# Pediatric Brainstem tumors: an updated perspective

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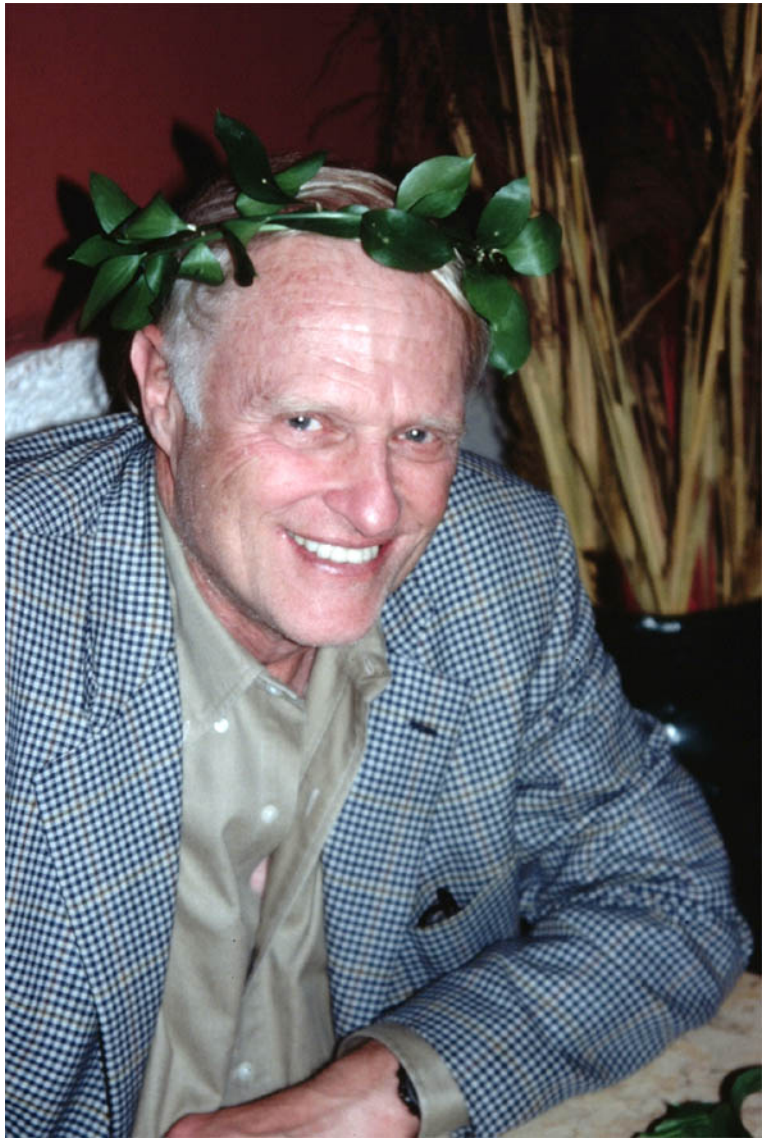
ב"ח "דנה" לילדים


