Complete Bilateral External Ophthalmoplegia: OMG, a ‘Grave’ Diagnosis
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ABSTRACT
Initial complaints of diplopia, left retrobulbar pain, and intermittent left periorbital swelling prompt diagnosis of Graves Ophthalmopathy. Seven months later, ptosis, exotropia, and complete bilateral external ophthalmoplegia compound the situation, leading to diagnosis of concomitant Ocular Myasthenia Gravis.

INTRODUCTION
This patient presented to the West Roxbury VA Eye Clinic with disabling asymmetric ptosis, concern for corneal exposure, exotropia, and complete bilateral external ophthalmoplegia. This paper will discuss the complex relationship between Graves Ophthalmopathy (GO) and Ocular Myasthenia Gravis (OMG) and review the current literature on treatment for each condition in isolation. Since there is no standard protocol for managing concurrent GO and OMG, treatment is typically customized for each patient. Available supplements to this case include MRI and CT imaging, serial photos and video footage of the limited extraocular muscle motility, and video footage of forced ductions testing.

CASE HISTORY
- 45 year old male of French-Canadian descent
- No previous ocular history available
- Allergy: Penicillin
- Medical history: R shoulder dislocation and repair, diet controlled dyslipidemia, incidental finding of 1cm nodule abutting thymus in 2007
- Smoker 1ppd x 20 years, with a cigarette on and off now

PREVIOUS HISTORY
- Pt was seen intermittently between October 2011 and December 2011 with initial evaluation by Neurology and subsequent consults with Ophthalmology and Endocrinology. History of pt not showing for appointments, imaging, lab testing, etc. Pertinent findings include:
  - October 2011
    - CC: diplopia x 5 months with intermittent left eyelid swelling and pain
    - Findings: OD restricted upgaze, OS restricted upgaze and proptosis
    - Probable Dx: Graves ophthalmopathy with lab confirmation of subclinical hyperthyroidism (TSH low, T4 normal)
December 2011

- Findings: + lid lag, lagophthalmos OS>OD, inferior scleral show OS, + chemosis and injection OU, right hypo-exotropia, forced ductions resistant vertically OD and resistant 360 OS
- MRI from 09/2011 brought by pt from outside clinic showed no enlargement of extraocular muscles
- Plan: START Methimazole 5mg PO Qdaily

- Laboratory & Imaging:
  - Elevated AchR blocking antibodies (+58 with reference <15)
  - CT ordered with 2mm slices (completed July 19, 2012)
    - Diffuse enlargement of the bilateral EOMs with sparing of the right & left LR and SO and right MR. Mildly enlarged muscle body of left medial rectus. Mild proptosis, mild apical crowding.
    - “hypodense pituitary lesion, when could represent a microadenoma or small pituitary cyst”
  - DDx: TED, OMG, oculopharyngeal dystrophy, CPEO (low)

July 27th, 2012 Admitted to West Roxbury VA hospital by Neurology to monitor immunosuppressive therapy given history of cancelled appointments. Pt was seen by Neurology and Ophthalmology and was started on Methimazole @ 5mg BID PO and 500mg IV Solumedrol.

PERTINENT FINDINGS

7/30/12 West Roxbury VA EYE CLINIC

CC: diplopia when not wearing eye patch, eyelids blocking vision

Ocular medications: ointment 6x/day and QHS OU, artificial tears bedside

Systemic Medications: Methimazole 5mg BID, post 3 doses of 500mg IV Solumedrol

FHX: (+)thyroid complications → mother, sister, maternal ½ sister

---------------------------------------------------------------
1) ACETAMINOPHEN TAB 650MG PO Q6H PRN pain Please do not extend total daily dose of acetaminophen of >4 grams/day between acetaminophen and percocet tablets.
2) ACETAMINOPHEN/OXYCODONE TAB 1 TABLET PO Q6H PRN No not extend 1 gram of acetaminophen total. Please monitor acetaminophen use.
3) CARBOXYMETHYLCELLULOSE SODIUM SOLN,OPH 1 drop OU Q4H PRN Please have at bedside for patient to use PRN.
4) Docusate CAP,ORAL 100MG PO BID PRN
5) Heparin INJ,SOLN 5000UNT/1ML SC Q8H
6) Methimazole TAB 5MG PO BID
7) OPHTHALMIC LUBRICANT OINT,OPH THIN RIBBON OS 6X/DAY PRN dry eye, please use at night
8) SENNA TAB 17.2MG PO QHS
Entrance Testing

