

Grand Rounds

A Tale of Two Zosters



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August 23, 2019

Patient Presentation

CC

2 week history of blurry vision, periorbital edema, scabbing rash

HPI

77 yo M with history of V1 dermatomal vesicular rash, admitted after a fall and found to have GI bleed and supratherapeutic INR, presenting to ophthalmology with vision loss OS, ophthalmoplegia x several days OS



History (Hx)

Past Ocular Hx – None

Past Medical Hx – Atrial Flutter, seizure disorder, HTN, HLD

Fam Hx – Non-contributory

Meds – Coumadin, Lisinopril, Atorvastatin, Furosemide, Phenytoin, Metoprolol

Allergies –None

Social Hx –Remote history of alcohol/tobacco use. Lives with family

ROS – Negative except inability to open L eye



External Exam

	OD		OS
VA	20/30		20/70
Pupils	4→3mm		5 mm, minimally reactive, trace rAPD
IOP	16 mmHg		23 mmHg
EOM	full		-3 in all gazes
CVF	full		full



Anterior Segment Exam

PLE or SLE	OD		OS
External/Lids	WNL		Scabbed vesicular rash on L forehead, extending to tip of nose not extending past midline Complete ptosis of LUL with LUL edema, erythema
Conj/Sclera	WNL		Chemosis, worse inferiorly, subconj heme
Cornea	Clear		Few dendritic staining lesions
Ant Chamber	Formed		Formed
Iris	Flat		Flat
Lens	NS		NS



Posterior Segment Exam

Fundus	OD		OS
Optic Nerve	Pink and sharp, no edema		Pink and sharp, no edema
Macula	WNL		WNL
Vessels	Normal caliber		Normal, no vasculitis
Periphery	WNL		No retinitis



External Exam – Day 2



External Exam – Day 2



Exam

- Over several days vision progressed to count fingers OS with complete ophthalmoplegia
- Stat MRI Brain/Orbits ordered
 - No cavernous sinus lesion, no sinus disease
 - Diffuse hyper-enhancement within retro-orbital intraconal fat, diffuse hyper-enhancement of left EOMs
 - Enhancement of L optic nerve sheath posterior to globe
 - Pachymeningeal enhancement over lateral left frontotemporal convexity concerning for intracranial extension



Plan

- Continued on broad spectrum IV antibiotics while inpatient
- Started IV Solumedrol 250 mg Q6H
- Completed 14 day course of acyclovir, discharged on PO doxycycline and augmentin per ID
- Discharged on oral prednisone 80 mg with slow taper over 2 months
- No improvement in exam prior to discharge



Patient Presentation #2

CC

Left eye pain

HPI

91 yo M with 3 week history of vesicular rash on L forehead, seen at OSH 3 weeks prior and treated with oral acyclovir, now presenting to PCC with worsening left eye pain, ptosis, periorbital edema



History (Hx)

Past Ocular Hx – History of cataract surgery

Past Medical Hx – AFib, HTN, Pacemaker

Fam Hx – Non-contributory

Meds – Aspirin, Diltiazem, Mirtazapine, Gabapentin

Allergies – Norco, Sulfa, Ampicillin, Contrast

Social Hx – Lives in nursing home

ROS – Negative except as above



External Exam

	OD		OS
VA	20/20		CF at <2 feet
Pupils	4→3mm	No RAPD	4→3mm
IOP	12 mmHg		11 mmHg
EOM	full		-4 in ADduction, elevation, depression, -2 in ABduction
CVF	full		Unable



Anterior Segment Exam

PLE or SLE	OD		OS
External/Lids	WNL		Healing vesicular rash on L forehead, extending to tip of nose not extending past midline Complete ptosis of LUL with LUL edema, erythema
Conj/Sclera	WNL		Chemosis, 2+ injection
Cornea	Clear		Descemet folds, microcystic edema
Ant Chamber	Deep and quiet		2+ Cell, 2+ Flare
Iris	Flat		Flat
Lens	PCIOL, clear		PCIOL, clear



Posterior Segment Exam

Fundus	OD		OS
Optic Nerve	Pink and sharp, no edema		Hazy view, no obvious disc edema
Macula	WNL		WNL
Vessels	WNL		No vasculitis
Periphery	WNL		No evidence of retinitis, necrosis

