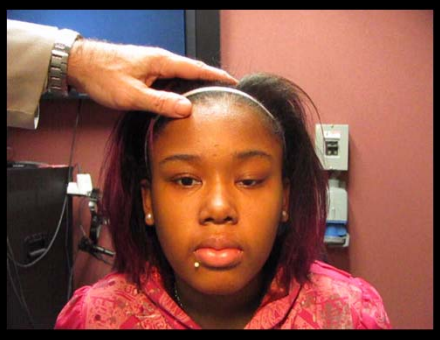
Cogan's Lid Twitch

- Begin with down gaze (10-20 sec.)
- Redirect to primary gaze
- Overshoot of upper lid



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EOM Paresis

- Medial rectus = most common
  - Pseudo internuclear ophthalmoplegia
  - Pseudo CN III palsy
- Isolated or mixed muscles
- "No rationale" for motility pattern
- Concomitant ptosis
- Pupil spared
- Orbicularis weakness

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52 y/o man with diplopia & ptosis

- C/O : recent onset ptosis OS x 2 wks
  - Worsens toward end of day
- Horizontal diplopia on right gaze
- VA = 20/20 OU
- PMHX: (+) borderline HTN

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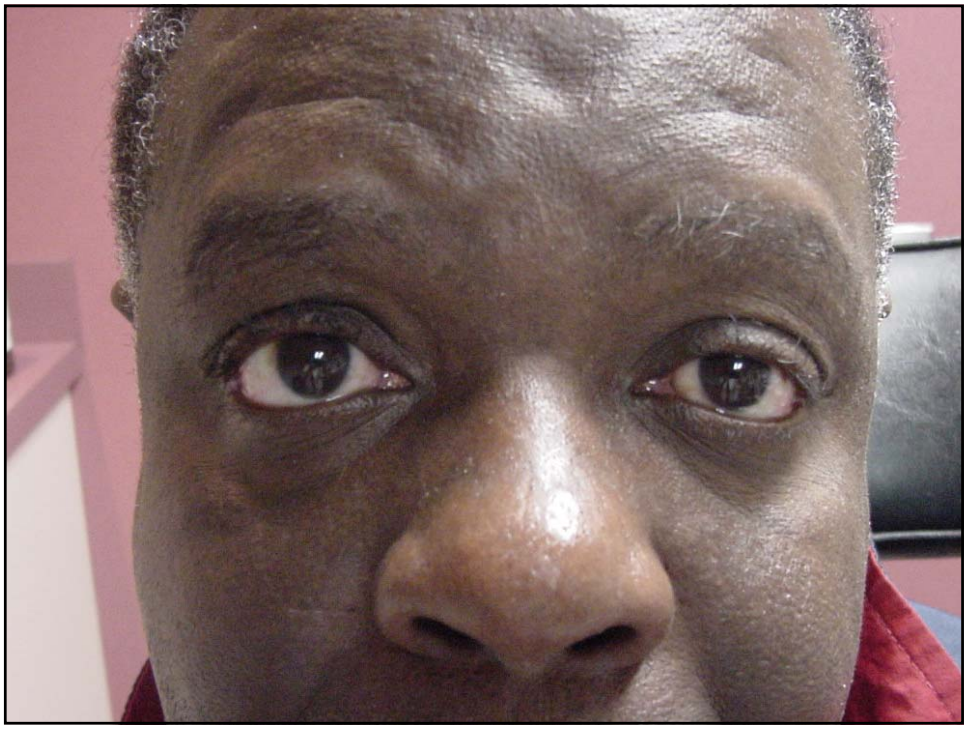

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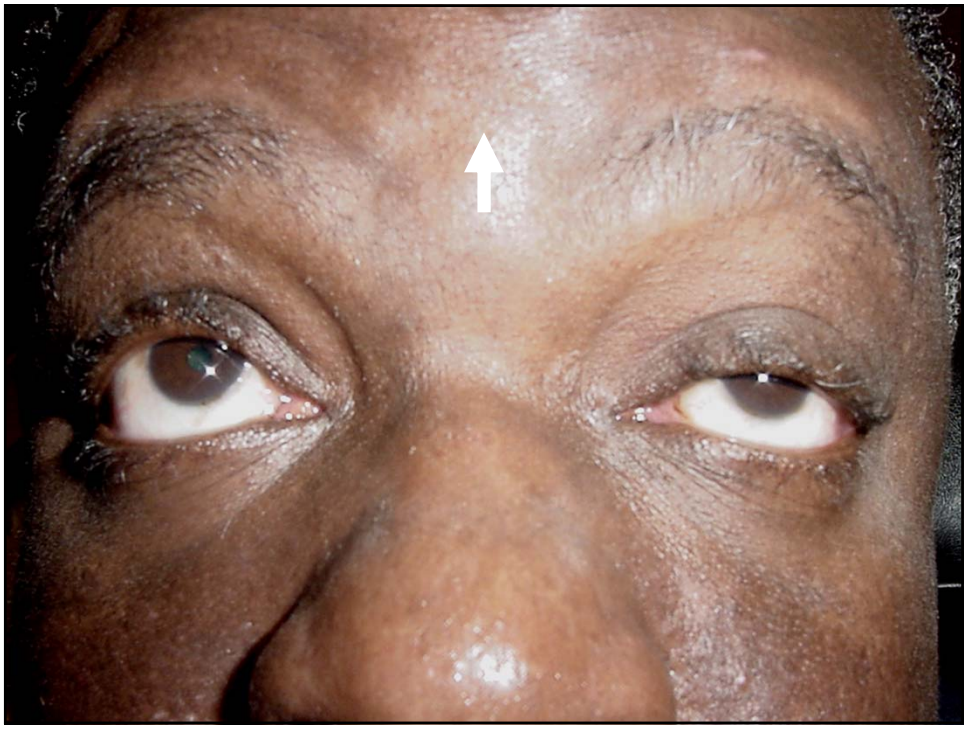

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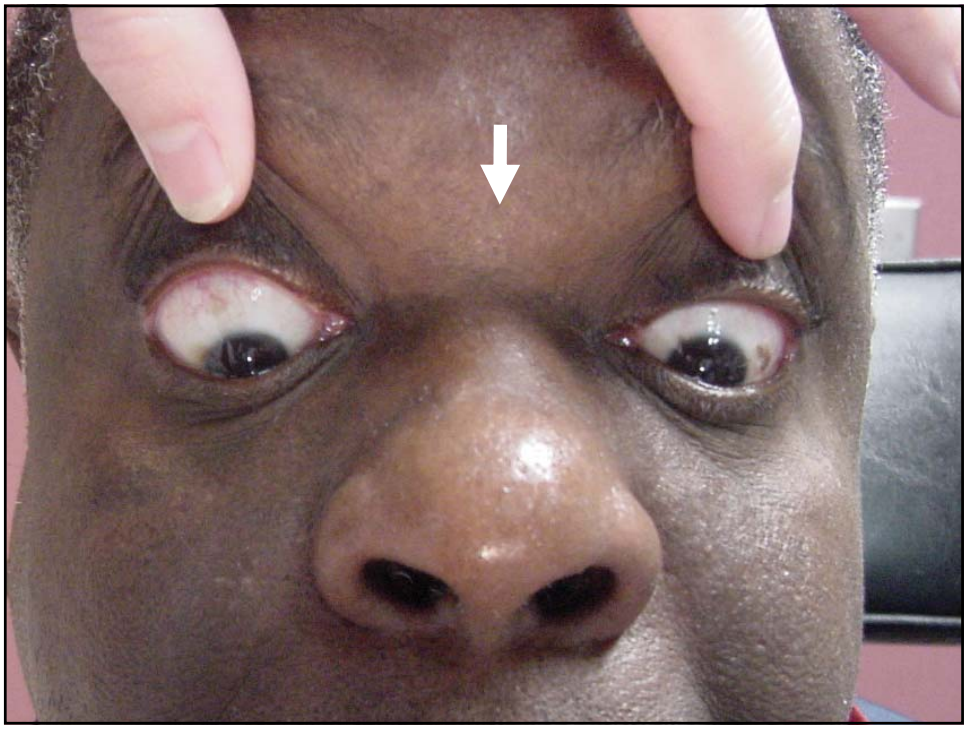