<table>
<thead>
<tr>
<th>VA sc:</th>
<th>OD 20/20- OS 20/30+, ph 20/20 holding lid up</th>
</tr>
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<tbody>
<tr>
<td>Visual Fields:</td>
<td>FTFC OD, OS</td>
</tr>
<tr>
<td>Pupils:</td>
<td>PERRL, -APD</td>
</tr>
<tr>
<td>EOM:</td>
<td>Complete external ophthalmoplegia R/L</td>
</tr>
<tr>
<td></td>
<td>No Bell’s Reflex R/L</td>
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<tr>
<td></td>
<td>No Convergence R/L</td>
</tr>
<tr>
<td>Color:</td>
<td>11/11 Ishihara OD and OS</td>
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</tbody>
</table>

Initial Visit to WX eye clinic 7/30/12

Up gaze

Right gaze

Left gaze

Down gaze

Additional Testing

<table>
<thead>
<tr>
<th>Krimsky:</th>
<th>14^BD and 25-30^ BI over OD, OS fixating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hertel:</td>
<td>Base 103, 23 / 27</td>
</tr>
<tr>
<td>Cranial Nerve Testing:</td>
<td>Slight hypoesthesia LV3</td>
</tr>
<tr>
<td>Ice Pack Testing:</td>
<td>No improvement in ptosis OD or OS</td>
</tr>
<tr>
<td></td>
<td>No dermopathy, Mild acropachy</td>
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Relevant Slit Lamp Examination Findings

| Lids OD/OS: | Palpebral Aperture: 7.0 / 5.5 mm
Inferior Scleral Show: 2.0 / 4.0 mm
MRD 1: -1.0 / -3.0 mm
No resistance to retropulsion OD and OS |
| --- | --- |
| Conjunctiva: | Injection of semilunar caruncle OU
1+ to 2+ inferior bulbar injection OS>OD
temporal chemosis OD |
| Cornea: | OD: few coarse SPK inferior
OS: inferior epithelial thinning and opacification with coarse SPK
(ANTERIOR SEGMENT PHOTOS AVAILABLE) |
| Intraocular Pressure: | OD: 12
OS: 16 |
| Posterior Segment: | OU: C/D 0.4 with flat, distinct margins, no pallor |

Chest CT Report:
“prevascular nodule representing either a focal thymic lesion or a single enlarged lymph node, unchanged in size since 2007”

Treatment: aggressive lubrication – see Treatment section for details

Systemic Treatment:
1) The IV pulsed steroids were followed by oral steroids with intention to taper: 100mg PO Qdaily x 1 wk, taper by 20mg per week until 10mg, then 5mg
2) Continue Methimazole @ 5mg BID

7/31/12 West Roxbury VA EYE CLINIC

| EOM: slight abduction OD, slight infraflection OD and OS |
| Forced ductions: No resistance in horizontal gazes, much more resistance infra and supraduction OD and OS |
| (VIDEO obtained) |
| Conjunctiva: 1+ to 2+ inferior injection OS>OD |
| Cornea: Less SPK OU |

Brain MRI Report:
1) “Persistent stigmata of thyroid related eye disease“: Proptosis, EOM diffuse enlargement with sparing of lateral recti
2) “4mm pituitary lesion with differential considerations incluing Rathke’s cleft cysts vs. pituitary microadenoma”

Systemic Treatment Modification: STARTED Mestinon (pyridostigmine) 30mg QID PO
Lab Results: Thyroid stimulating Immunoglobulin 274 (high)
8/1/12 West Roxbury VA INPATIENT WARD
- Pt noted upon waking, he could blink his eyes, feels like they are better.
- No bulbar conjunctival injection OD, 1+ inferior injection OS
- Slight OD abduction and adduction
- Systemic Treatment Modification: Mestinon increased to 30-60-30-60mg dosing

8/2/12 West Roxbury VA EYE CLINIC
- Blinking is better (VIDEO footage)
- OD has slight abduction
- Systemic Treatment Modification: Mestinon increased to 60mg QID
- Lab Results: low TSH, normal T4 free and total T3

8/3/12 DISCHARGED
- Continue Mestinon 60mg QID
- Continue Methimazole 5mg BID PO
- Continue with taper of oral steroids
- Continue with lubrication regimen

Final Lab Results:
- low TSH, normal T4
- AChR Binding Ab: 134, reference <0.30
- AchR Blocking Ab: 47, reference <15
DIFFERENTIAL DIAGNOSIS

