Ocular and Neuro-ophthalmic Manifestations of Systemic Disease

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Neuro-ophthalmic Disease

- Relatively "new" compared to other subspecialties
  - Ancient Egyptians performed cataract surgery
  - Ancient Greeks developed salves for infections
  - Limited knowledge regarding eye movement and perception
    - 1820's: believed globe moved around a fixed point at posterior surface
    - 1880's: believed cerebral cortex had little, if any, role in perception
  - 1918: Sir Gordon Holmes mapped retina on the visual cortex
  - 1927: Harry Moss Traquair describes our visual field as "*an island of vision or hill of vision surrounded by a sea of blindness*"
  - 1947: Dr. Frank Walsh published textbook on neuro-ophthalmology

Diplopia

- *Diplous* (Greek for double) + *ops* (Greek for eye)
- Often the first manifestation of many systemic disorders, especially muscular or neurologic disease [1]
- Incidence in United States is unknown
- Eye hospital in London, UK reported the incidence of diplopia as the chief complaint in 1.4% of the presenting cases [2]
- Polyopia: the perception of more than 2 images
  - Often a monocular phenomenon due to refractive aberrations
  - Cerebral polyopia due to extrastriate visual cortex lesions

1. Rucker JC. Oculomotor disorders. *Semin Neurol.* 2007 Jul. 27(3):244-56.
2. Morris RJ. Double vision as a presenting symptom in an ophthalmic casualty department. *Eye (Lond).* 1991. 5 (Pt 1):124-9.

Sudden Vision Loss

- Incidence unknown due to variable presentations
- The most he most common cause of painless sudden visual loss is ischemia
- Other etiologies include infection, inflammation, trauma, compression
- Functional visual loss: decreased visual acuity or loss of visual field with no underlying physiologic or organic etiology
  - Accounts for up to 5% of referrals to eye care providers [1]
  - 79% are female and 21% are male [2]

1. Bose S, Kupersmith MJ. Neuro-ophthalmologic presentations of functional visual disorders. *Neurol Clin* 1995;13(2):321-3
2. Griffiths PG, Eddyshaw D. Medically unexplained visual loss in adult patients. *Eye.* 2004 Sep. 18(9):917-22.

Cilioretinal Artery Occlusion

- The cilioretinal artery was first described by Müller in 1856
- Congenital anomaly
- Belongs to posterior ciliary artery system, so it usually arises from the peripapillary choroid or directly from one of the short posterior ciliary arteries
- Found in 49.5% of all patients or in 32% of eyes, bilateral in 14.6%
- Cilioretinal Artery Occlusion is a distinct clinical entity because it does not arise from central retinal artery
  - Non-arteritic cilioretinal artery occlusion alone
  - Arteritic cilioretinal artery occlusion associated with giant cell arteritis
  - Non-arteritic cilioretinal artery occlusion associated with CRVO or HRVO

Justice J, Lehmann RP. Cilioretinal Arteries: A Study Based on Review of Stereo Fundus Photographs and Fluorescein Angiographic Findings. Arch Ophthalmol. 1976;94(8):1355-1358.

Acute Retinal Arterial Ischemia: An Emergency Often Ignored

- Retinal arterial ischemia is a form of anterior circulation ischemic stroke caused by decreased blood flow in the ophthalmic branches of the internal carotid artery
- Transient ischemic attack (TIA), including amaurosis fugax, is well known to be a prodromal syndrome of ischemic stroke
- Among patients with TIA 10% to 15% have stroke within 90 days, with approximately half occurring within 48 hours
- Patients with TIA who survive the initial high-risk period have a 10-year stroke risk of 19%, and a combined 10-year stroke, myocardial infarction or vascular death risk of 43% (4% per year)

Biousse V. Acute Retinal Arterial Ischemia: An Emergency Often Ignored. Am J Ophthalmol. 2014 Jun;157(6):1119-21.