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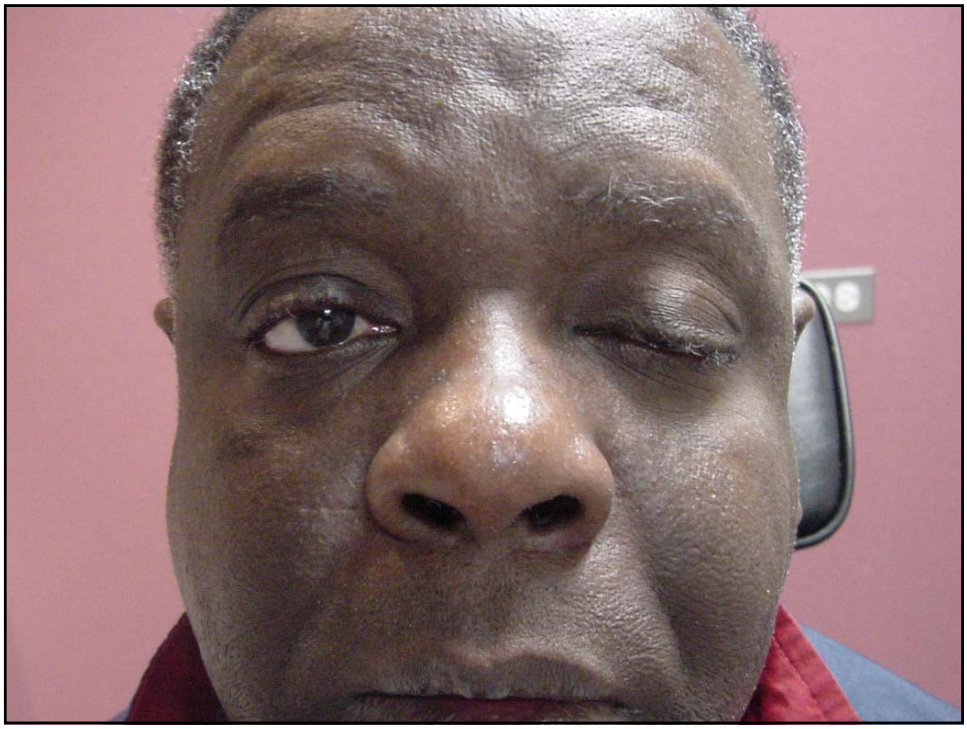

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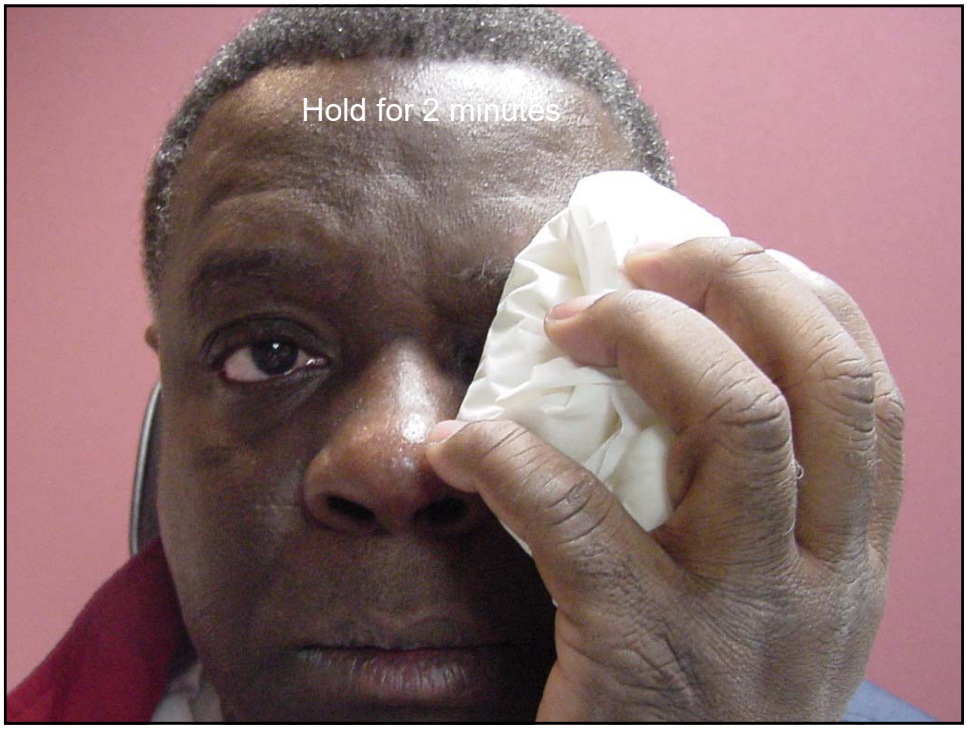

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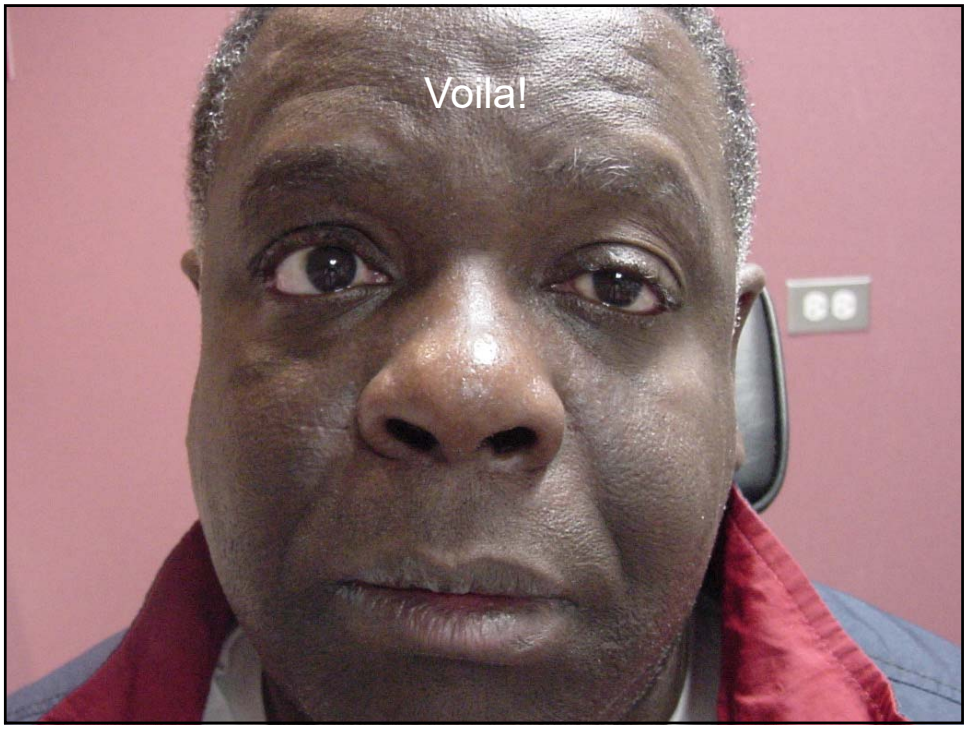

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Work-up for MG

- Anti-ACh receptor antibody titer
- Rule-out thymic disorders (chest CT/MRI)
- Ice pack test
- Sustained forced lid closure ("Simpson plus")
- Sleep test
- Single-fiber EMG
- Edrophonium chloride (Tensilon) test
- Thyroid/autoimmune dysfunction studies

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Anti-ACh Receptor Antibody Titer

- 80-90% positive for GMG
  - 50% of remainder positive for anti-MuSK
- 50-60% positive for OMG ("early MG")
- Correlation between clinical status and Anti-AChR titer (?)

Meriggioli MN, et al. *Expert Rev Clinical Immunol* 2012
Rodolico C, et al. *Front Neurol* 2020

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Single-fiber EMG

- High sensitivity/moderate specificity
- >95% positive for GMG
- 80-90% positive for OMG
- Useful if negative anti-ACh receptor antibody titer
- Long and technically difficult
- Requires good patient cooperation and skilled neurologist/neurophysiologist

Selvan AV. *Ann Indian Acad Neurology* 2011

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Thyroid Dysfunction Studies

- 9% males
- 18% females

Increased if over 60 yrs.

- Other autoimmune disorders with MG:
  - SLE
  - Sarcoidosis
  - Rheumatoid arthritis
  - Crohn's disease

Weizer JS, et al. *Can J Ophthalmol* 2001

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Rule-out Thymic Disorders (chest CT/MRI)

- Thymic hyperplasia = 65-70%
- Thymoma = 10-15%
  - Increased incidence with age
  - Male gender (?)
  - High serum AChR titers

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Edrophonium Chloride (Tensilon) Test

- Acetylcholinesterase inhibitor
- Rapid onset (30 sec.) & short duration (5 min.)
- Works best for ptosis
- 50-75% positive
- Caution with elderly/cardiac patients

Coll & Demer *Am J Ophthalmol* 1992

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16 y/o AA Male with Progressive Ptosis and Diplopia – pre and post IV edrophonium (Tensilon)

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Sleep Test

- Have patient take picture of face upon awakening & compare to end of day

morning

end of day

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Ice Pack Test

- Decreased acetylcholinesterase activity with hypothermia
- Apply over closed lid x 2 - 5 minutes (remeasure ptosis within 10 seconds)
- 80% positive for myasthenic ptosis
  - >/= 2mm improvement
- Works best on ptosis (not motility)

Golnick KC, et al. *Ophthalmology* 1999

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Management (acetylcholinesterase inhibitors)

- Mestinon (pyridostigmine)
  - Onset with 30 min.
  - Peak @ 1-2 hr.
  - Starting dose = 60mg po q3-4 h
  - *Diarrhea (common side effect)*
  - *Caution with asthma & cardiac disease*
- Prostigmine (neostigmine)
- Mytelase (abenonium)

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Management (Corticosteroids / Immunosuppressives)