ADMISSION
קבלה

# Fred Epstein: an “inspiration” giant

*“Everything I know about BS Tumors Is from my mentor Fred”*

*SC*

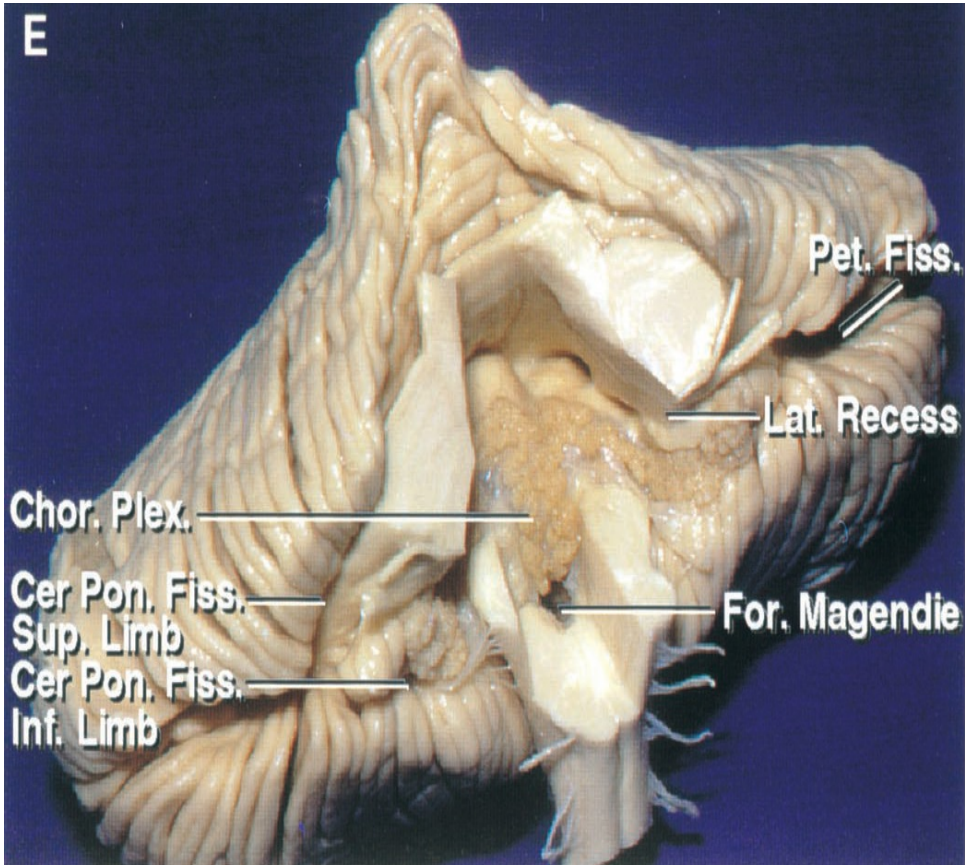


# Factors to be considered

- Age & Clinical presentation
- Anatomical/radiological classification
- Histo-Pathology and molecular biology
- Diagnostic methods
- Treatment options
- surgical selection & techniques
- Intraoperative monitoring
- Prognosis

