GRAND ROUNDS

OPHTHALMOLOGY

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Presenting history

- 68M referred to KCHC clinic for blurry vision
- No other ocular or visual complaints
- No past ocular history
- ROS: no flashes, floaters, curtains, diplopia, ophthalmoplegia

Presenting history (cont.)

- PMH: Parkinson’s disease, DM2
- Meds: sinemet
- All: nkda
- FH: no known glaucoma or blindness
- SH: no tob, etoh, illicit drugs; Indian American origin

Exam

- General: wheelchair bound, severe rigidity and bradykinesia when transferring to slit lamp chair
- BCVA: 20/70, 20/50
- Pupil: 3-2 ou, no rapd
- EOM: see video
- CVF: full ou
- Ta: 10/11

Slit lamp

- SLE
  - L/l: wnl ou
  - C/s: tr inj ou, conjunctivochalasis ou, nasal pterygium od
  - K: severe spk ou
  - Ac: d/q ou
  - Iris: r/r ou
  - Lens: ns ou
- DFE
  - Vit: clear ou
  - ON: 0.55 s/p ou
  - Macula: flat ou
  - Vessels: wnl ou
  - Periphery: wnl ou

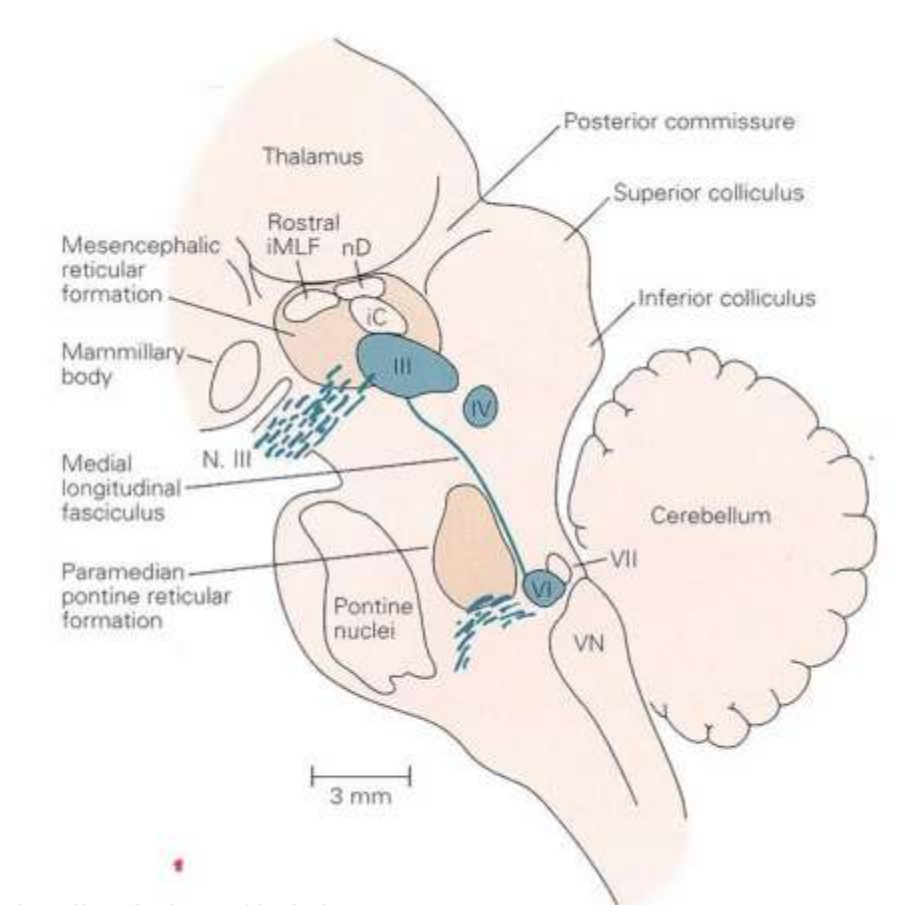
Recap

- Almost absent vertical saccades and smooth pursuit
- Hypometric horizontal saccades
- VOR essentially intact