- Corticosteroids (prednisone)
  - Begin with 5 mg/day with increase up to 50 mg/day
  - Treatment for about 1 year with gradual taper
- Immunosuppressives (maintenance therapy)
  - Azathioprine
  - Cyclosporin
  - Mycophenolate (CellCept®)
  - Eculizumab (Soliris®)
  - Efgartimob (VYVGART®)

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ARTICLE CLASS OF EVIDENCE

Randomized phase 2 study of FcRn antagonist efgartigimod in generalized myasthenia gravis

James F. Howard, Jr., MD, Vera Bril, MD, Ted M. Burns, MD, Renato Mantegazza, MD, Malgorzata Bilinska, MD, Andrzej Szczudlik, MD, Said Beydoun, MD, Francisco Javier Rodriguez De Rivera Garrido, MD, Fredrik Piehl, MD, PhD, Mariarosa Rottoli, MD, Philip Van Damme, MD, PhD, Tuan Vu, MD, Amelia Evoli, MD, Miriam Freimer, MD, Tahseen Mozaffar, MD, E. Sally Ward, PhD, Torsten Dreier, PhD, Peter Ulrichs, PhD, Katrien Verschueren, MSc, Antonio Guglietta, MD, Hans de Haard, PhD, Nicolas Leupin, MD, and Jan J.G.M. Verschuuren, MD, PhD, on behalf of the Efgartigimod MG Study Group

Correspondence
Dr. Leupin
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Neurology® 2019;92:e2661-e2673. doi:10.1212/WNL.0000000000007600

- Efgartigimob (VYVGART®)
  - anti-neonatal Fc receptor immunoglobulin G1 Fc fragment resulting in increased catabolism of IgG
  - AchR+ gMG patients
  - Weekly IV infusion X 4 weeks
  - Rapid reduction in IgG levels with improvement of symptomatology and daily lifestyle function

Howard JF, et al. *Neurology* 2019

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Management (worsening disease / myasthenic crisis)

- Plasmapheresis
  - Binds maverick antibodies
- IVIg
  - Re-regulates immune system

Zinman L, et al. *Ann NY Acad Sci* 2008

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Management (surgical)

- Thymectomy
  - Patients between puberty and 50 yrs. who are inadequately controlled with medical Tx
  - Any patient with thymoma
  - 85% clinical improvement
  - 35% drug free
  - Delayed benefit (requires 2-5 years)
  - Poor results in elderly

Mineo TC, et al. *Thoracic Surg Clin* 2010

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Management of Ocular Findings

- Diplopia:
  - Occlusion therapy
- Ptosis:
  - Ptosis crutches
  - Eyelid tape
  - Surgery (stable disease)
  - Oxymetazoline

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Research

JAMA Ophthalmology | Original Investigation

Association of Oxymetazoline Hydrochloride, 0.1%, Solution Administration With Visual Field in Acquired Ptosis
A Pooled Analysis of 2 Randomized Clinical Trials

Charles B. Slonim, MD; Shane Foster, OD; Mark Jaros, PhD; Shane R. Kannarr, OD; Michael S. Korenfeld, MD; Robert Smyth-Medina, MD; David L. Wirta, MD

IMPORTANCE Treatment of acquired blepharoptosis (ptosis) is currently limited to surgical intervention.

OBJECTIVE To examine the efficacy and safety of oxymetazoline hydrochloride, 0.1%, ophthalmic solution (oxymetazoline, 0.1%) in participants with acquired ptosis.

DESIGN, SETTING, AND PARTICIPANTS This pooled analysis of 2 randomized, double-masked, placebo-controlled, multicenter phase 3 clinical trials included participants 9 years and older with acquired ptosis and superior visual field deficit. The 2 studies were conducted across 16 and 27 sites in the United States. Patients were enrolled from May 2015 to April 2019. Analyses for the individual trials were initiated after database lock and completed on September 6, 2017, and May 16, 2019. Pooled analysis was completed on August 25, 2019.

INTERVENTIONS Participants (randomized 2:1) received oxymetazoline, 0.1%, or vehicle, self-administered as a single drop per eye, once daily, for 42 days.

MAIN OUTCOMES AND MEASURES The primary efficacy end point was change from baseline in the number of points seen on the Leicester Peripheral Field Test, a test to detect superior visual field deficits due to ptosis, on days 1 (6 hours after instillation) and 14 (2 hours after instillation). The secondary end point, change from baseline in marginal reflex distance 1, was assessed at the same time points.

RESULTS In total, 304 participants were enrolled (mean [SD] age, 63.8 [13.8] years; 222 women [73%]). Overall, 97.5% (198 of 203) of participants receiving oxymetazoline, 0.1%, and 97.0% (98 of 101) of participants receiving vehicle completed the studies. Oxymetazoline, 0.1%, was associated with a significant increase in the mean (SD) number of points seen on the Leicester Peripheral Field Test vs vehicle (day 1: 5.9 [6.4] vs 1.8 [4.1]; mean difference, 4.07 [95% CI, 2.74-5.39]; $P < .001$; day 14: 7.1 [5.9] vs 2.4 [5.5]; mean difference, 4.74 [95% CI, 3.43-6.04]; $P < .001$). Oxymetazoline, 0.1%, also was associated with a significant increase in marginal reflex distance 1 from baseline (mean [SD]: day 1: 0.96 [0.89] mm vs 0.50 [0.81] mm; mean difference, 0.47 mm [95% CI, 0.27-0.67]; $P < .001$; day 14: 1.16 [0.87] mm vs 0.50 [0.80] mm; mean difference, 0.67 mm [95% CI, 0.46-0.88]; $P < .001$). Treatment-emergent adverse events (TEAEs) occurred in 31.0% (63 of 203) of participants receiving oxymetazoline, 0.1%, and 35.6% (36 of 101) of participants receiving vehicle. Among participants receiving oxymetazoline, 0.1%, with a TEAE, 81% (51 of 63) had a maximum TEAE intensity of mild, and 62% (39 of 63) had no TEAE suspected of being treatment related.

CONCLUSIONS AND RELEVANCE Oxymetazoline, 0.1%, was associated with positive outcomes and was well tolerated in phase 3 trials after instillation at days 1 and 14, demonstrating its potential promise for the treatment of acquired ptosis, although further study is needed to elucidate the clinical relevance of these findings beyond 6 weeks.

Invited Commentary
page 1176

Supplemental content

Author Affiliations: Department of Ophthalmology, University of South Florida Morsani College of Medicine, Tampa (Slonim); Athens Eye Care, Athens, Ohio (Foster); Summit Analytical, Denver, Colorado (Jaros); Kannarr Eye Care, Pittsburg, Kansas (Kannarr); Comprehensive Eye Care Ltd, Washington, Missouri (Korenfeld); North Valley Eye Medical Group, Mission Hills, California (Smyth-Medina); Aesthetic Eye Care Institute & Eye Research Foundation, Newport Beach, California (Wirta).
Corresponding Author: Charles B.

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Pre-installation oxymetazoline hydrochloride 0.1%

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20 minutes after installation oxymetazoline hydrochloride 0.1%

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What patients with OMG will go on to convert to GMG?

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OMG Conversion to GMG

- Bever et al. 1983 n = 108 OMG
  - 49% converted to GMG
  - 83% within 2 years
- Grob 1999 n = 248 OMG
  - 66% converted to GMG
  - 78% within 1 year
- Kupersmith et al. 2003 n = 147 OMG
  - 36% converted to GMG (2 years)
    - Increased risk with positive AChR Ab's and age >50 years
  - *Only 7% conversion with prednisone*

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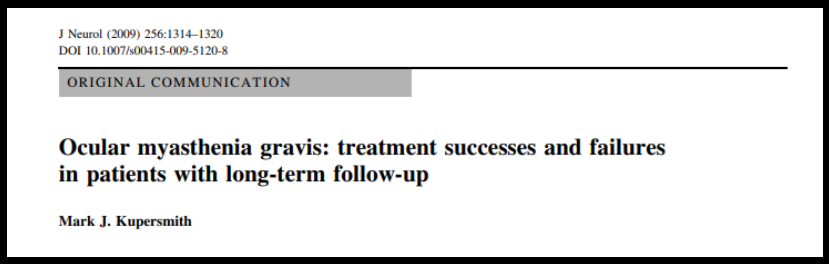

J Neurol (2009) 256:1314–1320
DOI 10.1007/s00415-009-5120-8

ORIGINAL COMMUNICATION

Ocular myasthenia gravis: treatment successes and failures in patients with long-term follow-up

Mark J. Kupersmith

- 87 patients with OMG
  - 55 given prednisone: 13% conversion to GMG
    - Average time to conversion = 5.8 yrs.
  - 32 no treatment: 50% conversion to GMG
    - Average time to conversion = 0.22 yrs.