Bilateral Exophthalmos

- Drug induced
- Inflammatory
- Injury
- Systemic thyroid disorder**
- Carotid cavernous sinus fistula
- Pseudotumor
- Cushing disease
- Obesity
- Idiopathic myositis and cellulitis
- Granulomatous disorders

Complete Bilateral External Ophthalmoplegia

- Guillian-Barre syndrome and its variants
- Midbrain infarction
- Myasthenia Gravis**
- Pituitary Apoplexy
- Metastasis
- Mucomycosis
- Botulism
- Phenytoin toxicity
- Trauma
- Wernicke’s encephalopathy

PRIMARY DIAGNOSES

- Graves Disease with Graves Ophthalmopathy
- Ocular Myasthenia Gravis with concern for Generalized Myasthenia Gravis
KB’s initial symptoms in October 2011 of five months of intermittent eyelid edema, left eye pain, and diplopia along with findings of OS>OD bilateral upgaze restriction, OS>OD bilateral exophthalmos, and laboratory tests consistent with subclinical hyperthyroidism pointed to an early diagnosis of Graves Disease (GD) and Graves Ophthalmopathy (GO). Graves Disease is an autoimmune condition that results in hypertrophy/hyperplasia of the thyroid and is associated with hyperthyroidism in 90% of patients. Ocular manifestations of Graves Disease, called Graves Ophthalmopathy, are the initial symptoms in 30-50% of patients and if CT or MRI imaging is obtained, 80% of patients have signs of GO. The CT scan in July 2012 revealed diffuse enlargement of the extraocular muscles including mild involvement of the left medial rectus and sparing of the lateral recti, superior obliques, and the right medial rectus (CT & MRI IMAGES available). Ocular involvement is due to a shared antigen between the extraocular muscles and the thyroid that results in proliferation of fibroblasts, expansion of adipose tissue, and secretion of glycosaminoglycans. Signs of GO include eyelid retraction with stare and lag, unilateral or bilateral exophthalmos, extraocular muscle restriction, and pain.

Upon initial presentation to the West Roxbury VA eye clinic in July 2012, KB had bilateral asymmetric ptosis OS>OD, complete bilateral external ophthalmoplegia, diplopia with exotropia, and bilateral orbicularis weakness. Our forced ductions testing revealed that ophthalmoplegia was not entirely due to a restrictive diagnosis. Both eyes were easily moved in lateral gazes, but were much more difficult to move in vertical gazes (VIDEO of forced duction testing). The discrepancy between forced ductions testing, ptosis, and exotropia increased our suspicion for Ocular Myasthenia Gravis (OMG). Myasthenia Gravis is an autoimmune disease against the acetylcholine receptor within the neuromuscular junction that results in fatigued weakness of the ocular, bulbar, limb, and respiratory systems that is worse in the afternoon or after exercise. The age distribution is bimodal with onset between 20-40 years old predominantly female, and between 50-70 years old predominantly male. 50% of patients initially present with ocular symptoms and 15% with thymoma. Of those patients with ocular symptoms, about 1/3 will remain solely with ocular myasthenia (OMG) and of the 2/3rds that progress onward, 94% will develop generalized myasthenia (GMG) within three years. The hallmark ocular signs of myasthenia are ptosis, Cogan’s lid twitch, orbicularis weakness, photophobia, and extraocular muscle weakness.

Diagnosis of MG was supported with the presence of acetylcholine receptor antibodies, which are a positive finding in 85% of generalized myasthenia and in 45-60% of patients with ocular myasthenia. Other possible diagnostic tests not performed on KB include: Tensilon
testing, single fiber electromyography, and repetitive nerve stimulation. Ice pack testing for one to two minutes can reveal a temporary improvement in ptosis, but is known to be less diagnostic in the setting of severe ophthalmoplegia. In addition, KB had discovered an interesting phenomenon. By rubbing his ptotic right upper eyelid closed for a few seconds then releasing it, the eyelid would temporarily retract!

The ability to distinguish between these two conditions is challenging because of the likely presence of both extraocular muscle dysfunction and eyelid abnormalities. Typically the inferior and medial recti are affected in GO resulting in esotropia, while in OMG any of the muscles can be affected. Note that exotropia in thyroid eye disease is rare. In addition, the retraction in Graves could mask the ptosis in myasthenia rendering the eyelids neutral in primary gaze.