Types of eye movement

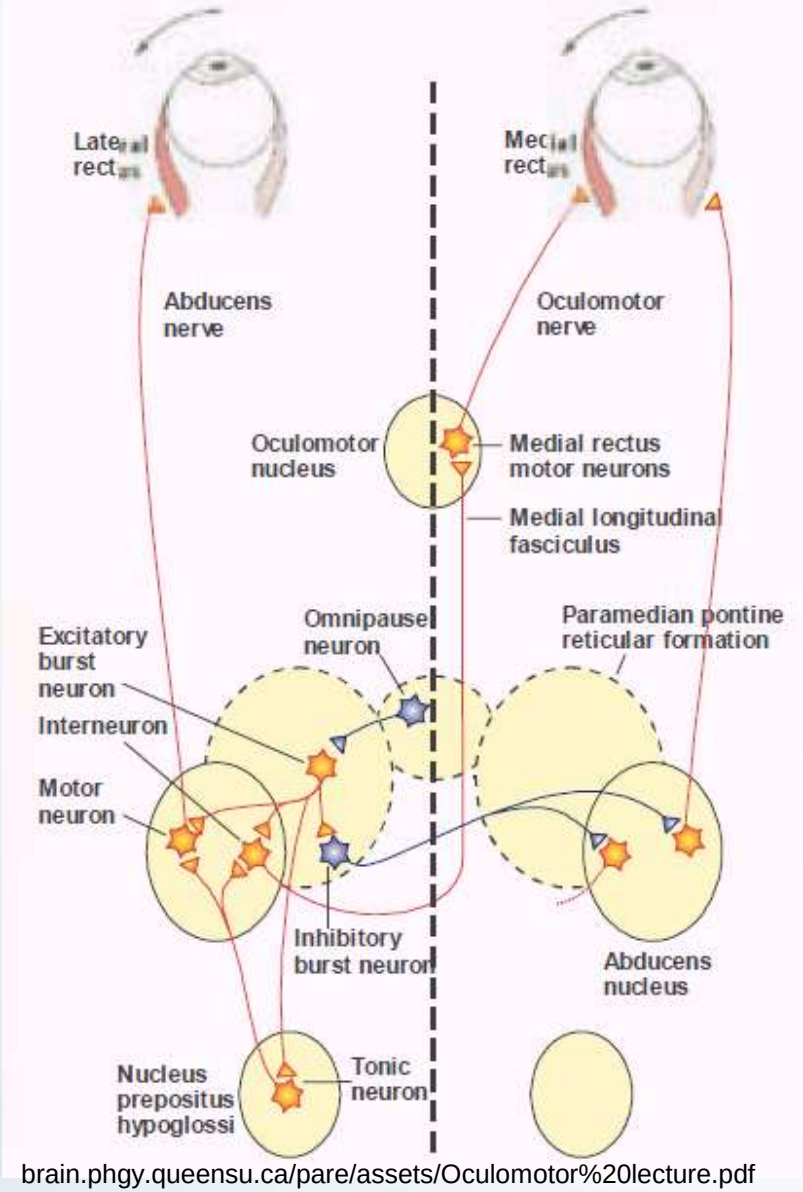
- Gaze Stabilization
  - Vestibulo-ocular
  - Optokinetic
- Gaze shifting
  - Vergence
  - Smooth Pursuit
  - Saccade

Neural motor centers for saccades



http://cueflash.com/decks/CONTROL_OF_EYE_MOVEMENTS_-_57

- Vertical
  - EBN in rostral interstitial nucleus (rostral iMLF)
- Horizontal
  - EBN in paramedian pontine reticular formation (PPRF)
- Cortex controls saccades via superior colliculus



brain.phgy.queensu.ca/pare/assets/Oculomotor%20lecture.pdf

Recap

- Almost absent vertical saccades and smooth pursuit
- Hypometric horizontal saccades
- VOR essentially intact

Differential diagnosis

- Progressive supranuclear palsy
- Acquired ocular motor apraxia
- Corticobasal degeneration
- Multiple system atrophy
- Idiopathic Parkinson’s disease

Impression:

68M h/o previously diagnosed Parkinson's disease presenting to eye clinic with vertical gaze palsy thought to be 2/2 progressive supranuclear palsy (PSP).

Plan:

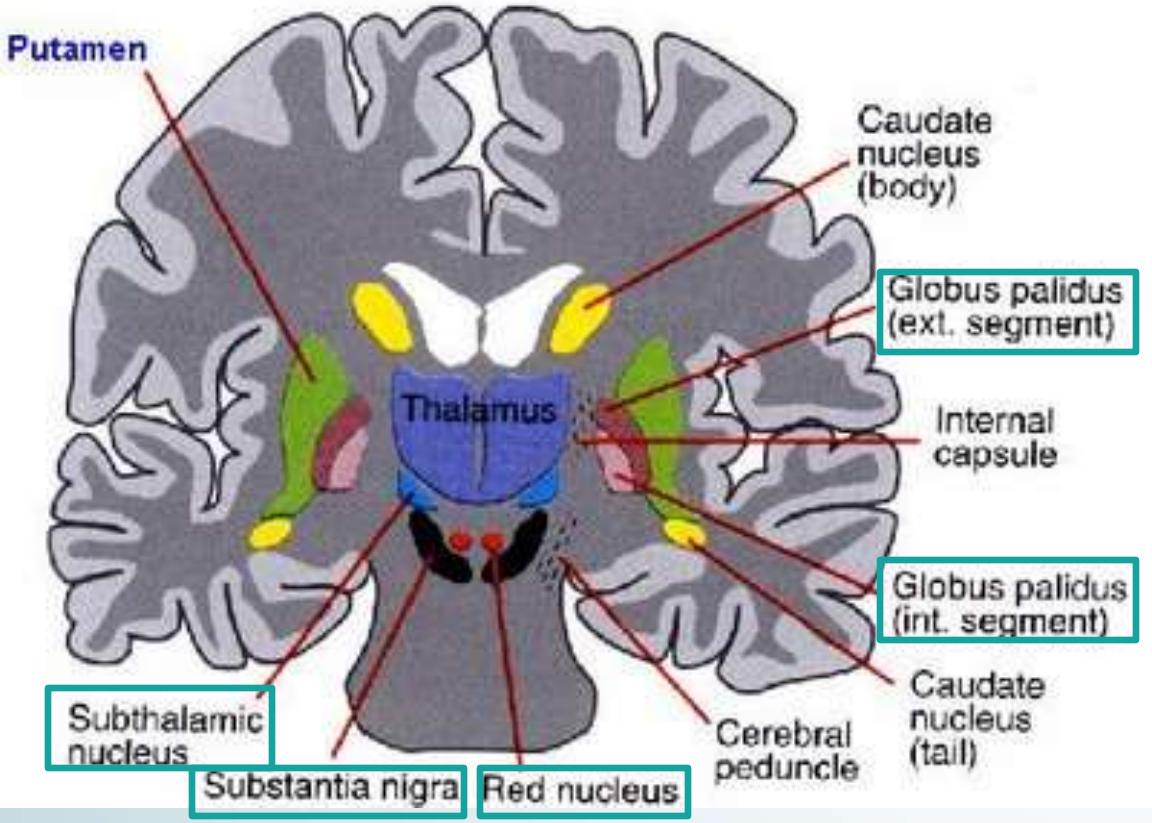
Discussion of:

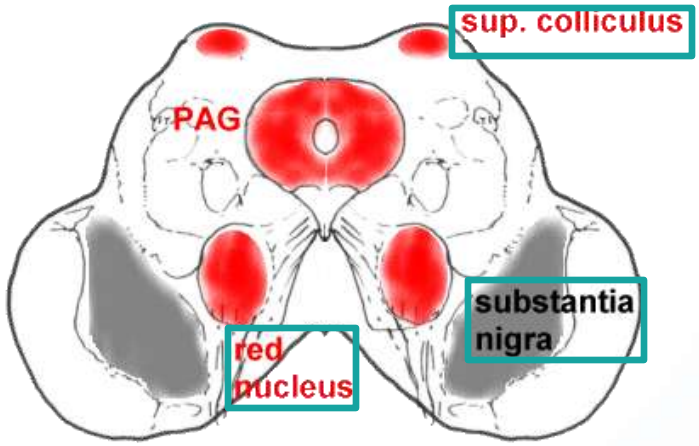
- Clinical features of PSP
- Current diagnostic criteria as well as potential future modalities to assist in the diagnosis
- Clues to distinguish PSP from closely related diseases

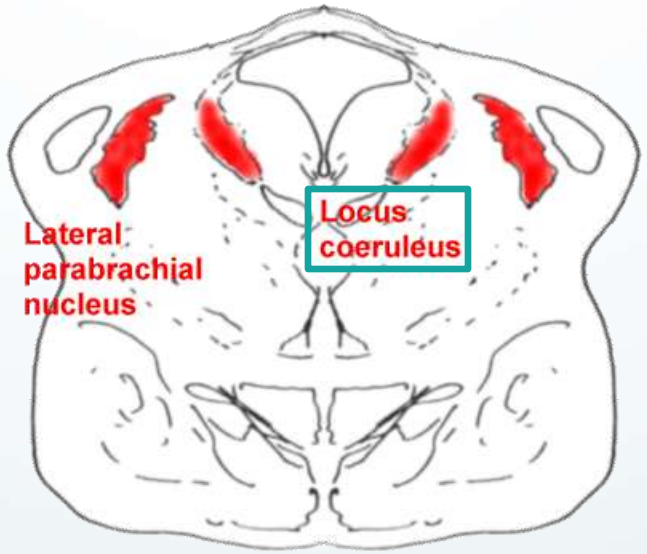
PROGRESSIVE SUPRANUCLEAR PALSY

Progressive supranuclear palsy (PSP)

- Rare neurodegenerative disorder characterized by motor and ocular symptoms
- J. Clifford Richardson first presented 8 cases in 1963 at ANA
- Richardson and John Steele authored the first paper the following year along with pathologist J. Olszewski
  - Richardson-Steele-Olszewski Syndrome







1. http://science-naturalphenomena.blogspot.com/2009/05/putamen.html
2. http://www.anaesthetist.com/icu/pain/pain3.htm

Epidemiology

- Incidence → ~1.5/100,000
- Average age of onset → 65
- Slight male predominance
- Median survival → 6-7 yrs from onset
  - Death usually from aspiration pneumonia or other infections related to immobility or from consequences of postural instability (ie. falls)

NINDS-SPSP diagnostic criteria

- Possible PSP
- Probable PSP
- Definite PSP

Possible PSP

- Gradually progressive disorder
- Onset age >= 40 years
- No evidence of other disease explanation
- Either vertical supranuclear palsy

  OR

  Both slowing of vertical saccades and prominent postural instability with falls in the first year of onset

Probable PSP

- Gradually progressive disorder
- Onset age >= 40 years
- No evidence of other disease explanation
- Vertical supranuclear palsy

  AND

  Prominent postural instability with falls in the first year of onset

Definite PSP

- Possible PSP or Probable PSP

  AND

  Histopathology typical of PSP

Supportive clinical features

- Symmetric akinesia or rigidity
- Abnormal neck posture
- Poor response to levodopa
- Early dysphagia and dysarthria
- Early cognitive impairment with at least two of:
  - Apathy
  - Impaired abstract thought
  - Decreased fluency
  - Frontal release signs

Exclusion criteria

- Recent history of encephalitis
- Alien limb syndrome, cortical sensory deficits, focal frontal atrophy
- Hallucinations or delusions unrelated to dopamine therapy
- Cortical dementia of Alzheimer type
- Prominent early cerebellar symptoms or unexplained dysautonomia

Exclusion criteria (cont.)