Kupersmith MJ. *J Neurol* 2009

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Drugs to Avoid with MG

- Beta blockers (including topical glaucoma meds)
- Selected antibiotics
  - macrolides, quinolones, ketolides (telithromycin - Ketek®)
- Ca+ channel blockers
- Quinine derivatives
- Statins
- Neuromuscular blocking agents (Botox)

Perrot X, et al. *Neurology* 2006

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Key Points

- Ptosis*
- Facial weakness
- Mixed EOM's
- Thymoma
- Progression from OMG to GMG

Variable course

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Thyroid Eye Disease

Thyroid-related Eye Disease
Graves' Orbitopathy
Graves' Ophthalmopathy

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Key Points

- Overview & pathophysiology of Graves' disease
- Ocular findings with TED
- Active vs. chronic disease
- Diagnostic studies
- Management

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Graves' Disease

- Hyperthyroidism (90%)
- Ophthalmopathy (40%)
- Dermopathy (10%)

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Epidemiology-Graves' Disease

- Most common cause of hyperthyroidism
- MAI = 20-50 / 100,000
- Incidence peak = 30-50 yrs.
- Female predilection
- Thyroid eye disease:
  - 50% of all Graves' disease
  - Typically develops within 1 year of hyperthyroidism
  - 16/100,000 women
  - 3/100,000 men
  - Severe disease greatest in older men
  - Vision threatening in 3-5% of patients (corneal exposure, optic neuropathy)

Smith TJ, et al. *N Engl J Med* 2016

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General Symptoms (catecholamine supersensitivity)

- Weight loss
- Irritability
- Nervousness
- Easy fatigability
- Hyperkinesia
- Tremor
- Diarrhea
- Excessive sweating
- Intolerance to heat
- Cardiac complications/atrial fibrillation (> age 60 yrs.)

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What causes this???

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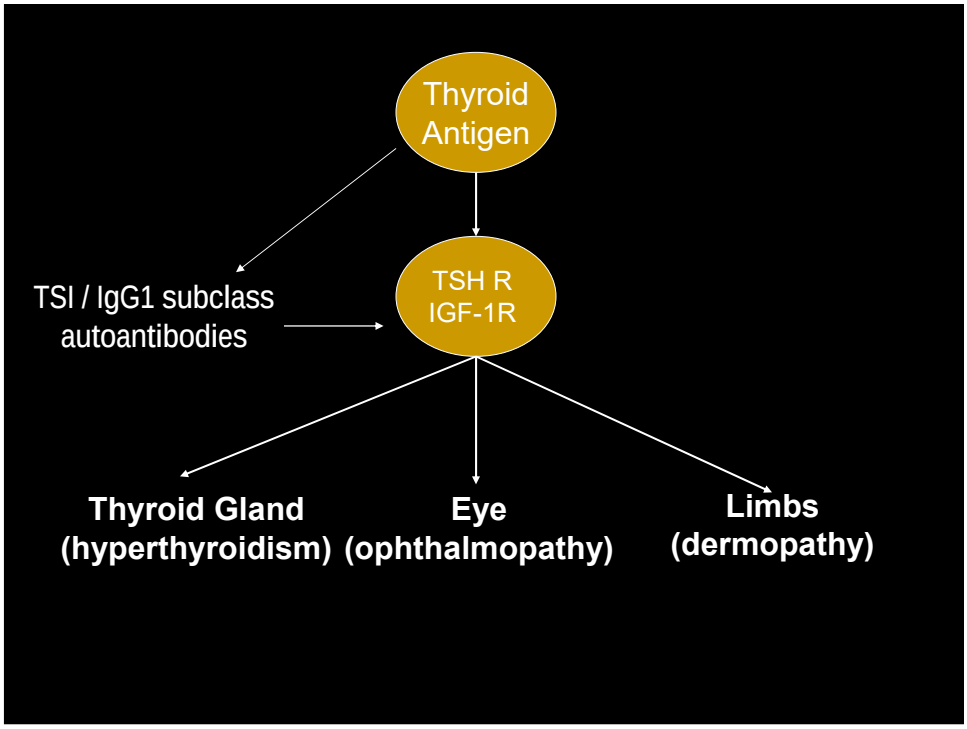

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Graves' Hyperthyroidism

- Autoimmune disorder with sensitization of T-lymphocytes by thyroid antigens
- Autoantibodies of IgG1 subclass (thyroid-stimulating immunoglobin) directed against *TSH receptors*
- Up-regulation of thyroid gland → hyperthyroidism

Weetman AP, et al. *J Clin Invest* 1990
Smith TJ, et al. *N Engl J Med* 2016

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Thyroid Eye Disease

- Hyperthyroidism (90%)
  - TED usually within 1 year of Dx
- Euthyroid / hypothyroid (10%)
- Fibroblast-mediated orbital inflammation
  - Orbital fat
  - Extraocular muscles

Smith TJ, et al. *N Engl J Med* 2016

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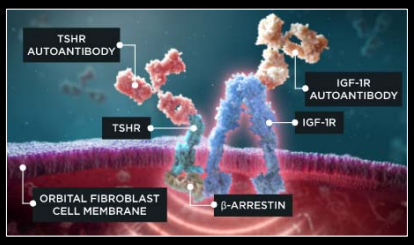
Pathophysiology of Graves' Ophthalmopathy

- IGF-1R & TSHR autoantibodies activate the IGF-1 and TSH receptors on orbital fibroblasts
- Activated orbital fibroblasts stimulate an inflammatory response involving orbital fat and EOMs



Krieger CC, et al. J Clin Endocrinol Metab 2016
Dik WA, et al. Exp Eye Res 2016
Krieger CC, et al. Endocrinology 2019
https://www.tepezza.com/hcp/tepezza-moa

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Orbital Fibroblast Differentiation
(Fat vs. Muscle Predominant Disease)

- Fibroblast-to-adipocyte differentiation (fat predominant):
  - Accumulation of orbital adipose tissue
  - Predominant driver for exophthalmos & compressive optic neuropathy
- Fibroblast-to-myocyte differentiation (muscle predominant):
  - EOM enlargement
  - Restrictive myopathy/diplopia

Liaboe CA, et al. webeye.oph.uiowa.edu 2016

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Eye Signs & Symptoms of TED

- Eyelid retraction
- Proptosis/diplopia
- Pressure/pain behind eyes
- Orbital/periorbital edema
- Eyelid lag in downgaze (Graeffe's sign)
- EOM restriction
- Ocular irritation/dryness
- Exposure keratopathy
- Loss of vision / compressive optic neuropathy

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NO SPECS Classification

- No physical signs/symptoms
- Only signs (eyelid retraction)
- Soft tissue involvement (0: absent, a:minimal, b: moderate, c: marked)
- Proptosis (0: absent, a: minimal, b: moderate, c: marked)
- Extraocular muscle signs (0: absent, a: limitation in extremes of gaze, b: evident restriction, c: fixation of globe (s))
- Corneal involvement (0: absent, a: stippling, b: ulceration, c: clouding, necrosis, perforation)
- Sight loss (optic neuropathy) (0: absent, a: visual acuity 0.63-0.5, b: visual acuity 0.4-0.1, c: visual acuity <0.1 to NLP)

Werner SC. *Am J Ophthallmol* 1969

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Clinical Activity Score (CAS)

1. Painful feeling behind globe
2. Pain on attempted gaze
3. Redness of eyelids
4. Redness of conjunctiva
5. Chemosis
6. Inflammatory eyelid swelling
7. Inflammation of caruncle or plica

Baseline

8. Increase of proptosis of >/= 2mm in last 1-3 months
9. Decrease in visual acuity in last 1-3 months
10. Decrease in eye movements of >/= 8 degrees in last 1-3 months

Follow up

Mourits M. Clinical Endocrinology 1989

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Eyelid Retraction *("Thyroid Stare")*

- Adrenergic overload
- *Infiltration of upper lid structures*
- Upper lid retraction *only* = *Graves'*
- Lower lid retraction = any proptosis

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Upper Eyelid Retraction & Lid-Lag on Downgaze (Graefe's Sign)

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Propotosis

- Orbital congestion:
  - Fluid
  - Fibrotic EOMs
  - Increased orbital fat
- Associated with lid retraction (upper & lower)
- Bilateral

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EOM Involvement
"I'm So Lazy!"