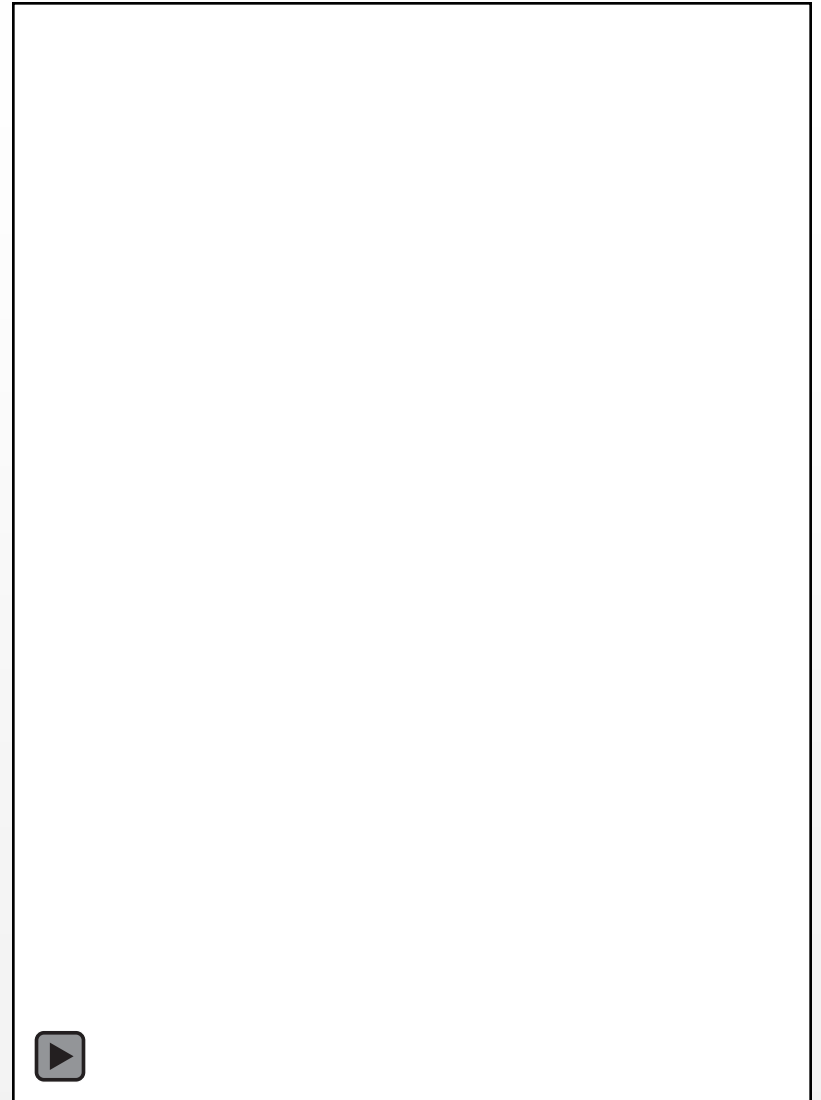


Exam

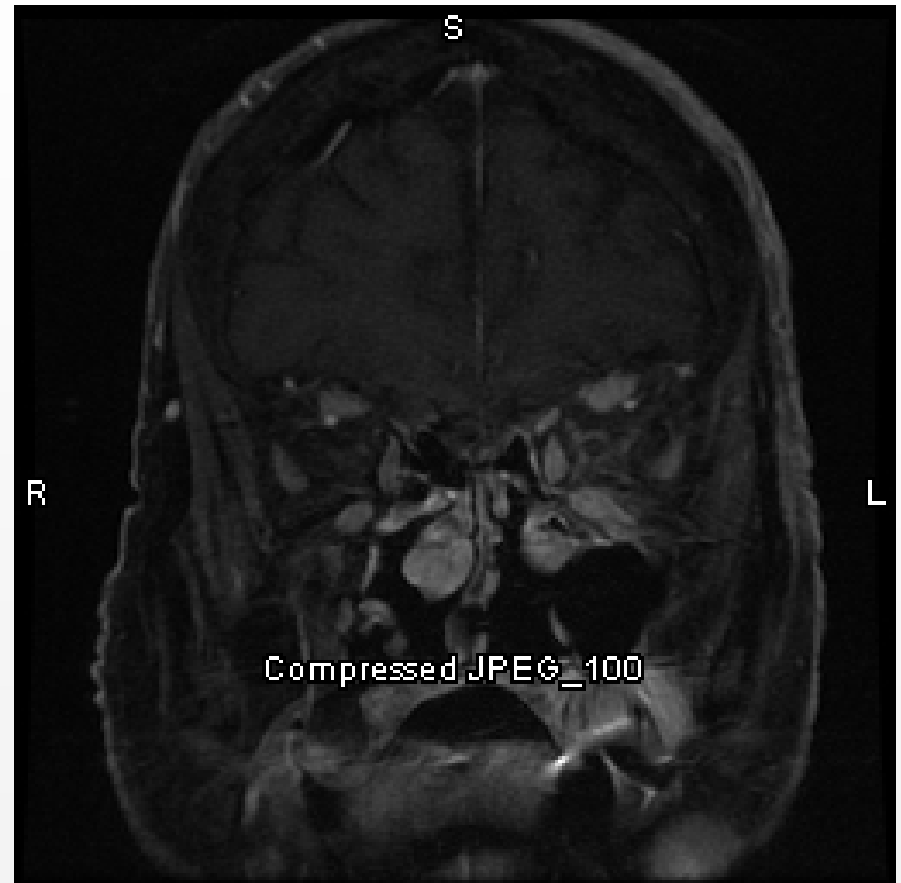
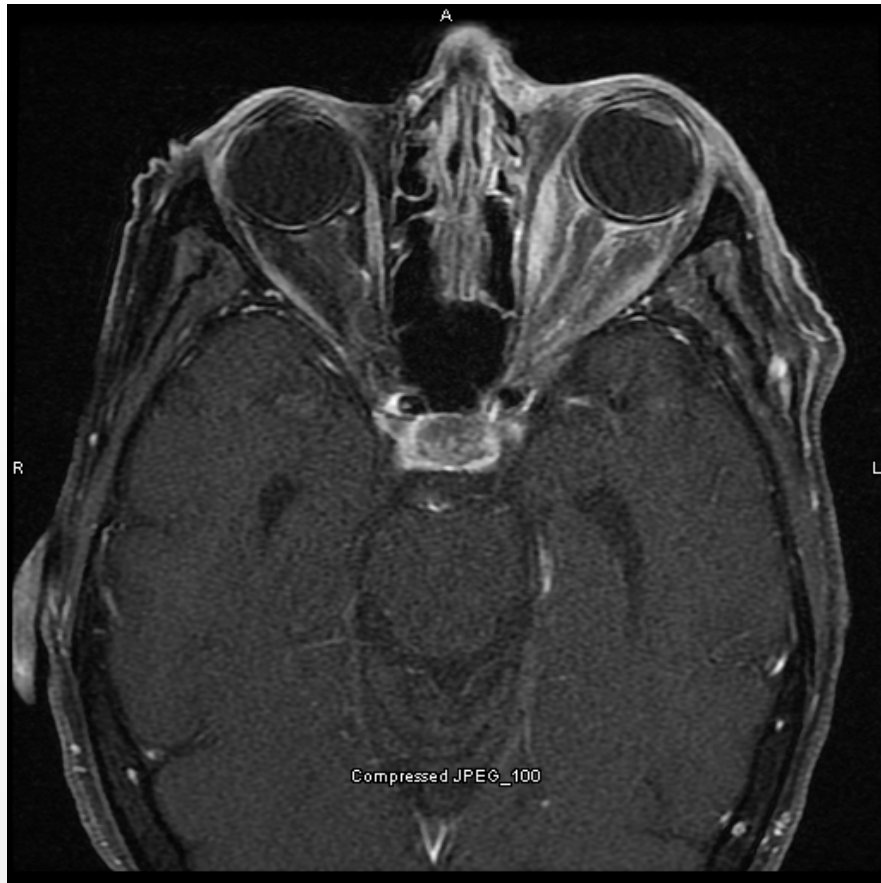
- Patient started on atropine QD OS, Pred Forte QID OS for keratouveitis
- Sent directly to Jewish Hospital for admission for IV acyclovir and imaging