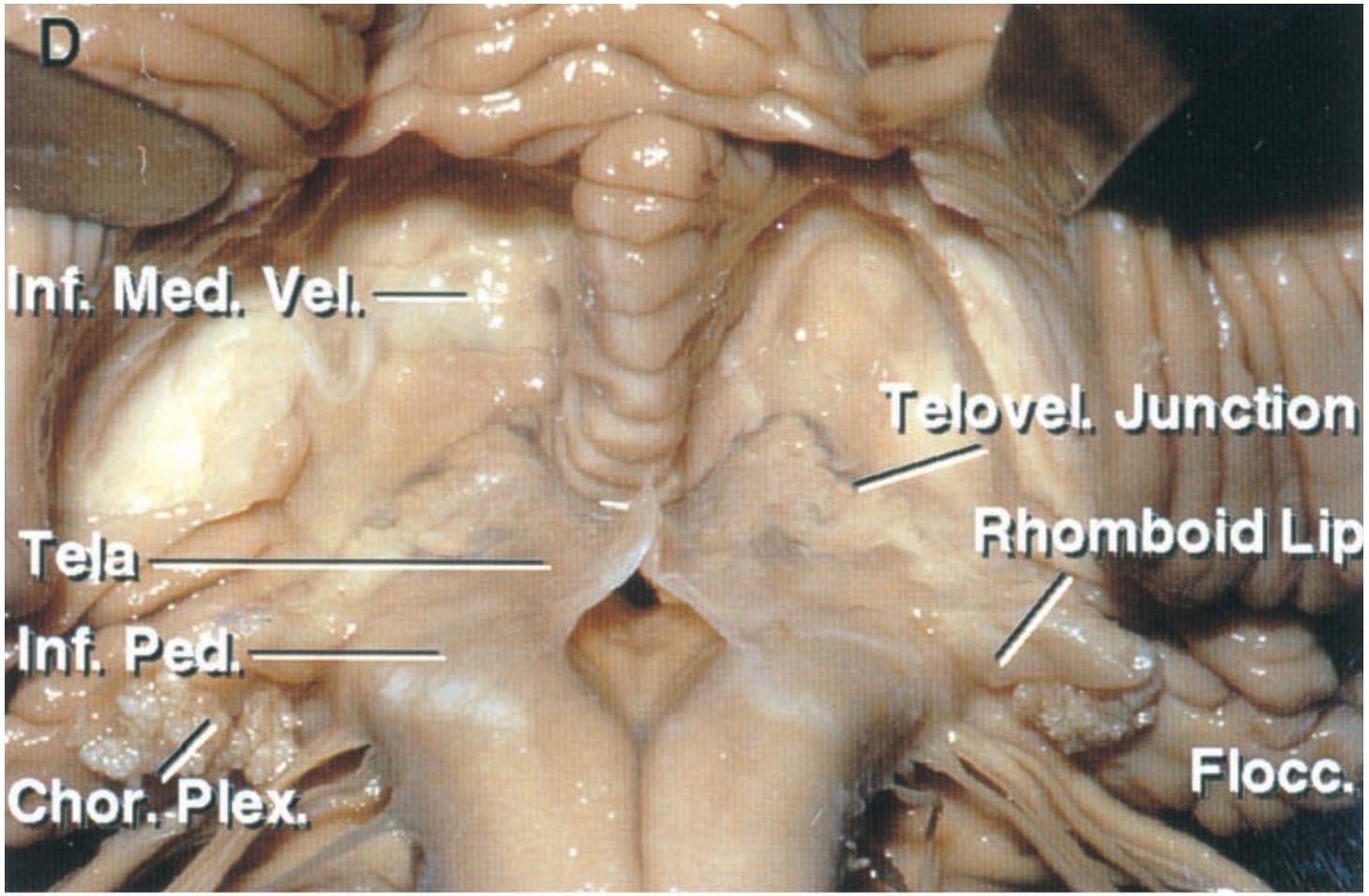
# Fourth ventricular floor anatomy

# Fourth Ventricle

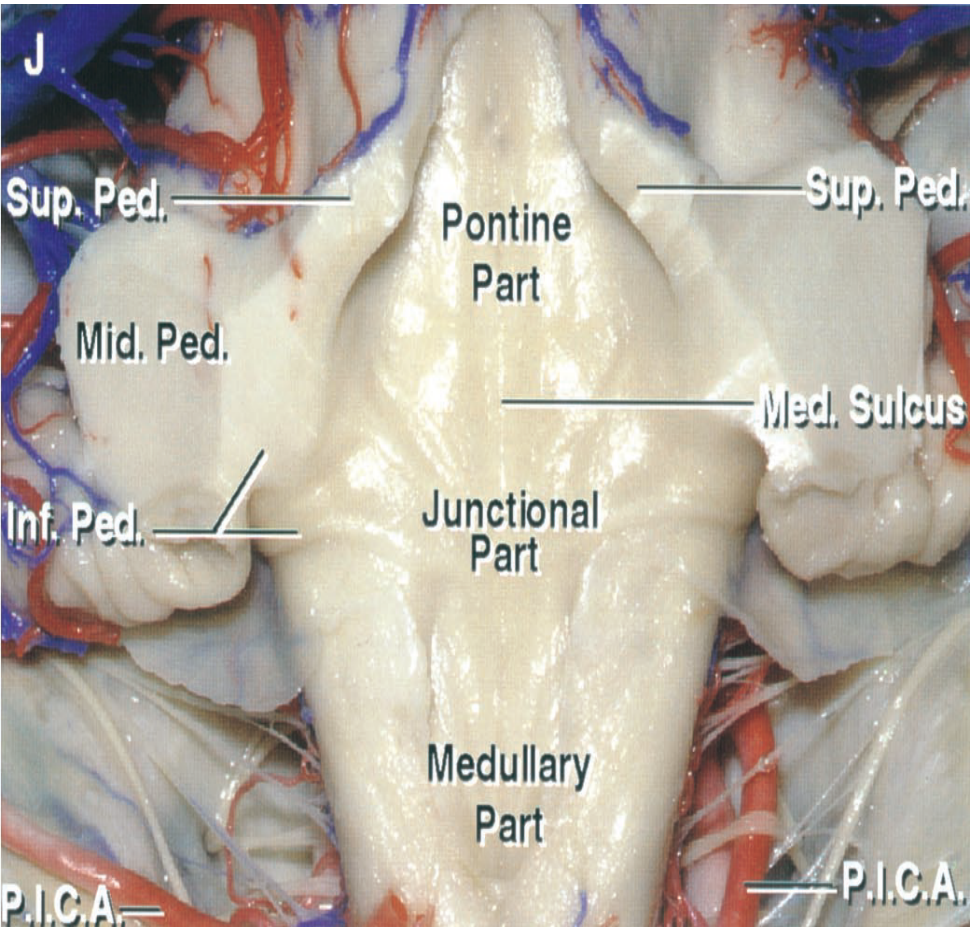



- Broad tent shaped midline cavity between cerebellum and brainstem
- Expansion of central canal of medulla oblongata
- Has a roof, floor and two lateral recesses