- Inferior rectus (supraduction deficit) = 60%
- Medical rectus (abduction deficit) = 50%
- Superior rectus = 40%
- Lateral rectus = 22%

Wiersinga WM, et al. *Ophthalmic Res* 1989

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48 y/o HM
Hyperthyroidism X 1 year
c/o diplopia on supraduction
exophthalmometry: 24/26 (base 111)
CAS: 4

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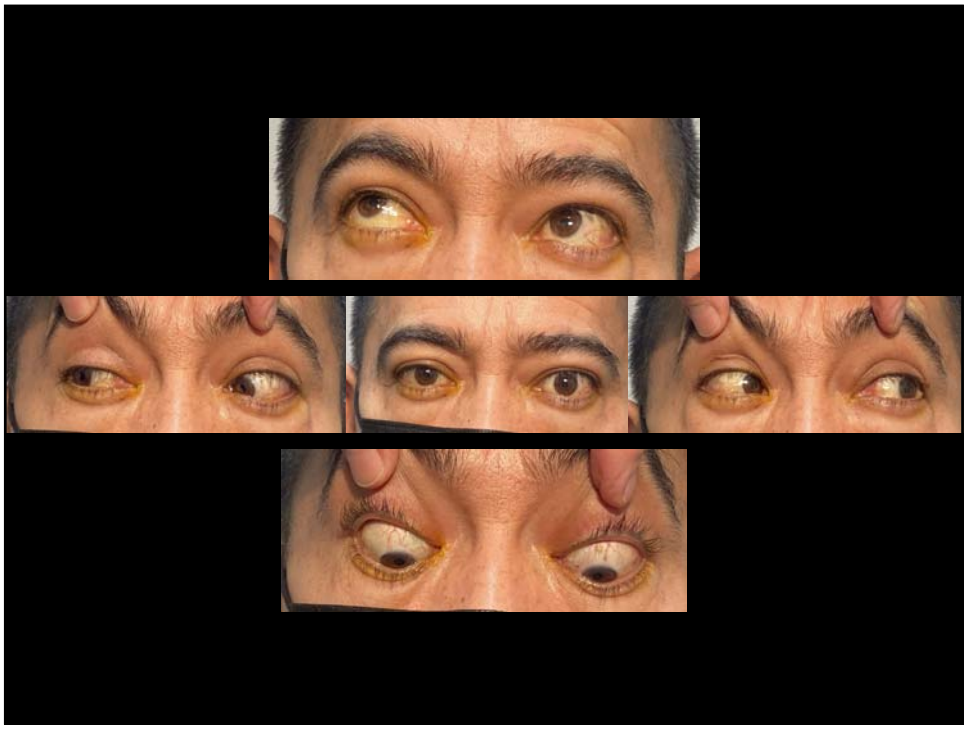

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Inferior Rectus Infiltration (Supraduction Deficit)

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Medial Rectus Infiltration (Abduction Deficit)

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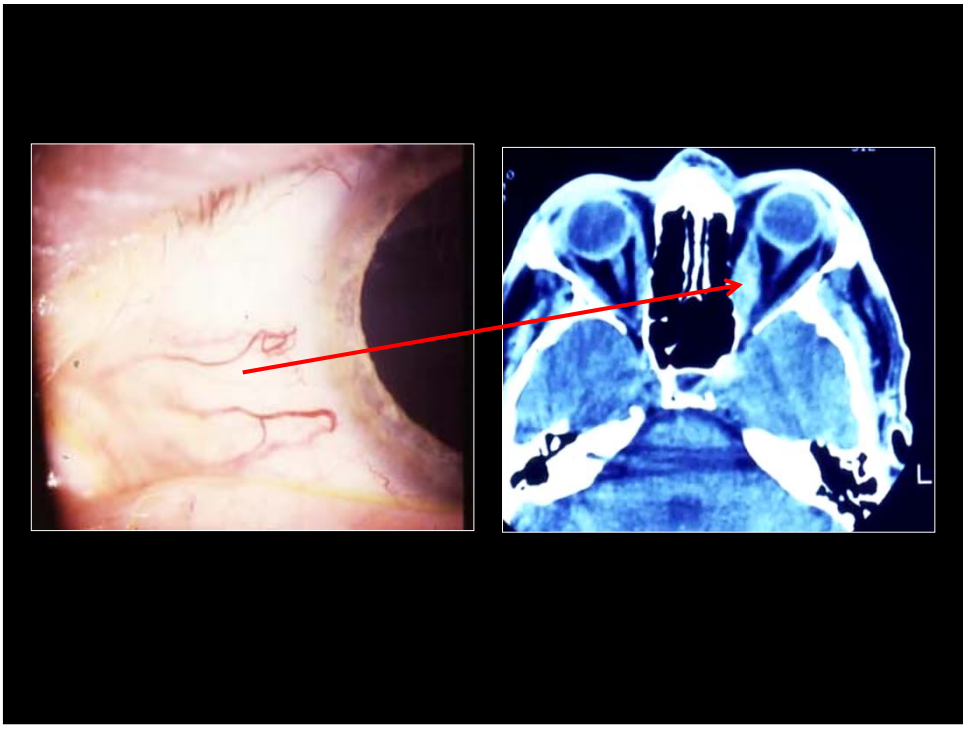

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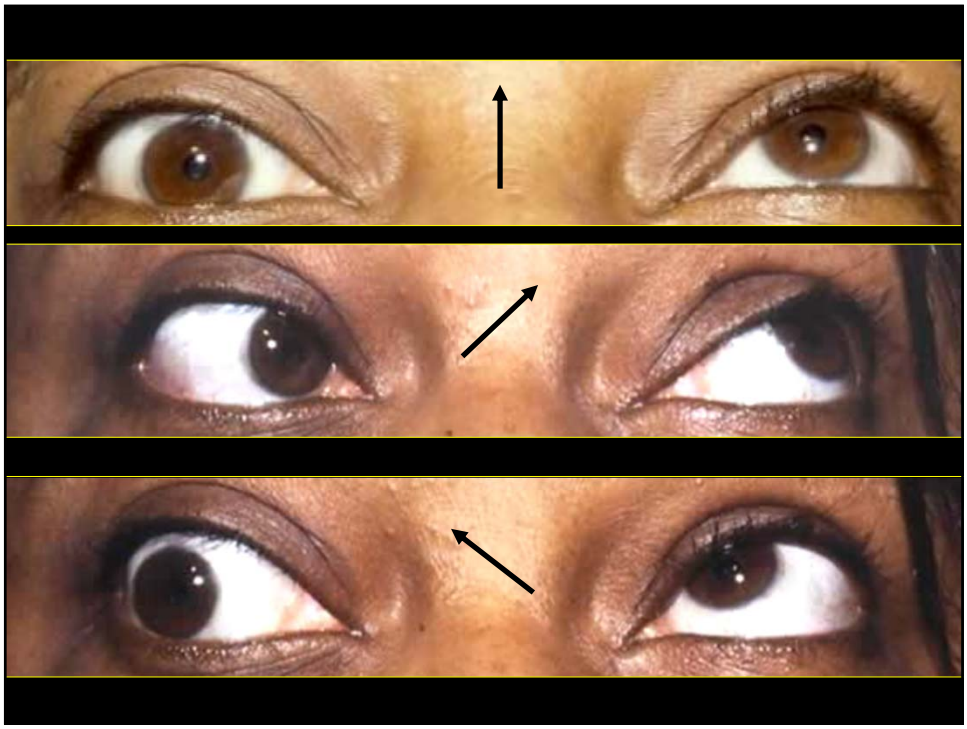
Characteristics TED Myopathy

- Diurnal variation in diplopia
  - Worse in am
- Gaze-induced IOP rise
  - Typically seen with inf rectus infiltration
- Head movement to minimize diplopia

92

93



94

Eyelid Edema

- "Jelly roll"
- "Finger-like"
- Diurnal variation:
  - Worse in am with improvement later in day
- Improved with head elevation & diuretics

95

Staging of Thyroid Eye Disease

- Active / progressive (inflammatory)
  - 6-24 months
- Chronic /stable (fibrotic)
- Newer data shows continuance of inflammation over time albeit at a reduced rate (OPTIC-X study)

Rundle FF, et al. *Clin Sci* 1945
Ozzello DJ, et al. *Orbit* 2021
Douglas RS, et al. *Ophthalmology* 2022

96

Diagnostic Studies

- CT
- MRI
- Ultrasonography
- Exophthalmometry
- Lids/motility measurements
- Thyroid function
  - Total T4 (elevated)
  - TSH (reduced)
  - TSI (elevated with active disease)

97

Thyroid Stimulating Immunoglobin (TSI) for Graves' Ophthalmopathy

- "Functional biomarker" of thyroid eye disease
  - Indicator of acute disease
  - May be only elevated marker with ophthalmopathy
  - May portend more severe course of ophthalmopathy

Ponto KA, et al. *Thyroid* 2010

98

Dysthyroid Optic Neuropathy

- 3-5% of TED
- EOM compression of optic nerve at orbital apex (increased orbital fat)
- Stretching of optic nerve (vascular disruption)
- Older diabetic men
- Abduction deficit ("fat" medial rectus)
- Absence of exophthalmos