Transient Ischemic Attack

- American Heart Association and National Stroke Association recommend all patients with presumed retinal ischemia (whether transient or permanent) undergo urgent brain imaging and etiologic testing similar to patients with cerebral ischemia
- Patients with abnormal diffusion-weighted MRI are diagnosed as having an acute stroke regardless of initial clinical presentation, and are admitted to the hospital and managed accordingly
- Patients with normal MRI results are evaluated within 24 hours in a dedicated TIA clinic, an emergency department observation unit, or a stroke center
- This is not routinely performed for patients with retinal ischemia in the United States!
  - Most are never sent to Emergency Room or a stroke neurologist for immediate evaluation
  - Most health professionals and public consider retinal TIAs benign with low risk of subsequent stroke
  - Time to treatment for retinal TIA: 48.5 days vs. for cerebral TIA: 15.2 days

Co-occurrence of Acute Retinal Artery Occlusion and Acute Ischemic Stroke

- Studied 33 consecutive patients with acute RAO who underwent diffusion weighted MRI within 7 days of the onset of symptoms
- Acute ischemic stroke detected in 24.2% of subjects with RAO
  - 37.5% of these had no neurologic signs or symptoms
  - Most infarction patterns were small, multiple and scattered
  - All had identifiable causes

Lee J, Kim SW, Lee SC, Kwon OW, Kim YD, Byeon SH. Co-occurrence of Acute Retinal Artery Occlusion and Acute Ischemic Stroke: Diffusion-weighted Magnetic Resonance Imaging Study. Am J Ophthalmol. 2014 Jun;157(6):1231-8.

Migraine Headaches

- Common cause of neuro-ophthalmic complaints
- Visual symptom most common
- Symptoms may also include photophobia, pupillary dilation and ophthalmoplegia

Clinical Pearls for Visual Aura

- Visual disturbances must be carefully evaluated
- Automated visual fields should be run to rule out neurologic defects
- When to consider neuroimaging:
  - Patient is over 45 years of age if there is no history of migraine headaches
  - All patients with significant change in character/frequency/duration of symptoms
  - Any non-classical symptoms or behavior of phenomenon

Giant Cell Arteritis

- Most common primary vasculitis in adults
  - Incidence in people over 50 is about 18 per 100,000 per year
  - Incidence increases with age and peaks in 8th decade of life
  - Highest prevalence in northern latitudes (Northern European descent)
  - Women 2 to 6 times more commonly affected than men
- Symptoms
  - Headache (most common)
  - Jaw claudication
  - Scalp tenderness
  - Vision loss (30 to 60% of patients)
  - Polymyalgia rheumatica present in 40%

1. Eberhardt RT, Dhadly M. Giant cell arteritis: diagnosis, management, and cardiovascular implications. Cardiol Rev. 2007;15:55–61.
2. Hunder GG. Epidemiology of giant cell arteritis. Cleve Clin J Med. 2002;69(Suppl 2):SII-79–SII-82.
3. Salvarani C, Cantini F, Bolardi L, Hunder GG. Polymyalgia rheumatica and giant-cell arteritis. N Engl J Med. 2002;347:261–271.

Giant Cell Arteritis

- Arteritic anterior ischemic optic neuropathy (AION)
  - Due to occlusion of the short posterior ciliary arteries
  - May also result from vasculitic ischemia of the choroid, the posterior optic nerve, or retina.
- 54% have initial visual acuity of finger counting or worse
- 50% of untreated individuals develop bilateral involvement days to weeks after presentation
- 44% report preceding episodes of transient vision loss
- 21.2% have visual complaints alone

1. Hayreh SS, Zimmerman B. Management of giant cell arteritis. Our 27-year clinical study: new light on old controversies. Ophthalmologica. 2003;217:239–259.
2. Birkhead NC, Wagener HP, Schick RM. Treatment of temporal arteritis with adrenal corticosteroids: results in 55 cases in which lesion was proven at biopsy. JAMA. 1958;163:821–827.
3. Gonzales-Gay MA, Blanco R, Rodriguez-Valverde V, et al. Permanent visual loss and cerebrovascular accidents in giant cell arteritis: predictors and response to treatment. Arthritis Rheum. 1998;41:1497–1504.
4. Hayreh SS, Podhajsky PA, Zimmerman B. Occult giant cell arteritis: ocular manifestations. Am J Ophthalmol. 1998;125:521–526.