So what came first, the chicken or the egg? In the literature, the concomitant conditions of Myasthenia Gravis and Graves Disease are discussed in case reports. Graves Disease occurs in 3-10% of patients with Myasthenia. Vice versa, Myasthenia Gravis occurs in only 0.14-0.2% of patients with thyroid eye disease. Therefore, it is much more likely that KB had Myasthenia first and developed Graves later than the other way around. That being said, the clinical presentation of patients in the literature does not reflect this probability. In patients with both conditions, findings of hyperthyroidism are the first sign in 54%, MG first in 37%, and simultaneously in 9% (3). KB is in the majority of patients in this respect as his clinical diagnosis of Graves preceded the diagnosis of Myasthenia, but it is far more likely that Graves developed after Myasthenia.

Marino et al investigated trends in patients with concurrent Myasthenia and one of three conditions: autoimmune thyroid disease (as in Graves Disease), non-autoimmune thyroid disease, or no thyroid disease. Comparisons of the three patient types were made with the following trends: 1) OMG was more frequent in autoimmune disease, 2) Severe generalized MG was more frequent in non-autoimmune or no thyroid disease, 3) patients with autoimmune thyroid disease and GO had a higher frequency of OMG than those without GO, 4) Thymic disease was less frequent in autoimmune thyroid disease. Based on these trends, KB is more likely to have OMG without GMG, but if it does progress it is less likely to be severe GMG.
TREATMENT AND MANAGEMENT

Treatment for GD is three-fold: encourage smoking cessation, correct thyroid dysfunction (although anti-thyroid therapy does not affect the course of GO), and treat for exposure keratopathy. After assessment of KB, treatment began with aggressive ocular lubrication. The left, more proptotic eye was of most concern because there were areas of inferior corneal thinning. We prescribed Lacrilube ointment for use at bedtime in both eyes and every two hours while awake in the left eye. Non-preserved artificial tears were placed at his bedside for use every hour while awake OU. We dispensed moisture chamber goggles for nighttime use as well as solar shield wrap-around sunglasses for outdoor protection. Within two days, we saw improvement in the degree of inferior bulbar conjunctival injection (PHOTOS) and less exposure keratopathy. The patient continued to use an eye patch to alleviate diplopia.

The treatment of GD was dictated by Endocrinology while the treatment of GO was managed by Ophthalmology and Optometry. KB’s subclinical hyperthyroidism was treated with 5mg BID Methimazole. As of his discharge, TSH levels were still low with normal total free T4. For the eye manifestations of Graves, three intravenous infusions of 500mg Methylprednisone were given over the initial 36 hours then discontinued. Oral prednisone 100mg PO daily for seven days was started with a 20mg taper per week down to 20mg then 10mg and finally 5mg. Liver function tests and glucose levels were monitored.

Treatment of Graves Disease in isolation typically begins with anti-thyroid therapy. Methimazole has a longer half-life, greater efficacy, and fewer side effects, such as rash, joint pain, inflammation, and agranulocytosis, than the alternatives. Improvement is usually seen in mild cases of disease within 3-4 weeks with remission in 30-50%. Radioiodine therapy is another treatment and the goal is to induce hypothyroidism, but without a short course of oral steroids it carries a 15% risk of worsening GO. A surgical thyroidectomy is also a consideration.

The recommendations for treatment of GO are outlined by consensus from the European Group on Graves Orbitopathy (EUGOGO). They dictate guidelines for classification of disease, appropriate initial referral and surgical referral, most appropriate time to start treatment, and recommended treatment for mild, moderate, and severe orbitopathy. In the moderate to severe disease state of KB, it was important to determine whether his disease process was active or inactive. A clinical activity scale of at least three of seven of the following indicates active disease: 1) spontaneous retrobulbar pain, 2) pain on attempted up or down gaze, 3) redness of the eyelids, 4) redness of the conjunctiva, 5) swelling of the eyelids, 6) inflammation of the caruncle and/or plica, 7) conjunctival edema. For moderate to severe active GO, the recommendation, after prior screening for liver dysfunction, hypertension, diabetes, and other systemic issues, is pulses of IV glucocorticoids 0.5g once weekly for 6
weeks, then 0.25g weekly for 6 weeks. KB exhibited at least 5 of 7 characteristics and was treated with three 500mg IV doses of Solumedrol. IV pulse treatment was more effective than high dose oral glucocorticoids, by 80% to 50% respectively. The total cumulative dose should not exceed 8g within one course of therapy due to possible liver toxicity. The recommendation for inactive GO is rehabilitation surgery such as extraocular muscle surgery or decompression. Following the initial dosing of IV Solumedrol, KB was placed on high dose oral Prednisone with a taper. In randomized and non-randomized trials for patients with GO, inter-pulse tapers of oral Prednisone did not increase the response rate. 82% responded to pulse treatment without the inter-pulse oral steroid taper vs. 68% with the pulse treatment and inter-pulse oral steroid taper. The protocol used in KB is a mix of both initial IV steroid pulse and oral steroid taper although it is not known whether the intention was to continue pulse therapy depending on his response. Keep in mind that the recommendations in the literature reviewed above are for the treatment of Graves only.