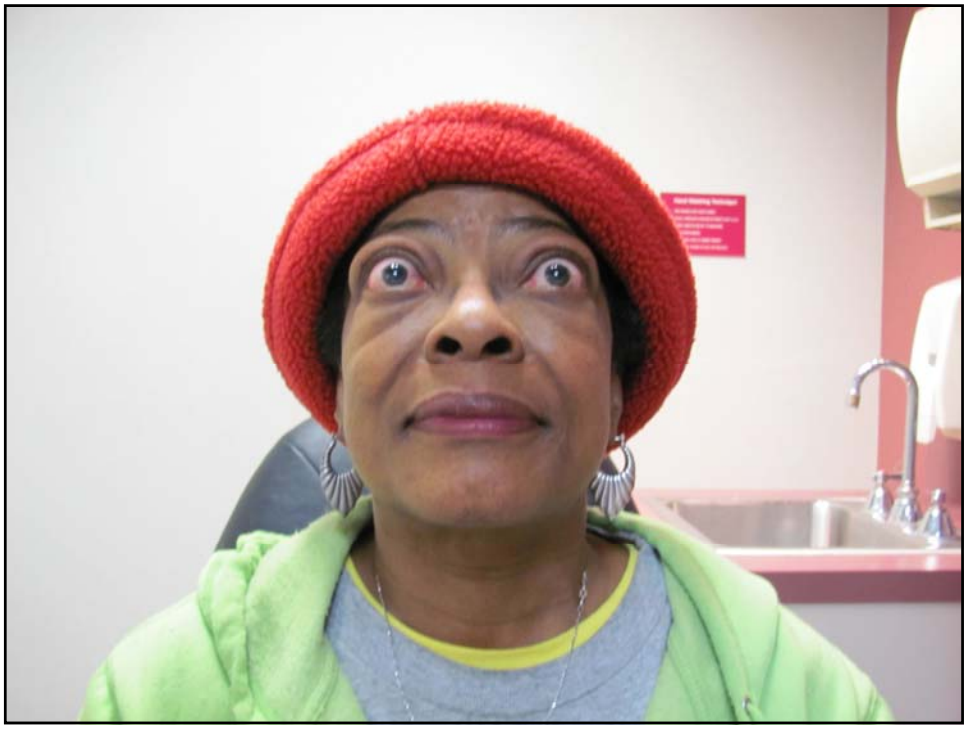
Bartalena L, et al. *N Engl J Med* 2009

99

62 Y/O Female

- C/o progressive vision loss OU
- Dx hyperthyroidism 8 mos. ago
- BVA:
  - 20/60 OD
  - 20/100 OS

100



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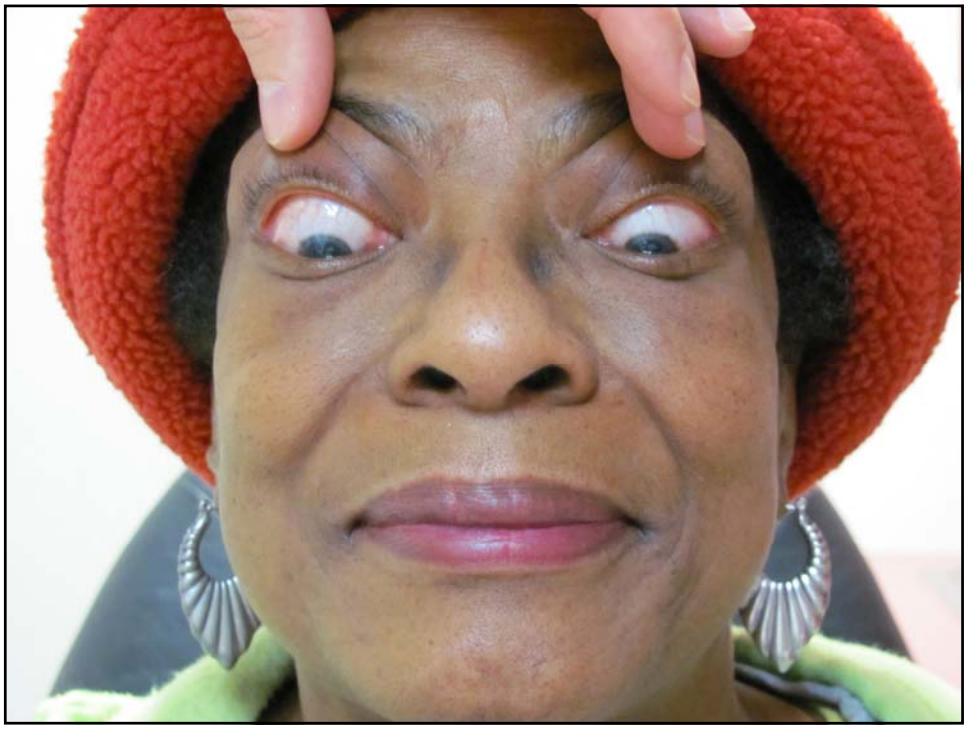
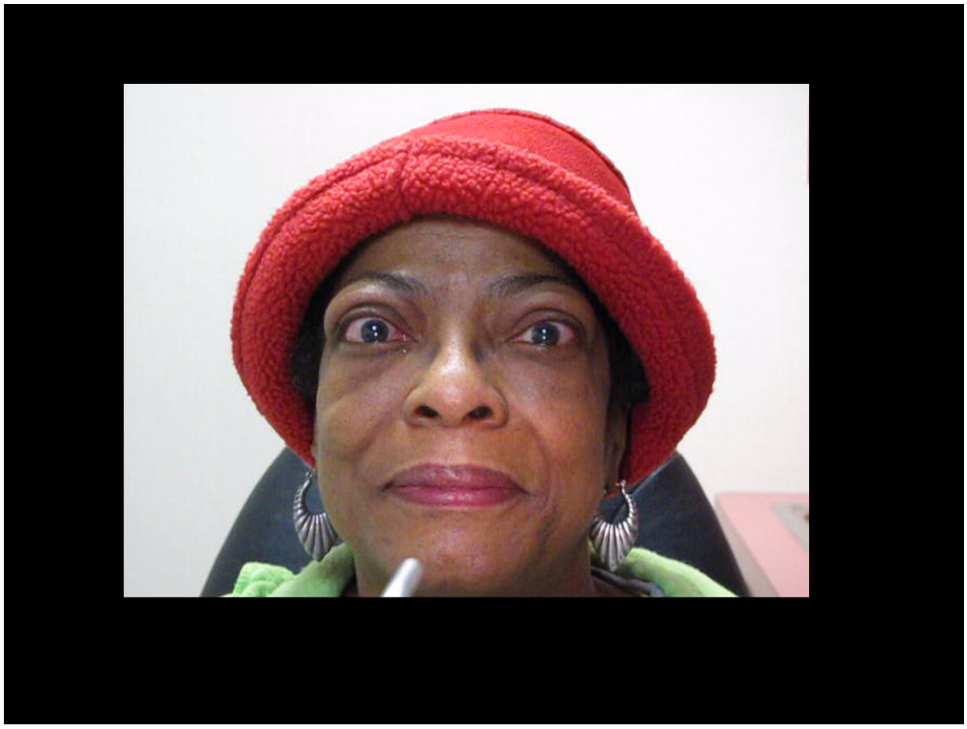


102

103

104



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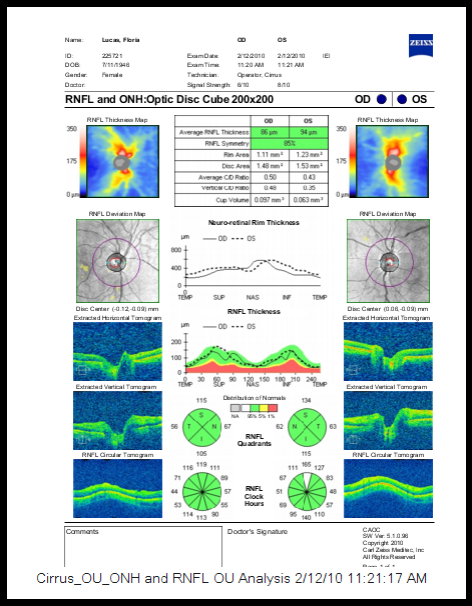
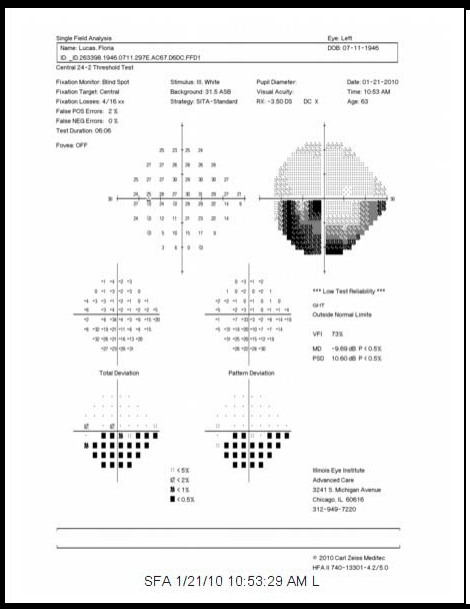
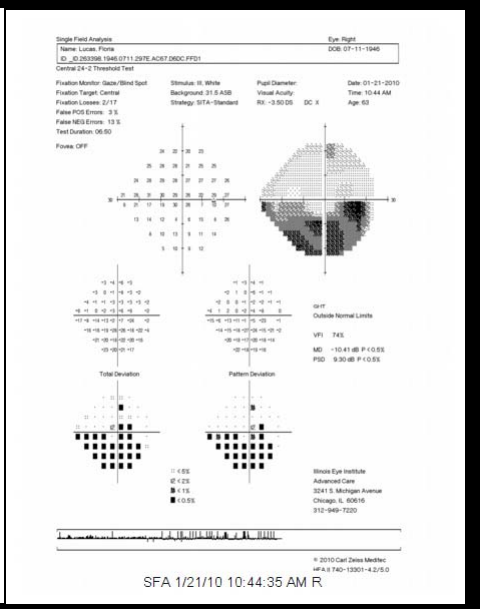