# Ventricular Roof



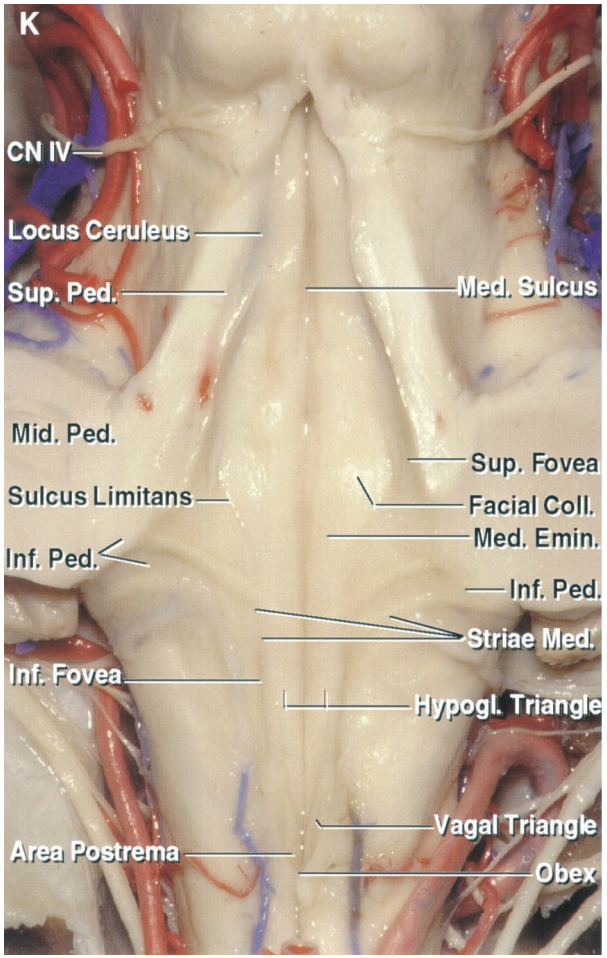
# Ventricular Floor




- Symmetrical rhomboid shape
- Three parts
  - Pontine
  - Junctional
  - Medullary

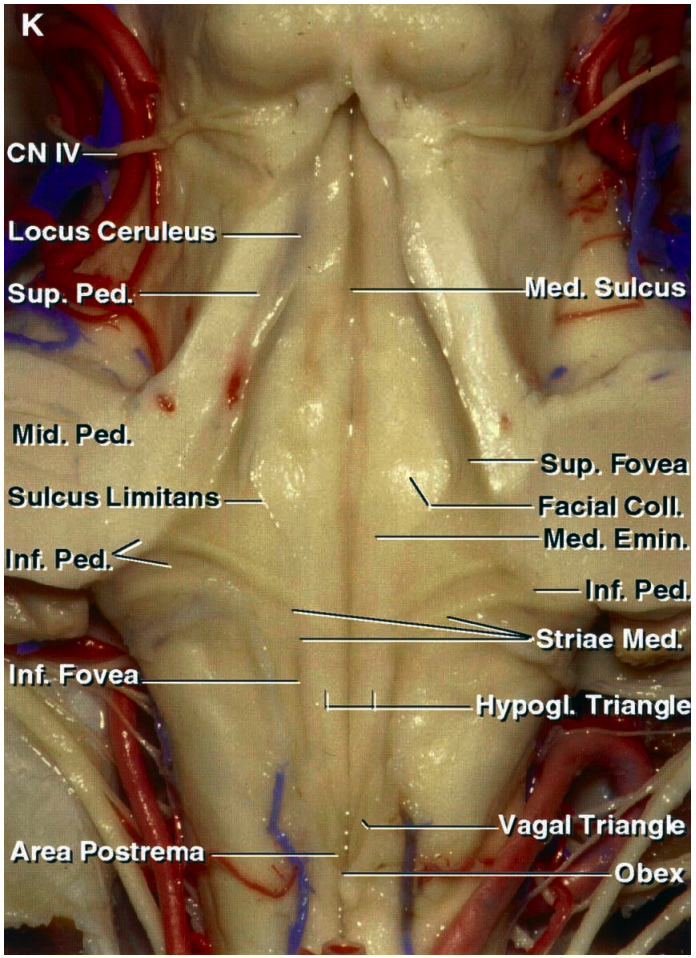
Underlying nuclei and fiber tracts raise floor