- Severe asymmetric parkinsonian signs
- Neuroradiologic evidence of relevant structural abnormalities
- Whipple’s disease confirmed by PCR

Oculomotor abnormalities

- Early stages
- Middle stages
- Late stages

- Slowness of vertical saccadic movements
- Hypometric horizontal saccades
- Reduced blinking
- Square wave jerks

Oculomotor abnormalities

- Early stages
- Middle stages
  - Supranuclear vertical gaze palsy
  - Lid retraction with rare blinking
  - Impaired convergence
  - Apraxia of eyelid opening or closing
- Late stages

Oculomotor abnormalities

- Early stages
- Middle stages
- Late stages
  - Supranuclear horizontal gaze palsy
  - Loss of oculocephalic reflexes
  - Blepharospasm
  - Disconjugate gaze

Clinical variants

- Richardson syndrome (classic PSP)
  - Early onset postural instability and falls
  - Supranuclear vertical gaze palsy
  - Cognitive dysfunction
  - Much shorter disease duration
  - Younger age at death

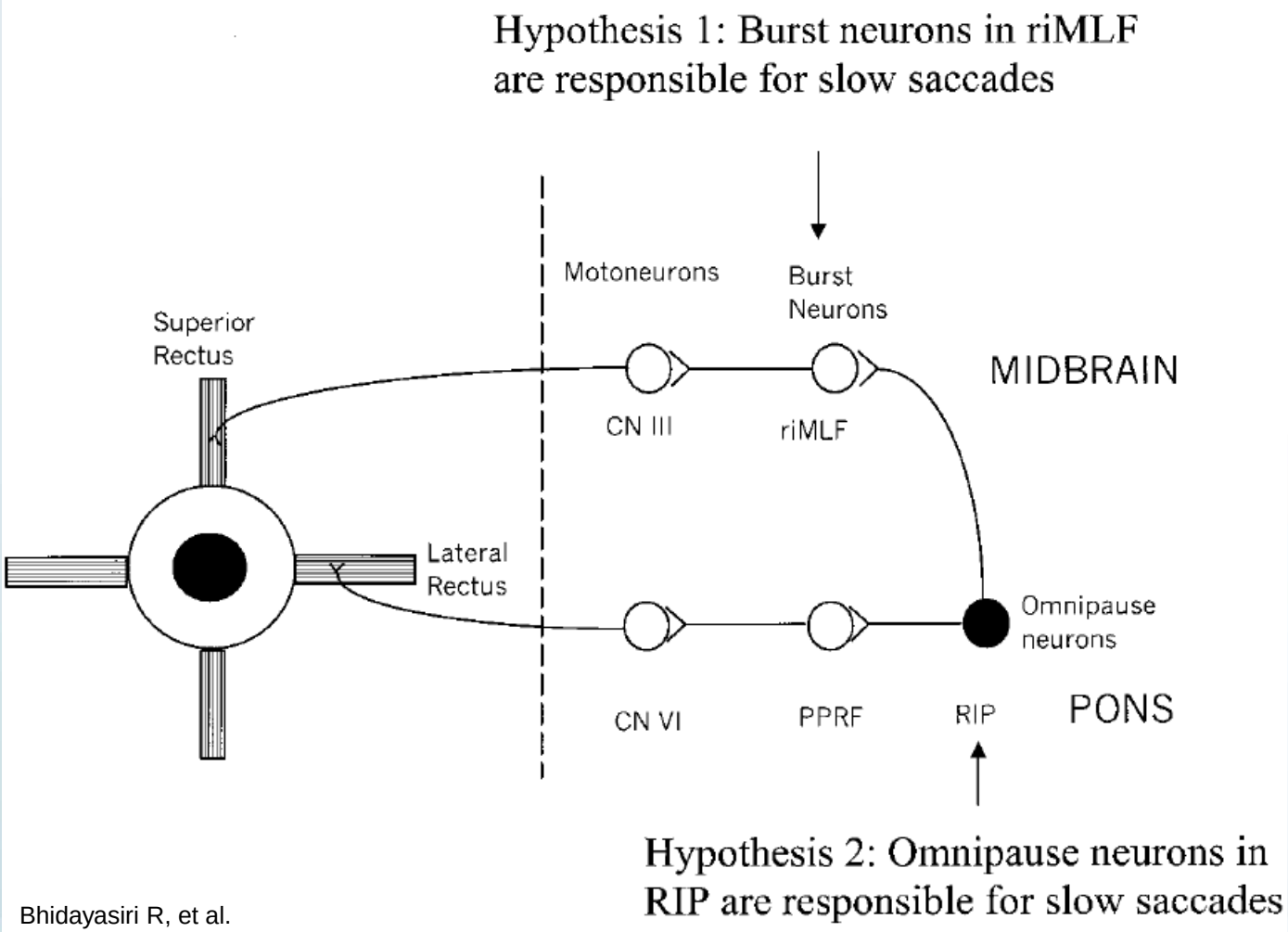
Clinical variants (cont.)