Cirrus_OU_ONH and RNFL OU Analysis 2/12/10 11:21:17 AM

106



SFA 1/21/10 10:53:29 AM L

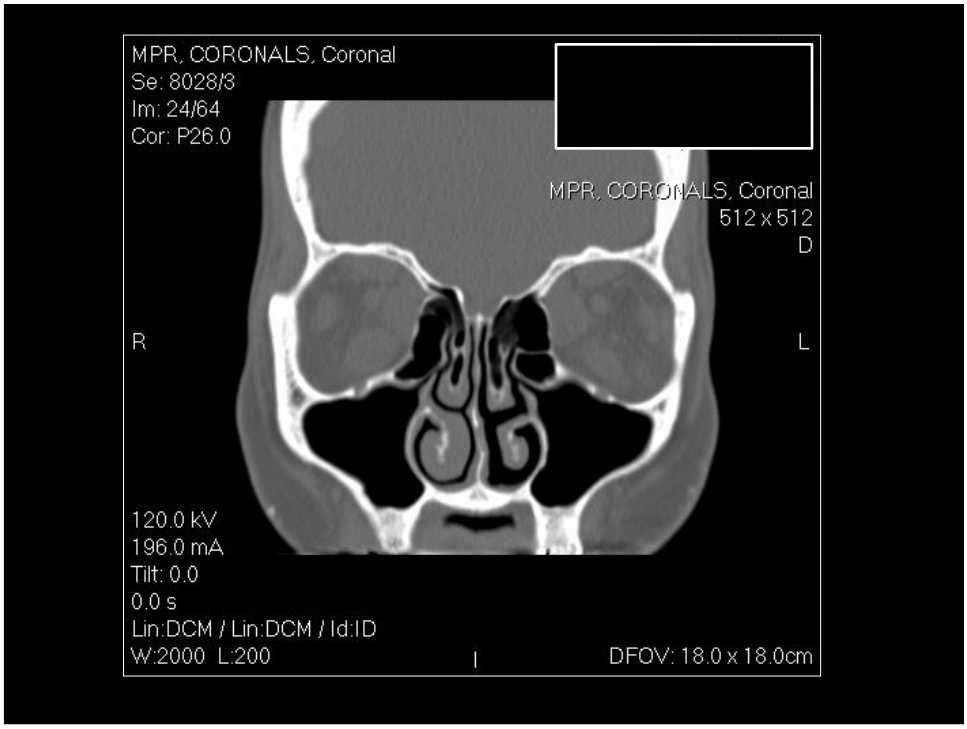


SFA 1/21/10 10:44:35 AM R

107


2MM ORBITS
Se: 3/3
Im: 27/59
Ax: S96.4
2MM ORBITS
512 x 512
D
R
L
120.0 kV
196.0 mA
2.0 mm/-1.01
Tilt: 0.0
0.0 s
Lin:DCM / Lin:DCM / Id:ID
W:2000 L:199
P
DFOV: 18.0 x 18.0cm

108


MPR, CORONALS, Coronal
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Im: 24/64
Cor: P26.0
MPR, CORONALS, Coronal
512 x 512
D
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L
120.0 kV
196.0 mA
Tilt: 0.0
0.0 s
Lin:DCM / Lin:DCM / Id:ID
W:2000 L:200
I
DFOV: 18.0 x 18.0cm

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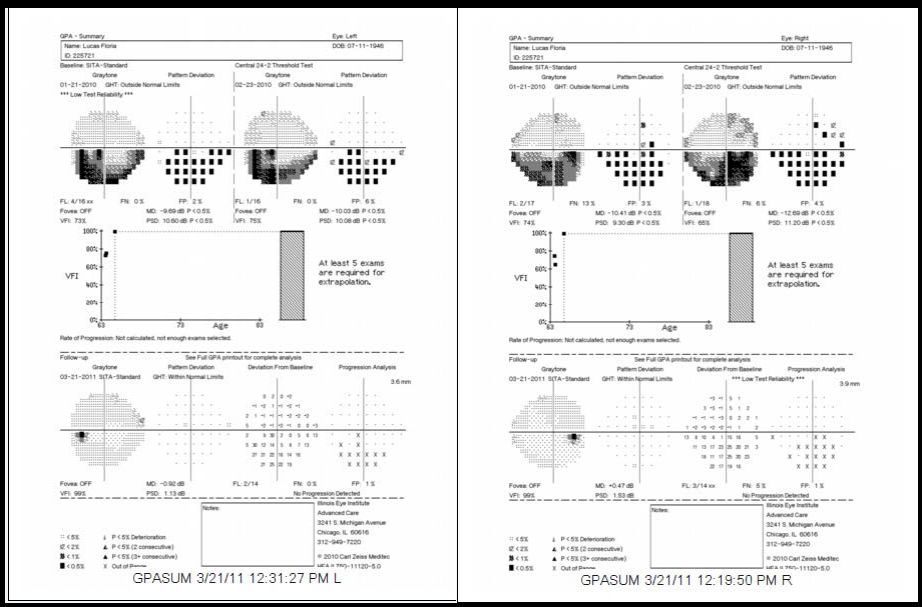
- Immediate orbital decompression
- Over next 14 mos:
  - Vision 20/20 OU
  - Normalization of visual fields

110

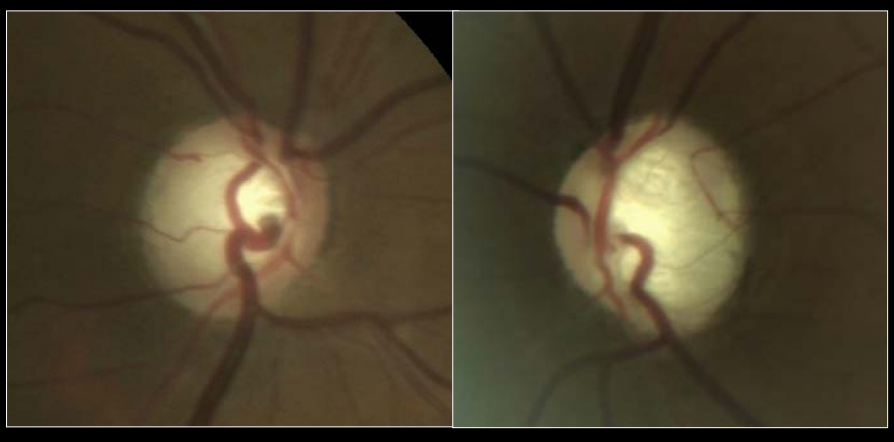


111

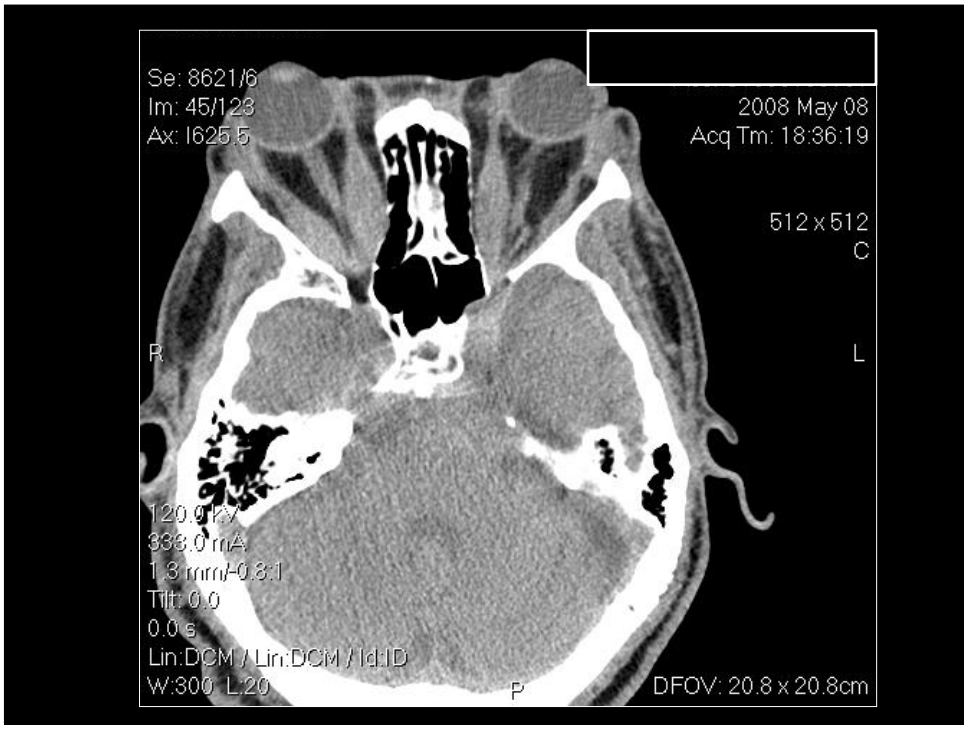
55 Y/O AA Man

- C/o progressive vision loss, OU x months
- Being treated for glaucoma
- BVA:
  - 20/60 OD
  - LP OS