# The floor of the fourth Ventricle



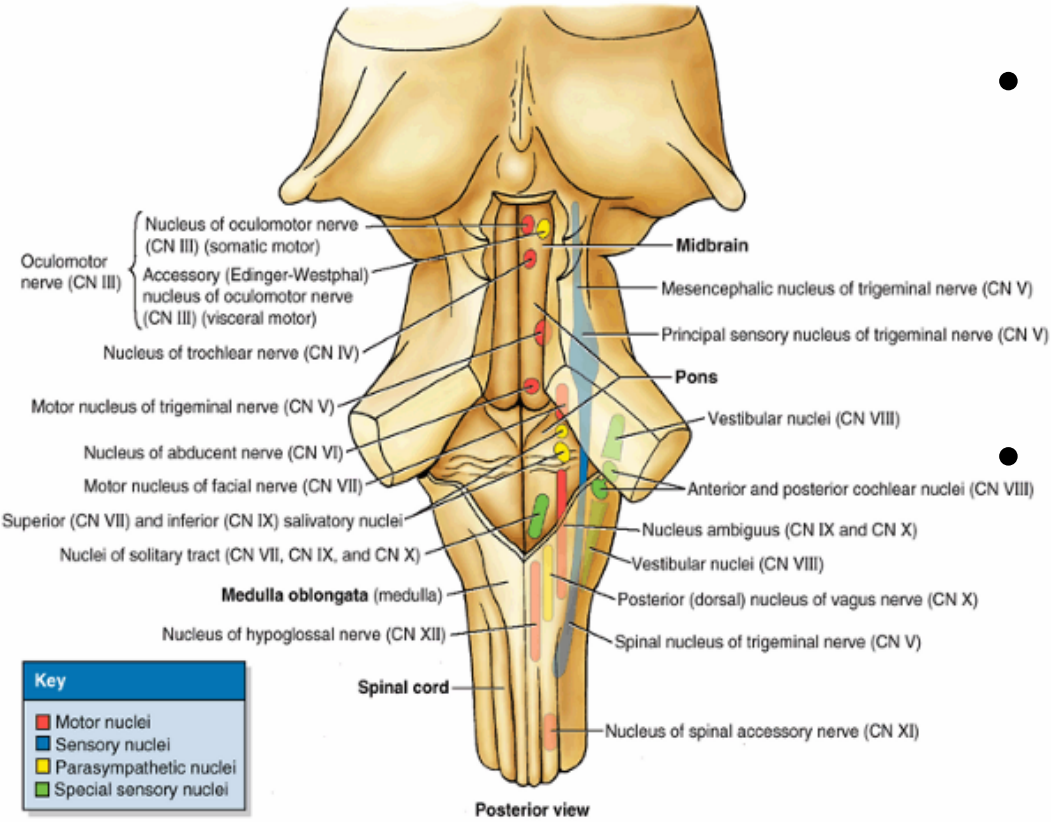

- Median sulcus divides floor longitudinally
- Sulcus limitans divides each half longitudinally into a median eminence and lateral vestibular area
- Striae medullaris course transversely joining inferior margins of inferior cerebellar peduncles

# Caudal Triangle




- Obex is the caudal tip
- Taeniae mark inferolateral margins
- Caudal limit of sulcus limitans is the inferior fovea
- Vagal, hypoglossal trigones and the area postrema form the calamus scriptorius

# Nuclei of ventricular floor




- Between the hypoglossal trigone and the area postrema is the ala cinera
- - the position of the vagal and glossopharyngeal sensory nuclei

# Brainstem functions

- Integrative functions
- Maintenance of consciousness
- Sleep wake cycle
- Muscle tone
- Posture
- Respiratory and cardiovascular control
- Cranial nerve functions: motor and sensory