- PSP-parkinsonism
  - Asymmetric onset of symptoms
  - Early bradykinesia
  - Tremor
  - Extra-axial dystonia
  - Moderate response to levodopa

Possible genetic basis

- Although PSP is usually sporadic, some studies have described a genetic cause
- H1 haplotype variant in the *MAPT* gene on chromosome 17 found in 95% of PSP patients (compared to 60% in general population)
- Other genes including *MOPB*, *STX6*, and *EIF2AK3* also implicated in various studies

Pathophysiology



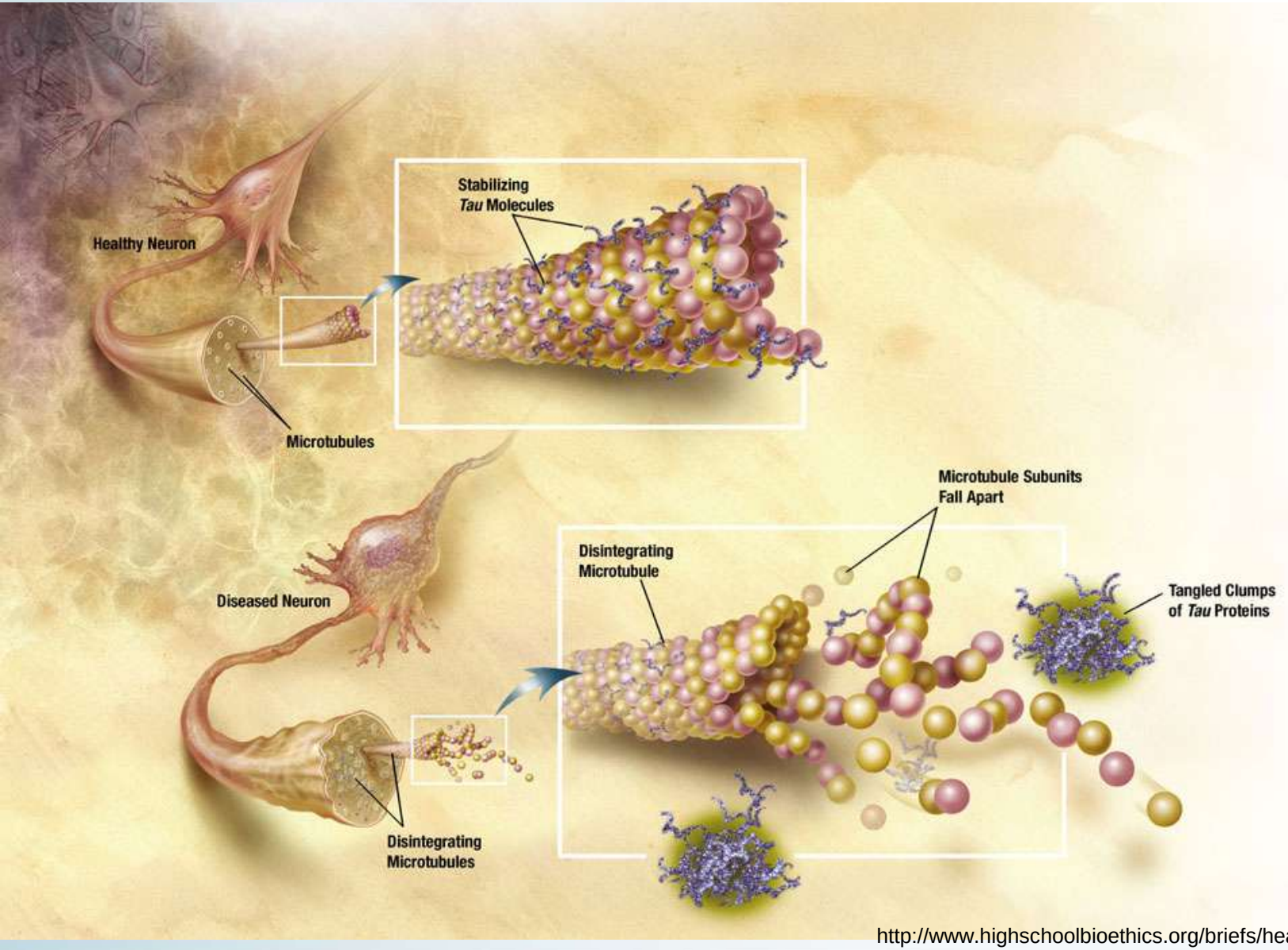
Bhidayasiri R, et al.

Tauopathies

- Group of diseases defined by accumulation of tau
- Tau – microtubule binding protein that contributes to microtubule assembly and stabilization
- Different isoforms of tau exist - each referring to the number of copies of the part of the protein that binds it to the microtubules
- Significant overlap exists between phenotypes of various tauopathies