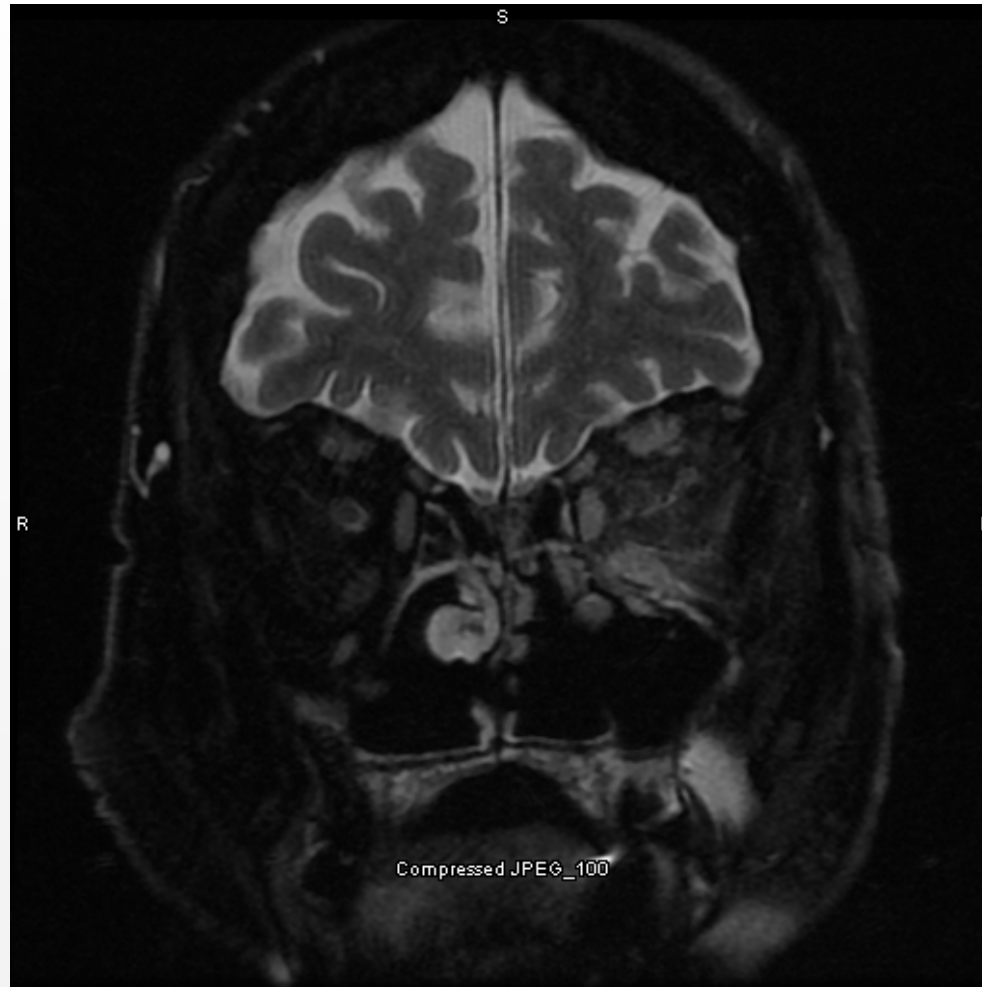
Exam



MRI Images



MRI Images



Assessment

- **Differential Diagnosis**
 - Orbital apex syndrome (OAS) secondary to Herpes Zoster Ophthalmicus
 - OAS secondary to bacterial/fungal infection
- Both patients diagnosed with orbital apex syndrome secondary to herpes zoster ophthalmicus, no evidence of secondary bacterial infection



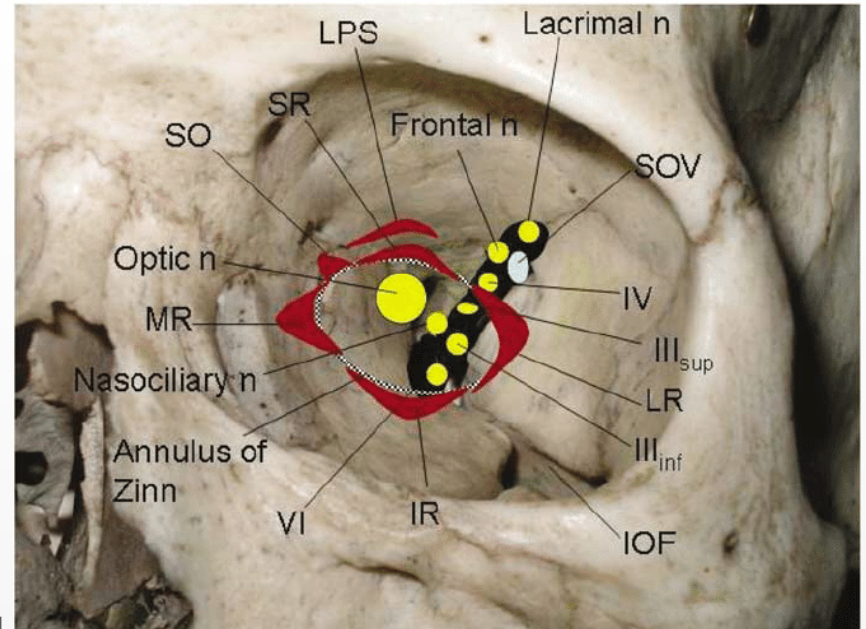
Plan – Patient #2

- IV acyclovir 1000 mg daily while inpatient, transitioned to PO to complete 2 week course
- Started on IV Solumedrol 250 mg Q6H while inpatient x 5 days
- Transitioned to 80 mg PO prednisone daily with slow taper to complete 2 month course
- Followed up in clinic two days ago with mild improvement in EOMs, no visual improvement