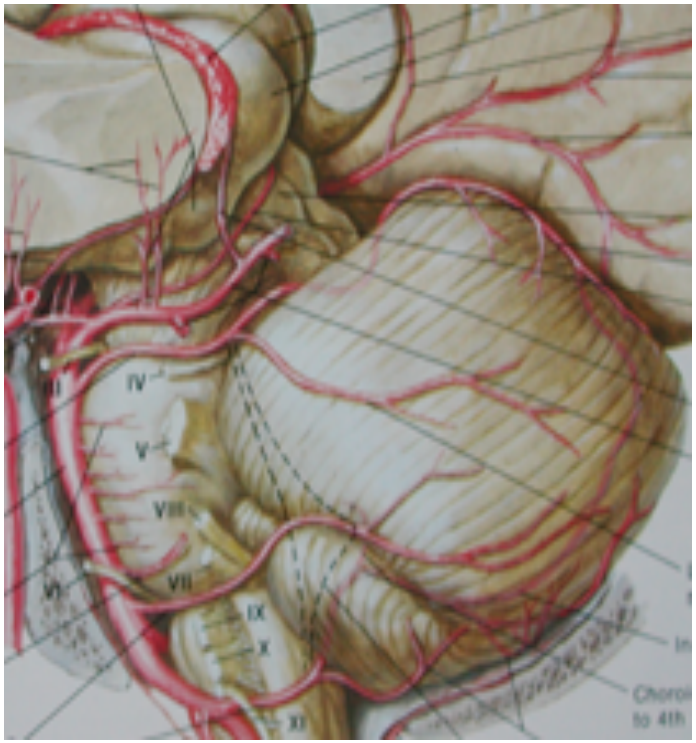
# Brainstem tumor symptoms

- Cerebellar
- Somatosensory
- Motor
- Cranial nerve function
- Level of damage may be determined by the injured cranial nerve

- See detailed addendum at end of presentation

# Pediatric tumors: Posterior Fossa

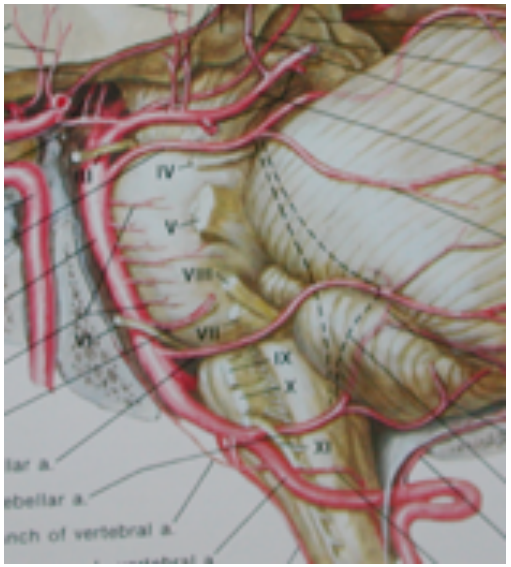
- **Midline**
  - **I Astrocytoma**
  - **II Medulloblastoma**
  - **III Ependymoma**
- **Lateral**
  - **Hemangioblastoma**

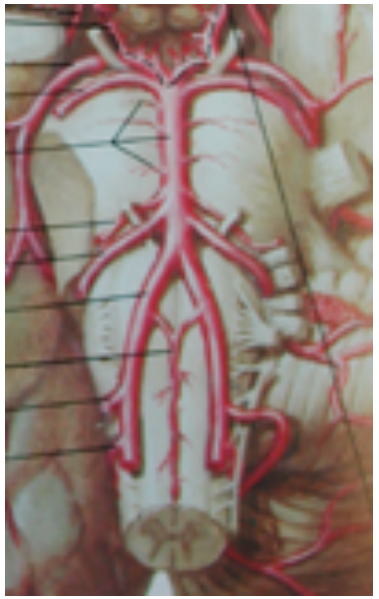


**Separate: Brain stem tumors**

# Brainstem Tumors

- Location
  - Midbrain
  - Pons
  - Medulla
  - Cervico-medullary
- Texture
  - Diffuse
  - Focal
  - Cystic