Histopathology

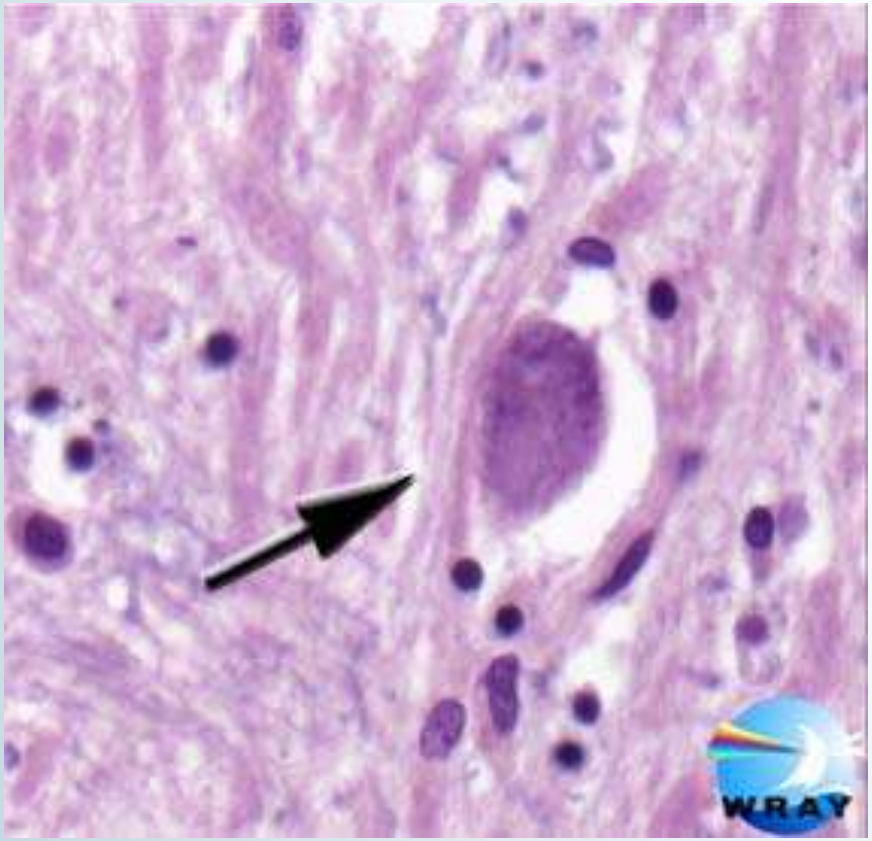
- PSP characterized by cerebral atrophy with pallor of substantia nigra and shrinkage of globus pallidus
- Neuronal loss and gliosis with abundant subcortical neurofibrillary tangles and neuropil threads
- Accumulation of insoluble hyperphosphorylated tau protein isoforms (increased four repeat tau)

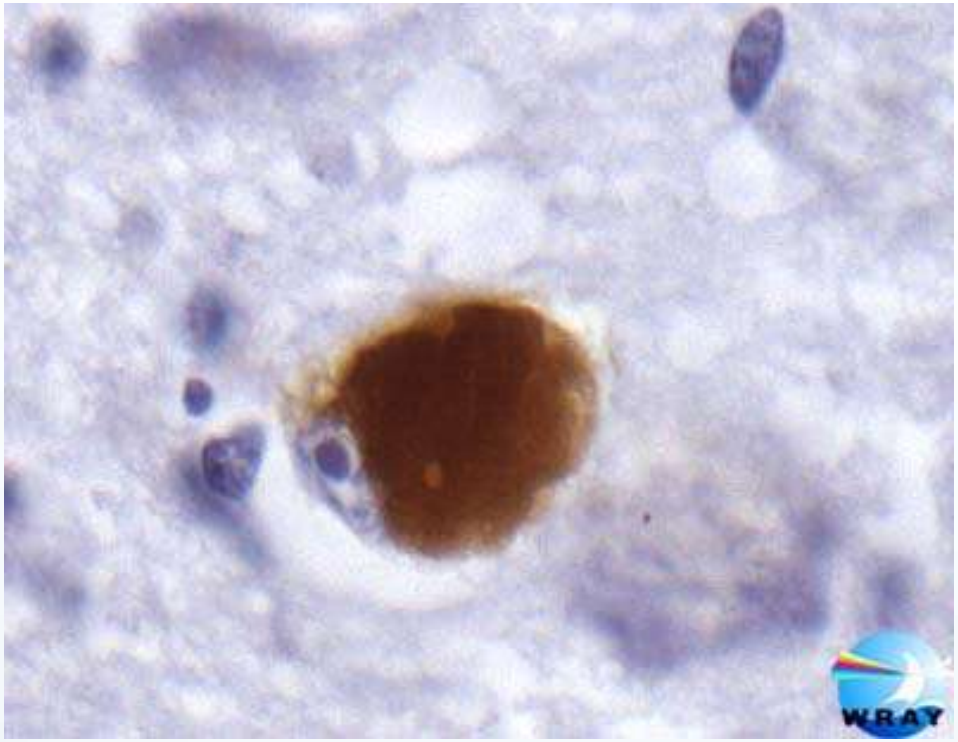


http://www.highschoolbioethics.org/briefs/head-head-nfl-brain-injury

Medical knowledge

http://repository.countway.harvard.edu/xmlui/bitstream/handle/10473/4568/Progressive_Supranuclear_Palsy.pdf?sequence=2