Discussion

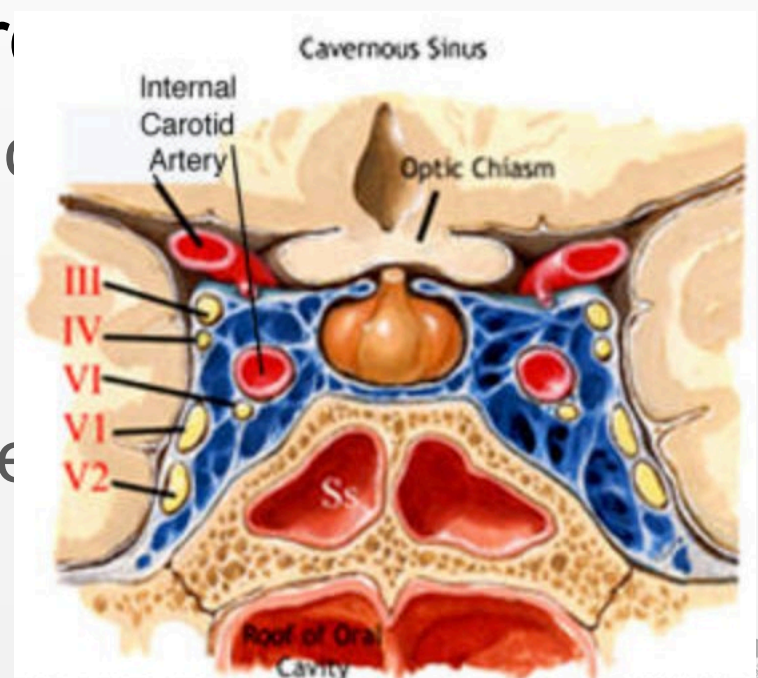
- **Orbital Apex Syndrome**
 - Vision loss
 - Paralysis
 - CN III
 - CN IV
 - CN VI
 - ophthalmic branch of V1
 - Periorbital and facial pain
 - Hypoesthesia of forehead
 - Chemosis/conjunctival injection



https://www.researchgate.net/figure/Anatomy-of-the-left-orbital-apex-highlighting-the-extraocular-muscle-origins-and-the_fig7_6776472

Similar Entities

- Superior Orbital Fissure Syndrome
 - Cranial nerve deficits including III, IV, V, VI
 - More anterior to apex, no optic nerve involvement
- Cavernous Sinus Syndrome
 - Multiple CN deficits that include III, IV, V, VI
 - Horner's
 - No optic nerve involvement



Discussion

- Etiology
 - Inflammatory
 - Sarcoidosis, SLE, GPA, Tolosa-Hunt, GCA, Orbital Pseudotumor, TED
 - Infectious
 - Bacterial orbital cellulitis
 - Fungal (mucor/aspergillus most common)
 - **Viral – Herpes Zoster**
 - Neoplastic
 - Head/neck tumors, neural tumors, metastasis, hematologic
 - Iatrogenic/Traumatic
 - Displaced bony fragments, shearing forces
 - Vascular
 - CC fistula, thrombosis
 - Other
 - Mucocele