Giant Cell Arteritis: Work Up and Diagnosis

- Suspect based on:
  - Patient history
  - Medical History
  - Clinical Examination
- Order lab work:
  - Complete blood cell count with differential
  - Erythrocyte sedimentation rate (ESR)
  - C-reactive protein (CRP)
- Order temporal artery biopsy
  - Diagnostic with 100% specificity
  - Relatively low sensitivity (15 to 40% false negative rate)

1. Bhatti MT, Tabendeh H. Giant cell arteritis: diagnosis and management. Curr Opin Ophthalmol 2001; 12:1217–20.
2. Burke A, Virmani R. Temporal artery biopsy of giant cell arteritis. Pathol Case Rev 2001; 6:265–73.

ESR and CRP

- In study looking at 119 patients with biopsy proven GCA:
  - ESR had a sensitivity of 86%
  - Elevated CRP had a sensitivity of 97.5%
  - Sensitivity of the ESR and CRP together was 99%
  - 1 of the 119 patients (0.8%) had normal ESR and normal CRP
  - 2 patients (1.7%) had elevated ESR and a normal CRP

Parikh M, Miller NR, Lee AG, Savino PJ, Vacarezza MN, Cornblath W, Eggenberger E, Antonio-Santos A, Golnik K, Kardon R, Wall M. Prevalence of a normal C-reactive protein with an elevated erythrocyte sedimentation rate in biopsy-proven giant cell arteritis. Ophthalmology. 2006 Oct;113(10):1842-5. Epub 2006 Aug 1.

Giant Cell Arteritis: Treatment

- Glucocorticosteroids are mainstay of treatment
- Initiated immediately and aggressively to suppress inflammation and preventing visual loss and ischemic stroke
- Route of administration debated (IV induction vs. PO only)
- Prednisone dosage varies widely in literature from 20 to 100 mg / day
  - Most patients respond to 40 to 60 mg / day
- Taper over 1 to 2 years

1. Salvarani C, Cantini F, Bolardi L, Hunder GG. Polymyalgia rheumatica and giant-cell arteritis. N Engl J Med. 2002;347:261–271.
2. Weyand CM, Goronzy JJ. Medium- and large-vessel vasculitis. N Engl J Med. 2003;349:160–169.

Giant Cell Arteritis: Treatment

- Over 50% have at least one relapse during taper
  - "smoldering" disease with persistent elevation of interleukin-6 levels
  - CRP and ESR can be within normal limits!
- Follow patients closely for at least one year after discontinuation of prednisone

1. Hayreh SS, Zimmerman B. Management of giant cell arteritis. Our 27-year clinical study: new light on old controversies. Ophthalmologica. 2003;217:239–259.
2. Weyand CM, Fulbright JW, Hunder GG, et al. Treatment of giant cell arteritis: Interleukin-6 as a biologic marker of disease activity. Arthritis Rheum. 2000;43:1041–1048.

Corticosteroids: Side Effects

- 58% of patients with GCA have at least 1 serious side effect
  - Acute myocardial infarction
  - Brain ischemia
  - Hypertensive crisis
  - Psychosis
  - Hyperosmolar decompensation of diabetes
  - Bone fractures
  - Impaired wound healing
- Arer there any other options?

Nesher G, Sonnenblick M, Friedlander Y. Analysis of steroid related complications and mortality in temporal arteritis: a 15-year survey of 43 patients. J Rheumatol. 1994;21:1283–1286.

Methotrexate

- Disease-modifying antirheumatic drug (DMARD)
- Chemotherapeutic Effect: competitively inhibits dihydrofolate reductase → inhibits synthesis of DNA, RNA and proteins
- Immunosuppressive Effect:
  - Inhibits enzymes involved in purine metabolism → accumulation of adenosine
  - Inhibits T cell activation
  - Suppresses intercellular adhesion molecule expression of T cells
  - Down regulates B cells
  - Increases CD95 sensitivity of activated T cells
  - Inhibits methyltransferase activity → deactivation of enzymes involved in immune system function
  - Inhibits binding of interleukin 1-beta to cell surface receptors

Methotrexate and Giant Cell Arteritis

- Up until recently, was most studied steroid-sparing agent
- 3 randomized placebo controlled trials compared methotrexate with placebo as adjunctive therapy with corticosteroids
  - Study methods criticized and contradictory results
  - 2 studies found no significant decrease in cumulative steroid dose or in relapse rate at 1 year among patients treated with corticosteroids and methotrexate compared with those treated with corticosteroids and placebo[1,2]
  - 1 study reported a significant decrease in cumulative steroid dose and relapse rate at 2 years among patients treated with adjuvant methotrexate compared with placebo[3]