Treatment of the ocular symptoms of myasthenia includes management of ptosis with ocular lubrication and use of an eye patch, frosted lens, ground or Fresnel prism to eliminate diplopia. In KB’s case, Neurology dictated treatment for Myasthenia. There are no randomized trials for anti-acetylcholinesterase medications but they are used as first line monotherapy in mild cases. More commonly anti-acetylcholinesterase agents are used in addition to immunosuppressive therapy. Anti-acetylcholinesterase treatment with Mestinon (pyridostigmine) was begun four days after admission starting with a more conservative dosing of 30mg BID x 2 days that was increased to 60-30-60-30mg x 2 days, and the final dose upon discharge was 60mg QID. The onset of action is 15-30 minutes with peak therapy at 2 hours and effects lasting 3-4 hours. The ptosis from the myasthenia was protecting the cornea from exposure keratopathy, so a positive response to Mestinon might have resulted in further corneal exposure. However, following the Mestinon treatment, more of KB’s blink was restored and proved advantageous.

There is retrospective evidence suggesting that there is less likelihood of progression to GMG with glucocorticoid treatment. Naturally, the decision to use high dose glucocorticoids requires weighing the effect of treatment against the potentially severe side effects. In one study of 56 patients with ocular myasthenia, 27 were treated with prednisone and three went on to develop general myasthenia after 2 years. Of the 29 patients treated with only anti-acetylcholinesterase therapy, 10 patients developed generalized myasthenia after 2 years. Immunosuppressive treatment with glucocorticoids carries a risk of myasthenic crisis. Therefore, high dose steroid IV or oral treatment must be monitored closely, often in a hospital setting, in the beginning stages. Alternatives to glucocorticoid treatment include Azathioprine, Cyclosporine, and Mycophenolate. Plasmapheresis and IV immunoglobulin are expensive alternatives but are typically used only in cases of myasthenic crisis.
The literature contains case reports of concurrent Graves and Myasthenia where the majority of cases begin with treatment for thyroid conditions with later development of diplopia, ptosis, or other symptoms, which prompts a diagnosis of Myasthenia. In cases when Myasthenia was suspected, the Tensilon test was widely used in addition to clinical observations. The telling factors of Myasthenia include presence of exotropia and variance of upper eyelid position, which can mask both retraction and ptosis. There is no standard protocol for medical treatment of concurrent Graves and myasthenia and the therapies employed in the case reports varies greatly. In general, thyroid-stabilizing medication is warranted, followed by varying success with anti-acetylcholinesterase agents, followed by high dose oral steroids. There are no case reports that utilize IV pulse steroid therapy as suggested by EUGOGO consensus for GO. Treatment aims to improve symptoms and alleviate diplopia, but never alleviates all impairments. In one case of a 34yo male, prompt treatment resulted in marked improvement, which begs the question that if KB had presented at the onset of his symptoms and had been followed closely, would he have evolved such profound ophthalmoplegia?

Three hypotheses have been proposed as to why these two conditions are associated: 1) that OMG and GMG are separate diseases with different disease associations, 2) a shared antigen cross reacts between the eye muscles and thyroid, 3) a common genetic background is shared between OMG and GO and a more disparate background between OMG and GMG.

When these two conditions are found in the same patient, the most important factor is the ability to provide interdisciplinary care. In the case of KB, neurology, endocrinology, ophthalmology, and optometry were involved. Communication is crucial to timely and coordinated treatment in the best interest of the patient. Unfortunately KB does not have a very strong record of attending scheduled appointments, so despite the efforts of all involved, his prognosis may be guarded. Since discharge on August 3rd, KB has no-showed or cancelled and rescheduled all of his appointments.
CLINICAL PEARLS

1) Differentiating OMG from GO
   - Presence of ptosis
   - Exotropia
   - Pattern of variability in “fatigueable” ocular motilities
     i. Most significant in AM for GO because of orbital congestion
     ii. More significant in PM for OMG because of fatigue

2) Does a restrictive process account for all clinical signs?
   - Importance of forced ductions in consideration of other processes

3) Importance of Interdisciplinary Care & Communication
WORKS CITED