# Anatomical & radiological classification-I *long-axis*

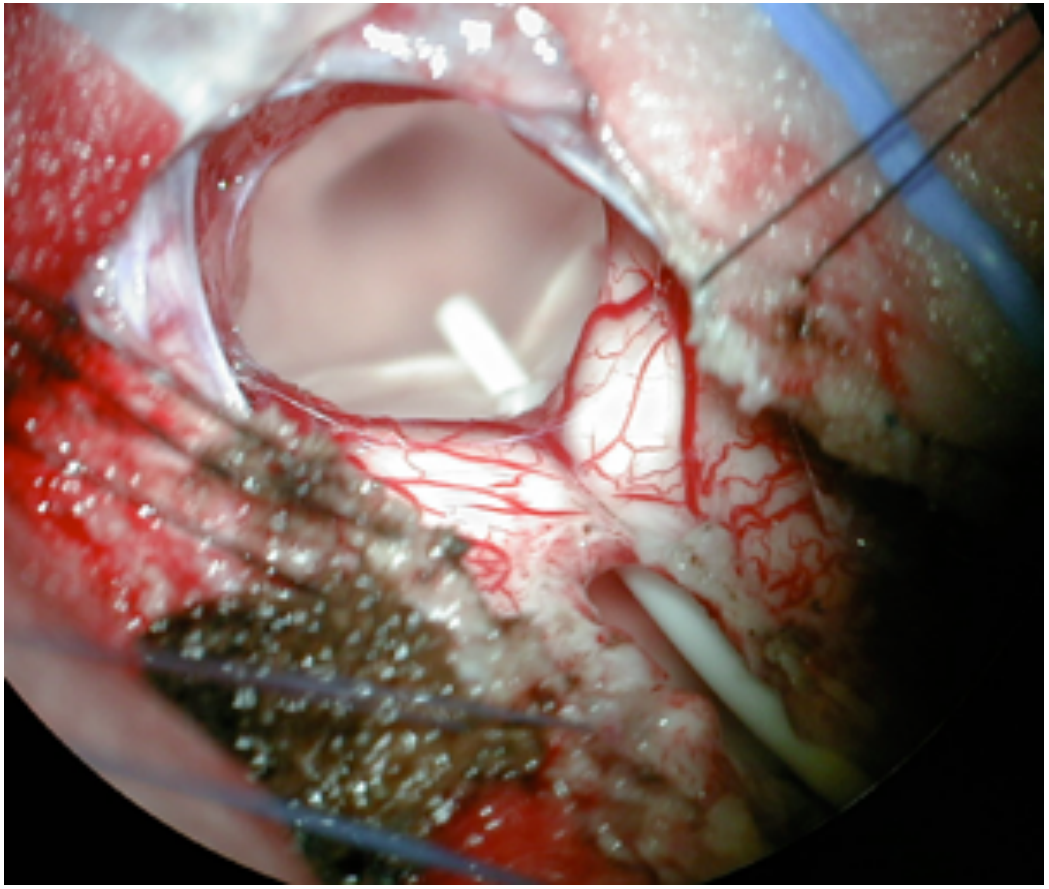
- Cervico-medullary
- Medulla
- Pons
- Midbrain
  - Tectal
  - Tegmental

# Anatomical & radiological classification-II *Relationship to stem*

- Intrinsic Vs epi-centered outside the stem…
- Diffuse or focal
- Exophitic
- Cystic?

- Enhancing?
  - (interestingly, most malignant DPG's do not enhance…)