1. Spiera RF, Mitnick HJ, Kupersmith M, et al. A prospective, double-blind, randomized, placebo controlled trial of methotrexate in the treatment of giant cell arteritis (GCA) Clin Exp Rheumatol.2001;19:495–501.
2. Hoffman GS, Cid MC, Hellmann DB, et al. for the International Network for the Study of Systemic Vasculitides (INSSYS) A multicenter, randomized, double-blind, placebo-controlled trial of adjuvant methotrexate treatment for giant cell arteritis. Arthritis Rheum. 2002;46:1309–1318.
3. Jover JA, Hernandez-Garcia C, Morado IC, et al. Combined treatment of giant-cell arteritis with methotrexate and prednisone: a randomized, double-blind, placebo-controlled trial. Ann Intern Med.2001;134:106–114.

Other Steroid-Sparing Options…

- Infliximab: monoclonal anti-TNF-α antibody
  - Theorized that there is abundance of the cytokine tumor necrosis factor-α (TNF-α) within giant cells, macrophages, and T cells
  - No significant benefit, trials discontinued[1]
- Azathioprine: immunosuppressant (transplants)
  - Small benefit over placebo after treatment for 1 year
  - High dropout rate (hepatotoxicity and carcinogenesis)[2]
- Cyclosporin A: immunosuppressant
  - No efficacy date provided by study
  - Poorly tolerated with high rate of premature termination[3]

1. Hoffman GS, Cid MC, Rendt-Zagar KE, et al. Infliximab for maintenance of glucocorticoid-induced remission of giant cell arteritis. Ann Intern Med. 2007;146:621–630.
2. Nuenninghoff DM, Matteson EL. The role of disease-modifying antirheumatic drugs in the treatment of giant cell arteritis. Clin Exp Rheumatol. 2003;21(6 Suppl 2):S29–S34.
3. Schaufelberger C, Hollby H, Bratt J, Nordborg E. No additional steroid-sparing effect of cyclosporine A in giant cell arteritis. Scand J Rheumatol. 2006;35:327–329.

IL-6 and Giant Cell Arteritis

- IL-6 is produced by macrophages (and other cells) within blood vessel wall of temporal arteries
- IL-6 is upregulated within inflamed arteries and in peripheral circulation
- Serum IL-6 levels mirror disease activity and decline with effective glucocorticoid therapy
- Pharmacologic inhibition of IL-6 system can ameliorate vascular inflammation

Tocilizumab (Actemra®)

- Humanized interleukin-6 receptor antagonist
- Interleukin-6 triggers synthesis of acute phase proteins, promotes the transition from acute-to-chronic inflammation and facilitates the development of specific immunity
  - Modulates activation, proliferation and differentiation of different T-cell subsets including CD8, Th17 and regulatory T cells
  - Stimulates terminal differentiation of B cells
  - Enhances the survival of plasma cells
  - Induces 'proinflammatory' phenotype in monocytes, endothelial cells and stromal cells
- FDA approved for adult patients with moderately to severely active rheumatoid arthritis who have used one or more disease modifying antirheumatic drugs without adequate relief
- May 2017: FDA approved for treatment of giant cell arteritis

Tocilizumab for Patients With Giant Cell Arteritis

- A Phase II, Randomized, Double-blind, Placebo Controlled Study of Tocilizumab in Patients with Giant Cell Arteritis
- Compared tocilizumab (8mg/kg every 4 weeks x 52 weeks) + prednisolone to placebo + prednisone
- 85% of subjects given tocilizumab vs. 40% given placebo reached complete remission by week 12
- Relapse-free survival was achieved in 85% in the tocilizumab group vs. 20% in the placebo group by week 52
- Cumulative prednisolone dose of 43 mg/kg in the tocilizumab group vs. 110 mg/kg in the placebo group after 52 weeks
- **IL-6 blockade is first treatment confirmed to be effective in GCA since cortisone was invented in 1948**

Villiger PM, Adler S, Kuchen S, Wermelinger F, Dan D, Fiege V, Bütidofer L, Seitz M, Reichenbach S. Tocilizumab for induction and maintenance of remission in giant cell arteritis: a phase 2 ramomised, double-blind, placebo-controlled trial. Lancet. 2016 May 7;387(10031):1921-7.