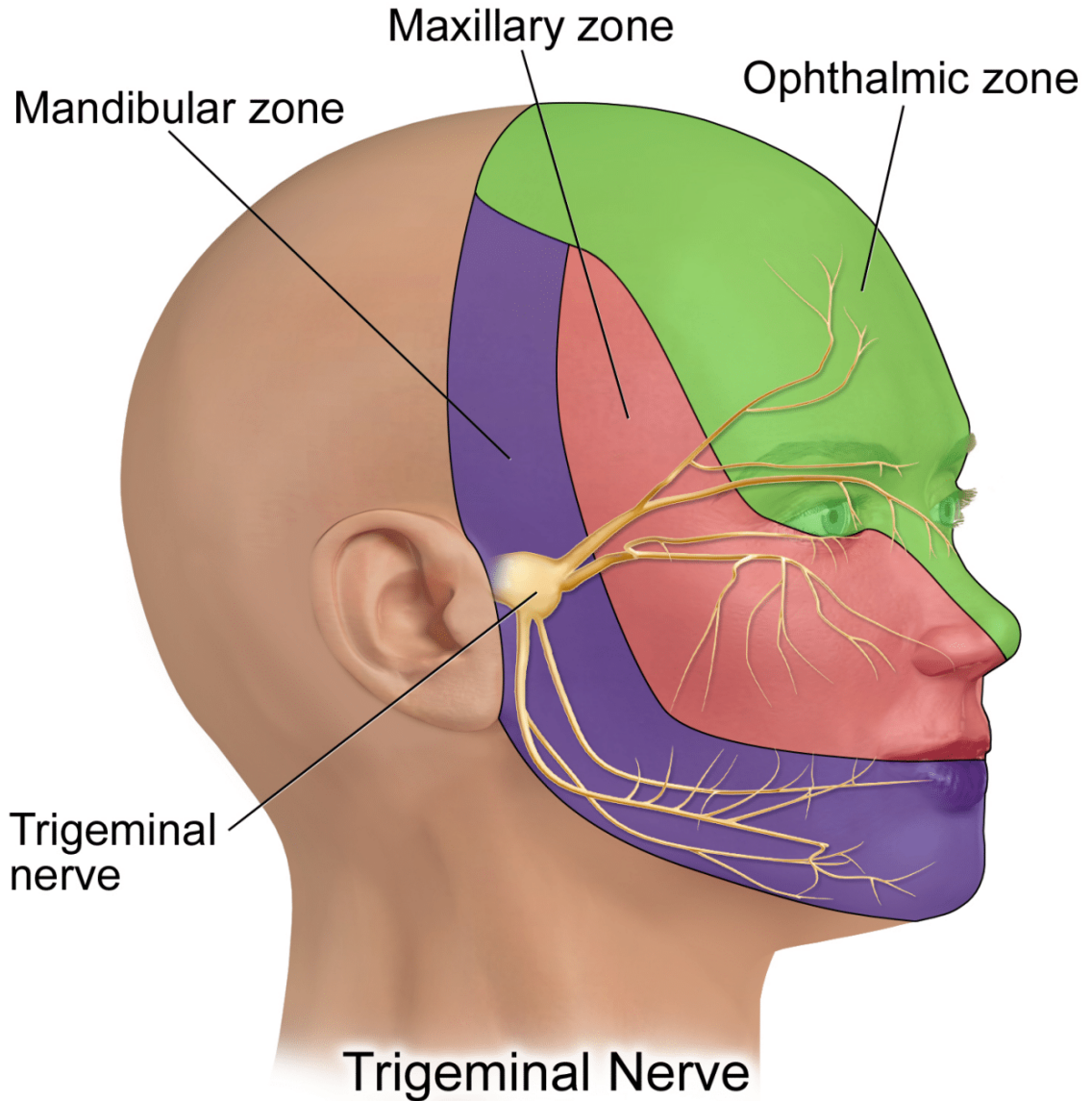
Herpes Zoster Ophthalmicus

- Varicella Zoster Virus (VZV)
- Reactivation of latent infection from dorsal root of sensory neurons
- Herpes Zoster Ophthalmicus – when reactivation occurs in V1
 - 10-25% of all Herpes Zoster cases
- Erythematous rash with papules, vesicles, pustules
- Risk for reactivation: Immunocompromised, diabetic, elderly



Herpes Zoster and OAS

- 20-70% of blepharitis, scleritis, acute
- Hutchinson
 - Predictor of
 - Specific to
- Orbital apex first described



Mechanism

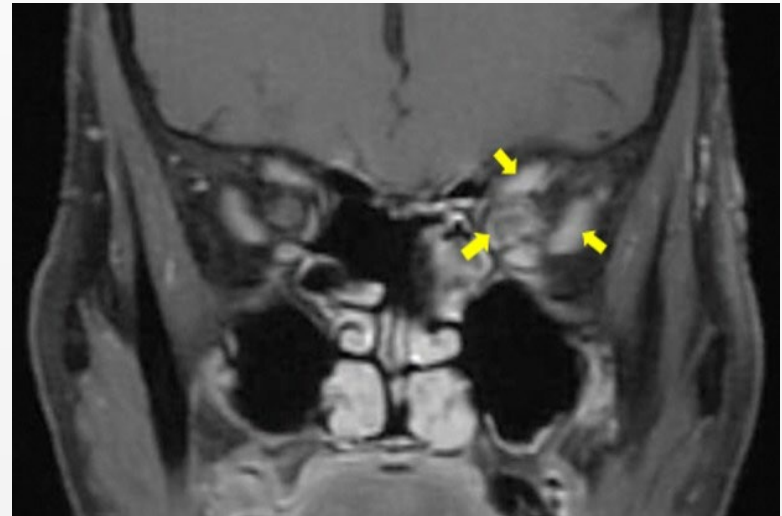
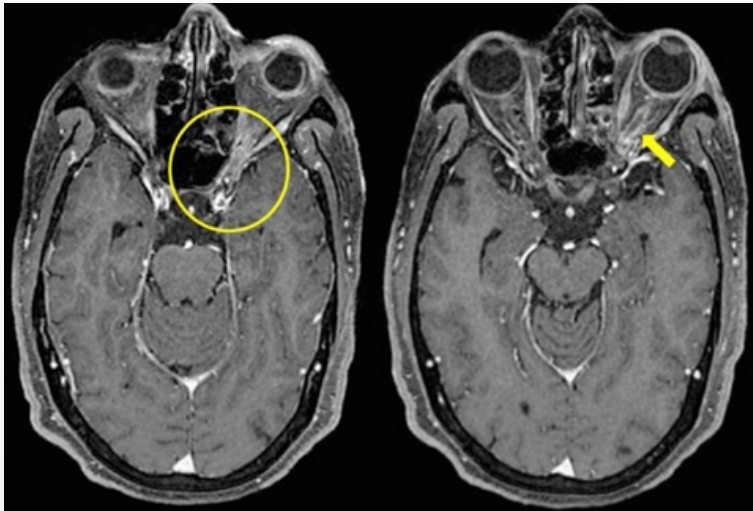
- Unclear what causes optic neuropathy and cranial nerve palsies
- Hypotheses
 - Perineural/Perivascular inflammation of posterior ciliary nerves and vessels with occlusive vasculitis/ischemia
 - Orbital soft tissue edema with direct compression of nerves
 - Direct spread of VZV from V to cranial nerves with virus replication and injury/immune-mediated response causing perineuritis, demyelination and inflammation