112



113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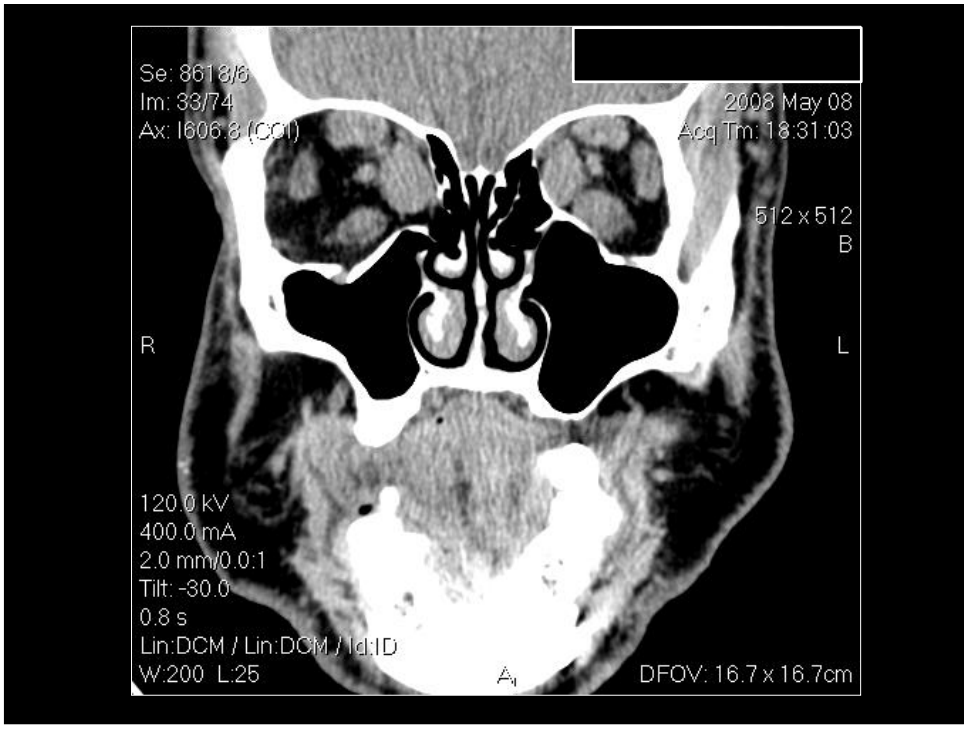
Im: 45/123
Ax: I625.5
2008 May 08
Acq Tm: 18:36:19
512 x 512
C
R
L
120.0 kV
333.0 mA
1.3 mm/-0.8:1
Tilt: 0.0
0.0 s
Lin:DCM / Lin:DCM / Id:ID
W:300 L:20
P
DFOV: 20.8 x 20.8cm

114


Se: 8618/6
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R
L
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400.0 mA
2.0 mm/0.0:1
Tilt: -30.0
0.8 s
Lin:DCM / Lin:DCM / Id:ID
W:200 L:25
A
DFOV: 16.7 x 16.7cm

115

Treatment of Thyroid Eye Disease

- Active disease:
  - Radiotherapy
  - Corticosteroids
  - Orbital decompression
  - Supportive therapy/ocular lubricants
  - Immunotherapy
- Chronic disease
  - Supportive therapy/ocular lubricants
  - Orbital decompression
  - Immunotherapy

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Immunotherapy

- Circulating *fibrocytes* become activated fibroblasts → orbital muscle & fat involvement
- Potential role for early immunotherapy
  - Rituximab (depletes CD20-positive B cells)
  - Teprotumumab (blocks orbital fibroblast IGF-1 receptors)

Bartelena L. Ophthal Plastics Reconstr Surg 2014
Smith TJ, et al. N Engl J Med 2017

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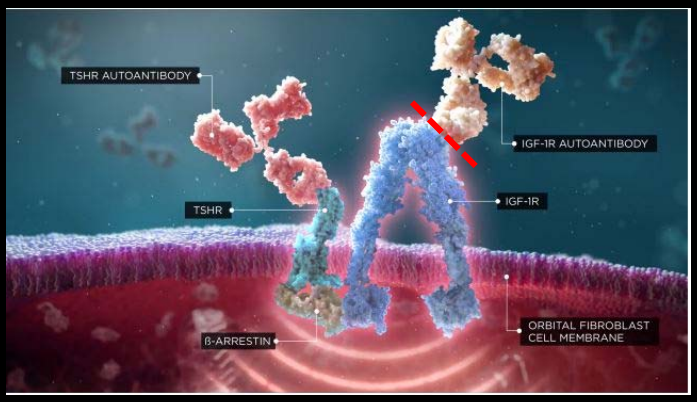
Teprotumumab (Tepezza®) for Active Thyroid Eye Disease

- Monoclonal antibody
- IGF-1R inhibitor
  - Blocks fibroblast IGF-1R/TSHR complex → inhibition of fibroblast activity
    - Reduction in extraocular muscular volume (reduction in proptosis and diplopia)
    - Reduction in orbital fat volume (reduction in proptosis)

MacDougald OA, et al. *Trends Endocrinol Metab* 2002
Chen J, et al. *Invest Ophthalmol Vis Sci* 2004
Douglas RS. *Eye* 2019
Patel A, et al. *Am J Ophthalmol* 2019

118



- IGF-1R linked to TSHR (β-arrestin) on orbital fibroblasts
- Blockage of IGF-1 ⟶ downregulation of TSHR & reduced fibroblastic activity
- Infusion therapy q 3 weeks X 8 sessions

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Teprotumumab for the Treatment of Active Thyroid Eye Disease

Raymond S. Douglas, M.D., Ph.D., George J. Kahaly, M.D., Ph.D., Amy Patel, M.D., Saba Sile, M.D., Elizabeth H.Z. Thompson, Ph.D., Renee Perdok, M.S., James C. Fleming, M.D., Brian T. Fowler, M.D., Claudio Marcocci, M.D., Michele Marinò, M.D., Alessandro Antonelli, M.D., Roger Dailey, M.D., et al.

- 24-week results of teprotumumab v. placebo
  - 83% v. 10% reduction in proptosis (p<0.0001)
    - Mean change in proptosis of -2.82 mm v. -0.54 mm
  - 59% v. 21% improvement in clinical activity/inflammation score (p<0.001)
  - 68% v. 29% improvement in diplopia (p<0.001)
  - 13.79 v. 4.43 improvement in GO-QOL score (p<0.001)

Douglas RS, et al. *N Engl J Med* 2020

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Results After 3 Infusions of Teprotumumab

Image and permission courtesy of Roger Dailey, MD, FACS.

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Side effects

- Muscle spasm (25%)
- Hearing loss (10%)
- Hyperglycemia (> 10%)
- Hair loss (>10%)
- Headache (>10%)
- Infusion site reactions (1-10%)

- Dysgeusia (10%)
- Fatigue (>10%)
- Xerostomia (1-10%)
- GI disturbance (>10%)
- Exacerbation of inflammatory bowel disease (frequ. not known)

- Most SEs transient
- Consult with endocrinology if pre-existing DM
- 5-7% flair-ups
- Contraindicated with pregnancy

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Supportive Therapy for TED

- Artificial tears / ointments
  - Lacrimal gland infiltration / dry eye
  - Exposure keratopathy
- Eyelid taping at bedtime
- Head elevation at bedtime
- Don't smoke!

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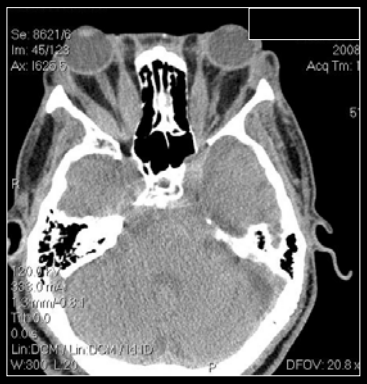
Surgery for TED: Sequence of Options

1. Orbital decompression
   - Correction of optic neuropathy/proptosis
   - Removal of bone & orbital fat
2. Strabismus surgery
   - Correction of ocular misalignment
3. Lid surgery
   - Correction of lid retraction / blepharoplasty



124

Risk Factors for TED

- Genetic factors:
  - 61% positive family history
- Environmental factors:
  - Cigarette smoking
    - 2X more likely to develop Graves' disease
    - 7.7X more likely to develop ophthalmopathy in patients with Graves'
  - Selenium Depletion
  - Stress

Krassas GE, et al. *Eur J Endocrinol* 2006
Kong JJ, et al. *Clin Endocrinol* 2014

126

What about management of underlying hyperthyroidism?

127

Systemic Treatment of Hyperthyroidism

- Anti-thyroid meds
  - Methimazole (Tapazole)
  - Carbimazole (Neomercazole)
  - Propylthiouracil (PTU)
- Radioactive iodine
- Thyroidectomy

Limited impact on orbitopathy

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Key Points

- Overview & pathophysiology of Graves' disease
- Ocular findings with thyroid eye disease
- Active vs. chronic disease
- Diagnostic studies
- Management

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Thanks!

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ILLINOIS COLLEGE OF OPTOMETRY

150 YEARS

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