Standardized Prednisone-Taper Protocols: GiACTA

Daily Prednisone Dosage
- Week 1: 60 mg
- Week 2: 50 mg
- Week 3: 40 mg
- Week 4: 35 mg
- Week 5: 30 mg
- Week 6: 25 mg
- Week 7: 20 mg
- Week 8: 15 mg
- Weeks 9-10: 12.5 mg
- Week 11: 10 mg

Daily Prednisone Dosage
- Week 12: 9 mg
- Week 13: 8 mg
- Week 14: 7 mg
- Weeks 15-16: 6 mg
- Weeks 17-18: 5 mg
- Weeks 19-20: 4 mg
- Weeks 21-22: 3 mg
- Weeks 23-24: 2 mg
- Weeks 25-26: 1 mg
- Weeks 27-52: placebo

Study of RoActemra/Actemra (Tocilizumab) in Patients With Giant Cell Arteritis (GiACTA)

- Phase III, double blind, randomized, controlled trial
- 251 patients from 76 sites across 14 countries
- Results show tocilizumab + six month steroid regimen more effectively sustained remission through one year compared to a six or 12-month steroid only regimen
- October 4, 2016: The US Food and Drug and Administration granted Breakthrough Therapy Designation status for treatment of multiple autoimmune disease
- May 22, 2017: FDA approval announced

FDA grants breakthrough therapy designation for Genentech's Actemra (tocilizumab) in giant cell arthritis, a form of vasculitis [news release]. http://www.businesswire.com/news/home/20161004006731/en/FDA-Grants-Breakthrough-Therapy-Designation-Genentech; Published October 5, 2016. Accessed October 5, 2016.

Doxycycline Induced Intracranial Hypertension

- Increased intracranial pressure associated with drugs including tetracycline, minocycline and doxycycline
- Proposed mechanism: Drug affects cyclic adenosine monophosphate at the arachnoid granulations which interferes with the energy dependent absorption
- Time to develop intracranial hypertension is unknown
  - In largest review of intracranial hypertension induced by minocycline, time of onset ranged from 2 weeks to 1 year
- Raised intracranial pressure persists for 2 to 5 weeks after discontinuing tetracycline

Chiu AM, Chuenkongkaew WL, Cornblath WT, Trobe JD, Digre KB, Dotan SA, Musson KH, Eggenberger ER. Minocycline treatment and pseudotumor cerebri syndrome. Am J Ophthalmol.1998;126:116–121.

Intracranial Hypertension: Signs and Symptoms

- Asymptomatic
- Headaches (99%)
- Transient vision loss
- Diplopia
- Tinnitus
- Nausea
- Normal to decreased visual acuity, color vision and contrast sensitivity
- Papilledema
- No spontaneous venous pulsation
- Visual field defects

Medication Induced Intracranial Hypertension

- Vitamin A toxicity
- Tetracycline
- Oral contraceptives
- Nalidixic acid
- Lithium
- Steroid use / withdrawal

Oral Contraceptives

- Pseudotumor cerebri
  - Exact mechanism uknown
  - Some case-control studies show no association[1,2]
  - Why predominantly in obese women of childbearing age?
    - Female sex hormones + endocrinologically active adipose tissue lead to the syndrome in genetically predisposed individuals[3]
    - Retinoic acid (which has been linked to pseudotumor cerebri) influenced by both estrogen and adipose tissue.[3]
- Sinus venous thrombosis

1. Giuseffi V, Wall M, Siegel PZ, Rojas PB. Symptoms and disease associations in idiopathic intracranial hypertension (pseudotumor cerebri): a case-control study. Neurology.1991;41:239–244.
2. Ireland B, Corbett JJ, Wallace RB. The search for causes of idiopathic intracranial hypertension. A preliminary case-control study. Arch Neurol. 1990;47:315–320.
3. McGeeney BE, Friedman DI. Pseudotumor Cerebri Pathophysiology. Headache. 2014 Jan 16. doi: 10.1111/head.12291. [Epub ahead of print]