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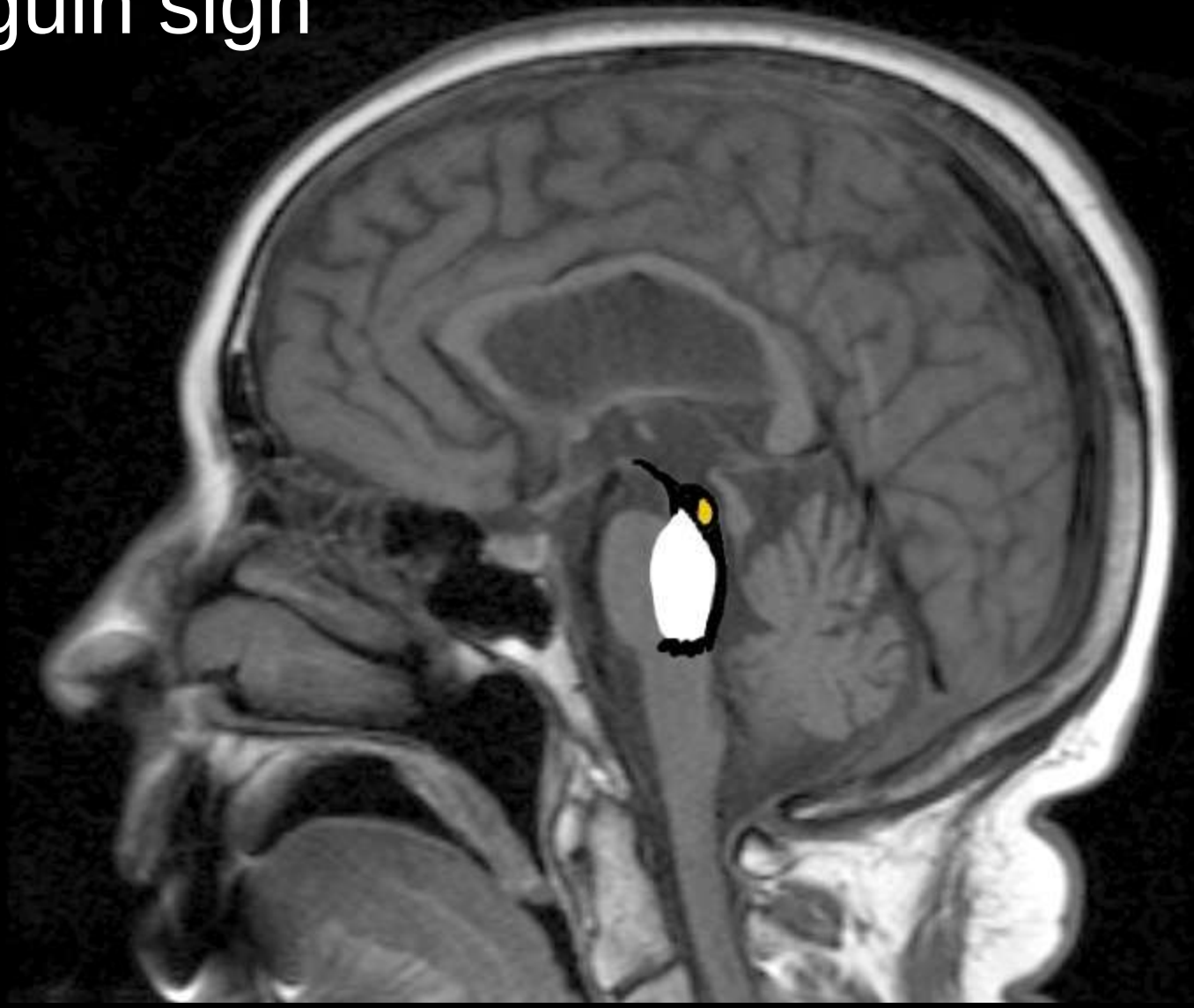
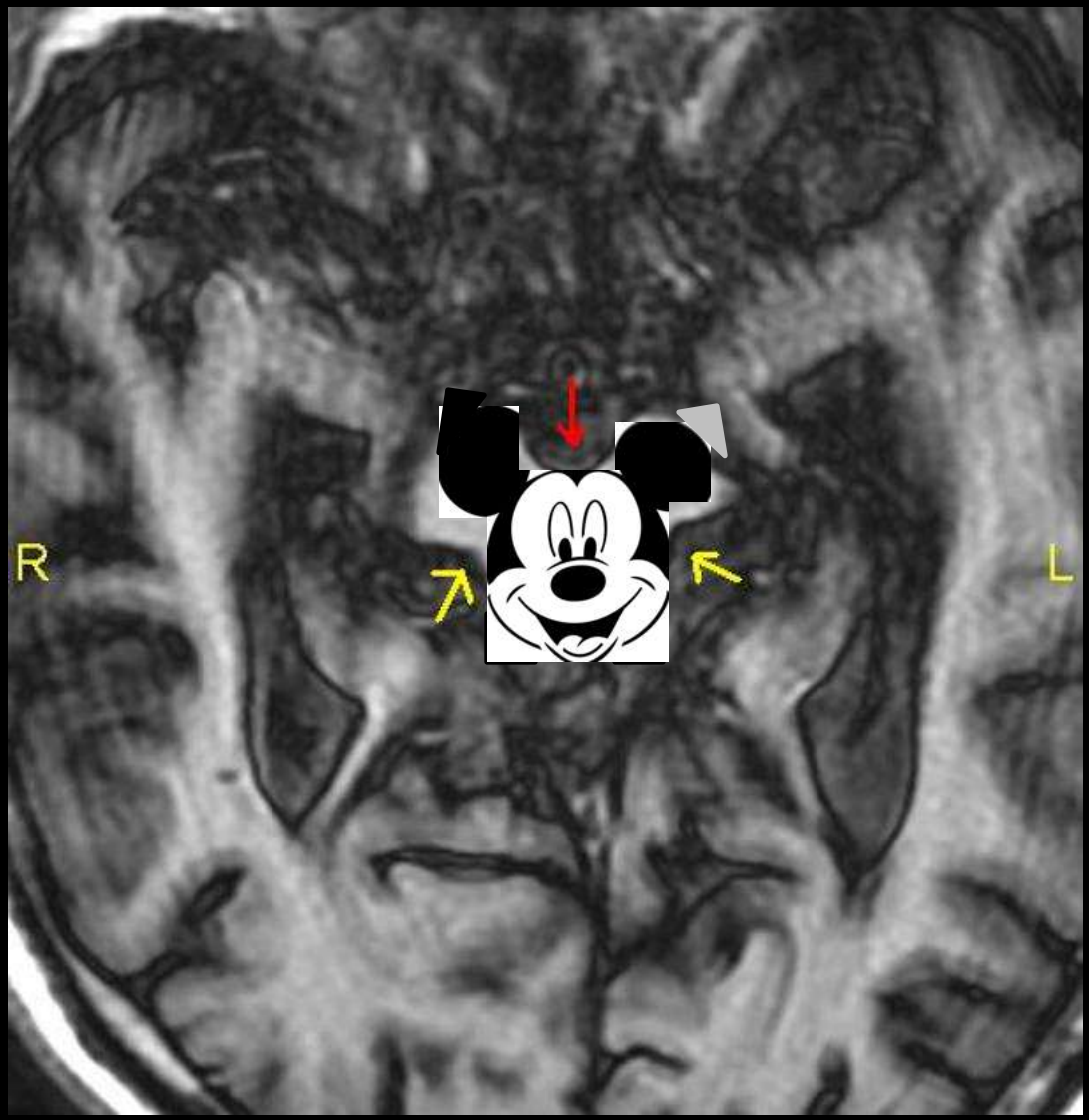
Penguin sign