Discussion

– MRI Findings

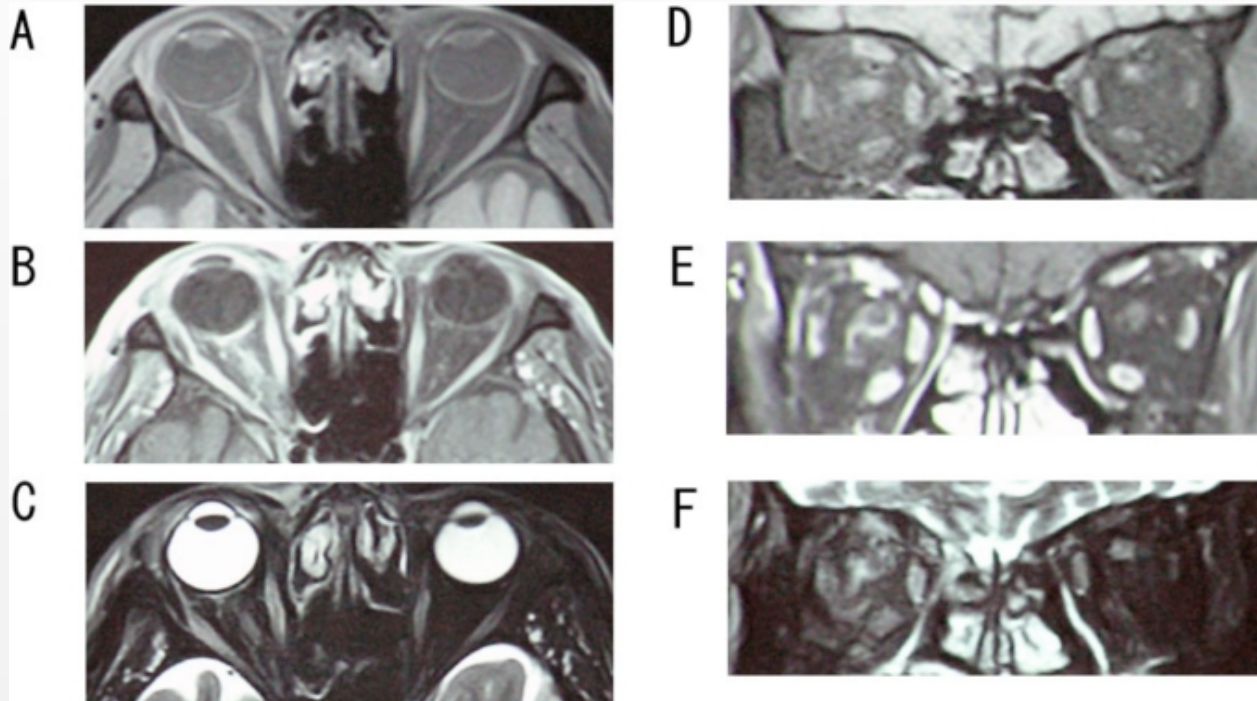
- Enhancement of retro-bulbar optic nerve sheath
- Enhancement of orbital soft tissues
- Myositis