Optic Nerve Sheath Meningioma

- Benign
- 20% of all orbital meningiomas, 30% of all optic nerve neoplasms
- Arise from arachnoid cap cells of the optic nerve sheath
- May be direct extension from intracranial meningioma
- Mean age at presentation: 40 years old
- 25% of all ONSM found in children, worse prognosis
- Three times more common in women
- Increased risk in patient with neurofibromatosis type II
- Treatment: observation vs. radiation therapy
- Surgical intervention not recommended

Pituitary Adenoma

- Pituitary adenomas are benign, slow growing tumors
- Comprise 10-15% of all intracranial tumors
- Classified as micro < 1 cm or macro > 1 cm
- Secretory vs. nonsecretory
- Nonsecretory more likely to have visual effects, in addition to causing hypopituitarism. Also may compress other nearby neurologic structures.
- Secretory are functioning tumors, symptoms depend on hormone secreted

Pituitary Adenoma

- Pituitary gland anterior lobe secretes 6 hormones:
  - thyroid-stimulating hormone (TSH)
  - adrenocorticotropic hormone (ACTH)
  - follicle-stimulating hormone (FSH)
  - luteinizing hormone (LH)
  - growth hormone (GH)
  - prolactin (PRL)
- Posterior pituitary gland secretes vasopressin and oxytocin
- Most tumors arise from anterior lobe increasing in size creating both systemic & visual effects (due to impingement on anterior notch of chiasm)
- Tumor growth can be asymmetric; therefore, visual field loss asymmetric

Orbital Pseudotumor

- Second most common inflammatory process of orbit (5-10% of orbital processes)
  - Orbital pseudotumor
    - Female:male ration 1:1
    - Mean age 45
    - 97% unilateral (except pediatrics)
  - Idiopathic orbital myositis
    - Female:male ratio 2:1
    - Mean age 37
    - 50% bilateral
- Signs include diplopia, proptosis, conjunctival injection, chemosis, periorbital edema, ptosis
- Cardinal sign is worsening pain with eye movement
- Visual function usually normal in orbital myositis
- Visual function may be decreased due to compressive optic neuropathy

Orbital Pseudotumor

- Pathogenesis unknown; however, likely immunologic
- Orbital myositis has been associated with systemic lupus erythematosus, rheumatoid arthritis and Crohn's disease
- May spontaneously resolve after 3 to 6 weeks
- Treatment recommended to relieve pain, diplopia, limit muscle fibrosis and prevent recurrences
- Dramatic improvement after 3 days of systemic steroids

Myasthenia Gravis

- Autoimmune disease
- Antibodies block acetylcholine receptors at neuromuscular junction
- Ocular involvement with myasthenia gravis
  - 70% initially present with ocular signs
  - 90% of all show ocular signs
- Ocular signs:
  - 10% ptosis only
  - 90% ptosis and extraocular muscle weakness

Ocular Mysthenia Gravis

- 50 to 80% progress to general myasthenia gravis
- 10 to 20% have spontaneous remission
- Younger patients = better prognosis

Work Up

- Tensilon test
  - Watch false positives!
  - Low sensitivity (60%)
- Electromyography
- Blood work
  - Ach antibodies
  - Thyroid panel
  - ANA
  - DM
- Mediastinal imaging
  - 70% have thymic hyperplasia
  - 5 to 20% have thymoma

Clinical Tests

- Sleep Test
  - Complete ocular examination and external photographs
  - Patient then rests in darkened room and encouraged to sleep
  - After 30 minutes patient is awakened and immediately photographed
  - Measure palpebral fissures, ocular alignment and motility
  - Improvement lasts two to five minutes
- Ice Test
  - Lower temperature reduces action of acetylcholinesterase
  - Measure palpebral fissures
  - The patient is instructed to close eyes for two minutes, then palpebral fissures are assessed again
  - Ice pack applied to closed eye(s) for two minutes, then the size of the palpebral fissure is immediately assessed
  - Test is positive if the size of the fissure is greater after cooling than after rest
  - MG patients usually exhibit 2 mm or more increase
  - **90% sensitive and 100% specific for MG**

Treatment

- Pharmacologic:
  - Anti-acetylcholinesterase agents
  - Immunosuppressive agents
- Thymectomy
- Plasmapheresis

Soliris (eculizumab)