http://www.radpod.org/2007/02/23/progressive-supranuclear-palsy/

Morning glory sign



Potential uses of MRI for diagnosis

- Oba, et al
  - Average midbrain area on mid-sagittal MRI significantly smaller with PSP than with PD, MSA, and normal controls (although some overlap with PSP and MSA)
  - Ratio of midbrain area to pons area significantly smaller in PSP than with PD, MSA, and normal controls
- Quattrone, et al
  - MR parkinsonism index = [(P/M)*(MCP/SCP)]
  - Value significantly larger with PSP (median 19.42) than in PD (9.40), MSA (6.53), and controls (9.21) with no overlap

Management

- No cure for PSP and current therapy usually ineffective
- Dopaminergic drugs can provide nominal or transient improvement
- Palliative therapy – PT, ST, walker, wheelchair, gastrostomy tube
- Ambien, botulinum toxin, AT

PSP vs Idiopathic Parkinson's disease (PD)

- PSP may be indistinguishable from idiopathic PD in the early stages
- Reduced or attenuated response to dopaminergic medications
- Early postural instability and falls
- Tremors are rare with PSP
- Normal cardiac MIBG

Ocular motor apraxia

- Typically a congenital condition
- Acquired ocular motor apraxia much less commonly described in literature
  - Bilateral frontoparietal lobe lesions and infarcts
  - Cardiopulmonary surgery
- Loss of volitional saccades (especially horizontal) and smooth pursuit

Back to our patient

- Referred to Neurology for continued management and titration of dopaminergic medications
- MRI pending
- Ophthalmology planning on cataract surgery to help contrast sensitivity and reduce risk of falls

Take home points

- PSP is a rare neurodegenerative progressive disorder characterized by early postural instability and vertical gaze palsy
- Often misdiagnosed as PD – consider PSP in cases when ocular signs and early postural instability are prominent findings
- Diagnosis is made clinically although advances in MRI research may soon help in making an earlier diagnosis

Reflective practice

- This case allowed me the opportunity to see a classic presentation of the relatively rare entity, progressive supranuclear palsy. By taking care of this patient and educating myself about his disorder, I gained a deeper understanding of PSP and its closely related diseases. I believe our service did an outstanding job in accurately diagnosing the patient's condition, educating him about the condition and our recommendations, and caring for him in a respectful and resourceful manner.

Core competencies

- **Patient care:** The case involved thorough patient care and attention to the patient's complaints. A sincere effort was made to urge patient to follow up with Neurology.
- **Medical knowledge:** This presentation allowed me to review the presentation, differential diagnosis, proper evaluation, and diagnostic criteria for PSP.
- **Practice based learning and improvement:** This presentation included a current literature search of developing and current diagnostic strategies for PSP.
- **Interpersonal and communication skills:** Every effort was made to communicate with the patient the importance of following up with Neurology.
- **Professionalism:** The patient was treated with respect at all times and was diagnosed in a timely manner.
- **Systems based practice:** Good communication between our service and Neurology ensured that the patient received proper management of his condition.

References

- Bhidayasiri R, et al. Pathophysiology of slow vertical palsy in progressive supranuclear palsy. Neurology. Dec 2001.
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- Oba, et al. New and reliable MRI diagnosis for progressive supranuclear palsy. Neurology. June 2005.
- Goldberg M. The control of gaze. 2000.
- Stanford, et al. Progressive supranuclear palsy pathology caused by a novel silent mutation in exon 10 of the tau gene. Brain. 2003.
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Thank you!

- Dr. Elmalem
- Dr. Calderon
- Patient and his wife