Lee, Chun-Yuan, et al. "Orbital apex syndrome: an unusual complication of herpes zoster ophthalmicus." *BMC infectious disease* (2015)

MRI Findings

- Diffuse enhancement of orbit
- Edematous muscles posterior to globe
- Optic nerve sheath swelling



<https://www-ncbi-nlm-nih-gov.proxy.lib.umich.edu/pmc/articles/PMC2694601/>



Treatment

- No standard guidelines on treatment
- Many authors report success with antiviral + systemic steroids
- Antivirals → reduce shedding, halt new vesicle formation, prevent recurrence
 - Best if initiated within 72 hours of rash
- Steroids → reduce orbital inflammation
 - Dworkin *et al.* recommend 60 mg daily w/ slow taper



Literature

Complete Unilateral Ophthalmoplegia in Herpes Zoster Ophthalmicus

Srinivasan Sanjay, MBBS, MRCS(Edin), Errol Wei'en Chan, MBBS, Lekha Gopal, MBBS, FRCS(Edin), Smita Rane Hegde, MBBS, MS(Ophthal), and Benjamin Chong-Ming Chang, MB, BCh, BAO, FRCS(Irel), FRCS(Edin), FRCOphth(Lond)

- 20 cases in English literature documented between 1968-2008
 - HZO preceded ophthalmoplegia in 75% by an avg of 9 days
 - All patients had complete/incomplete ptosis
 - 90% concurrent anterior segment inflammation
 - 20% had optic neuropathy, 85% fixed, dilated pupil
 - 65% (13) treated with steroids/acyclovir



Literature



- Results

- 65% (13) had complete resolution of ophthalmoplegia in up to 1.5 years w/ average of 4.4 months
- 20% (4) with no improvement
- 75% had improvement in optic neuropathy



Literature

Herpes Zoster Ophthalmicus with Orbital Apex Syndrome— Difference in Outcomes and Literature Review

Jie Jie Lim , MD , Yu Ming Ong, MBBS, MOphthal, M. Zain Wan Zalina, MBBch BAO, MS (Ophthal) & May May Choo, MBBS, M.Med, M.Oph, FRCS

Pages 187-193 | Received 27 Dec 2016, Accepted 03 May 2017, Published online: 16 Jun 2017

- 9 cases described from 2008-2018
 - 2 immunocompromised, otherwise elderly
 - 7/9 treated with IV acyclovir and oral or IV steroids with steroids used for 10 days up to 3 months
 - 4 patients regained significant vision, others did not due to pallor, corneal scarring or delayed presentation



Conclusions

- Herpes Zoster Ophthalmicus is extremely common, up to 25% of zoster cases
- Look for immunocompromised state in young patients (HIV, medications)
- Orbital apex syndrome is a rare, but potentially devastating complication
- Initiate antivirals early! Best if initiated within 3 days of rash
- Steroids shown to be useful in combination with antivirals
- Vaccinate!



Vaccines

- **Shingrix – 2017**
 - Recombinant Zoster Vaccine
 - 50+ years
 - 2 doses, 2-6 months apart
 - >90% protection against HZV and post-herpetic neuralgia (PHN)
- **Zostavax – 2006**
 - Old vaccine, live virus
 - Not protective against post herpetic neuralgia
 - Overall only ~51% efficacy, less in patients older than 70



References

- Verhaeghe, Florent, et al. "Orbital apex syndrome secondary to herpes zoster ophthalmicus." *Journal of Neuro-Ophthalmology* 36.2 (2016): 147-151.
- Lim, Jie Jie, et al. "Herpes Zoster Ophthalmicus with Orbital Apex Syndrome—Difference in Outcomes and Literature Review." *Ocular immunology and inflammation* 26.2 (2018): 187-193.
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- Sanjay, Srinivasan, et al. "Complete unilateral ophthalmoplegia in herpes zoster ophthalmicus." *Journal of Neuro-Ophthalmology* 29.4 (2009): 325-337.
- Shirato, Suguru, et al. "Magnetic resonance imaging in case of cortical apex syndrome caused by varicella zoster virus." *The open ophthalmology journal* 2 (2008): 109. Lee, Chun-Yuan, et al. "Orbital apex syndrome: an unusual complication of herpes zoster ophthalmicus." *BMC infectious diseases* 15.1 (2015): 33.
- <https://www.fda.gov/media/75975/download>
- Butsch, Florian, et al. "Prognostic value of Hutchinson's sign for ocular involvement in herpes zoster ophthalmicus." *JDDG: Journal der Deutschen Dermatologischen Gesellschaft* 15.5 (2017): 563-564.



Questions?