- Humanized monoclonal antibody
- Approved for AChR Ab positive patients with generalized myasthenia gravis
- Intravenous infusion once a week x 5 weeks, then every 2 weeks
- Binds to C5 complement protein → inhibits the activation of terminal complement → protects the neuromuscular junction from the destructive effects of antibody-mediated complement activation
- Well tolerated, most common side effect headache

Howard JF, Utsugisawa K, Benatar M, et al. Safety and efficacy of eculizumab in anti-acetylcholine receptor antibody-positive refractory generalised myasthenia gravis (REGAIN): a phase 3, randomised, double-blind, placebo-controlled, multicentre study. *Lancet Neurol.* 2017.

Graves' Disease

- Autoimmune disease
- Thyroid-stimulating immunoglobulins (TSIs) bind to and activate thyrotropin receptors → thyroid gland to grow and increases synthesis of thyroid hormone
- B and T lymphocyte-mediated autoimmunity directed at thyroglobulin, thyroid peroxidase, sodium-iodide symporter and the thyrotropin receptor

Graves' Ophthalmopathy

- Two clinical phases:
  - Inflammatory - deposition of glycosaminoglycan in the extraocular muscles
  - Fibrotic

Graves' Disease - Treatment

- Anti-thyroid medications to reduce production or hormones
  - Methimazole
  - Propylthiouracil
- Beta-blockers decrease the effect of the hormones
- Radioactive iodine
  - Caution with thyroid eye disease
- Thyroidectomy

Graves' Orbitopathy – New Treatment

- Teprotumumab: fully human monoclonal antibody that inhibits insulin-like growth factor type 1 receptor
- Treatment of Graves' Orbitopathy to Reduce Proptosis with Teprotumumab Infusions in a Randomized, Placebo-Controlled, Clinical (OPTIC) study
  - Received 8 intravenous infusions every three weeks for 21 weeks
  - First injection was 10 mg/kg followed by 20mg/kg for the remaining 7 infusions
  - Endpoint: 2mm or more reduction in proptosis
  - 82.9% of patients receiving teprotumumab vs. 9.5% in the placebo group achieved endpoint
- December 13, 2019: The Dermatologic and Ophthalmic Drugs Advisory Committee (DODAC) of the FDA voted unanimously that the potential benefits of teprotumumab outweigh the potential risks for the treatment of thyroid eye disease

Hearing Loss and Teprotumumab

- 10% of patients in phase 2 and 3 studies experienced hearing loss
- Symptoms reversed when drug discontinued
- Study published in the Journal of the Endocrine Society
  - Charts reviewed of patient's receiving at least 4 infusions
  - Patients with hearing symptoms were referred for audiogram testing and patulous eustachian tube (PET) testing
  - 28 patients in analysis, 13 (46%) complained of hearing symptoms
  - Autophony, ear plugging sensation, hearing loss or muffled hearing most common
  - Hearing symptoms developed after a mean of 3.6 infusions
  - 3 patients (23%) had sensorineural hearing loss documented on audiogram or patulous eustachian tube documented on PET testing
    - 1 patient has had some improvement, then other 2 had no significant improvement 3 months after discontinuing the medication

Kossler A, Sears CM, Dosiou C. Hearing Loss and Teprotumumab. *J Endocr Soc*. 2021;5(Suppl 1):A839. Published 2021 May 3. doi:10.1210/jendso/bvab048.1713

Recommendations

- Consider performing a baseline audiogram with PET testing
- Perform audiograms with PET testing for patients that develop hearing symptoms during or after therapy
- Hearing loss is a concerning adverse event and its mechanism and reversibility should be further studied

Abducens Nerve Palsy

- Complicated:
  - Brainstem
  - Subarachnoid
  - Middle cranial fossa
  - Cavernous sinus
  - Orbital
- Isolated:
  - Pediatrics
  - Young adults
  - > 50 years old

Sarcoidosis

- Abnormal collection of inflammatory cells (granulomas)
- 5-10% of those with sarcoidosis develop central nervous system involvement
  - Of those, 50-70% have abnormalities of cranial nerves
  - CN VII most commonly affected, has best prognosis
- 1% of those will have neurosarcoidosis alone without involvement of any other organs
- Seizures present in 15% of cases
- 10% mortality

Thank You!

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