# Cervico-medullary
# 3y old Presented with drooling & torticollis
# Astrocytoma:

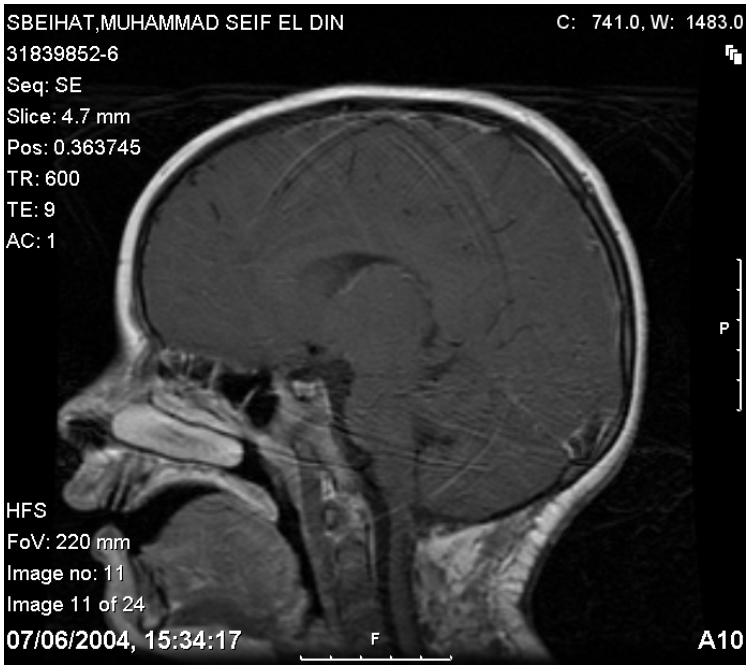
***Note dorsal direction after hitting pyramid decussation***

2 years after surgery:

Local recurrence..

V+C chemotherapy---CR

No evidence of disease 7 years later

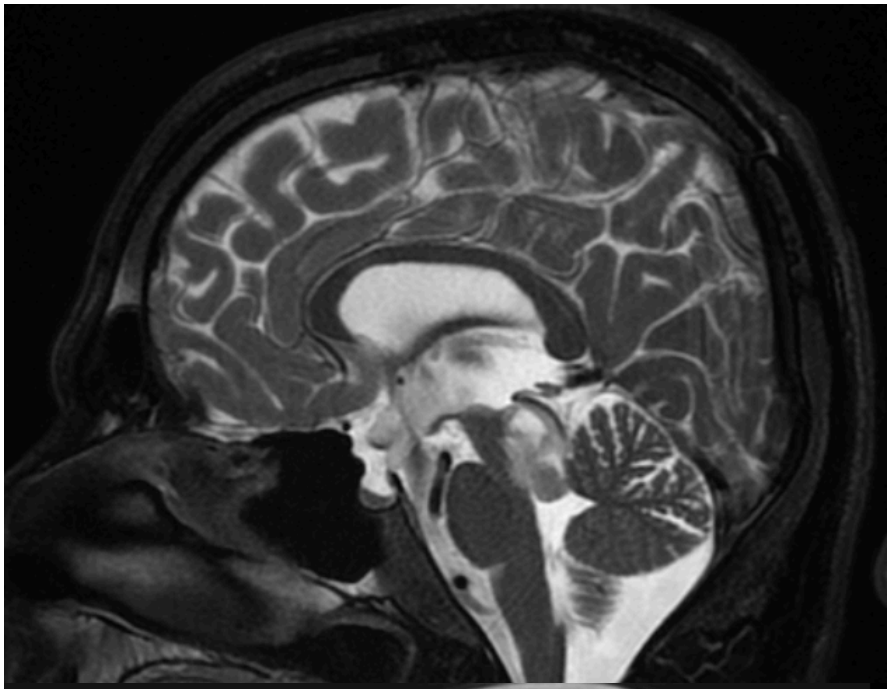


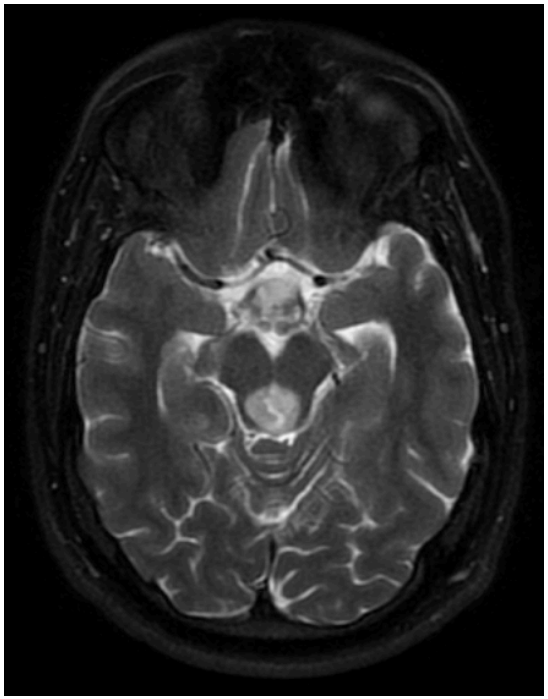

2 years later

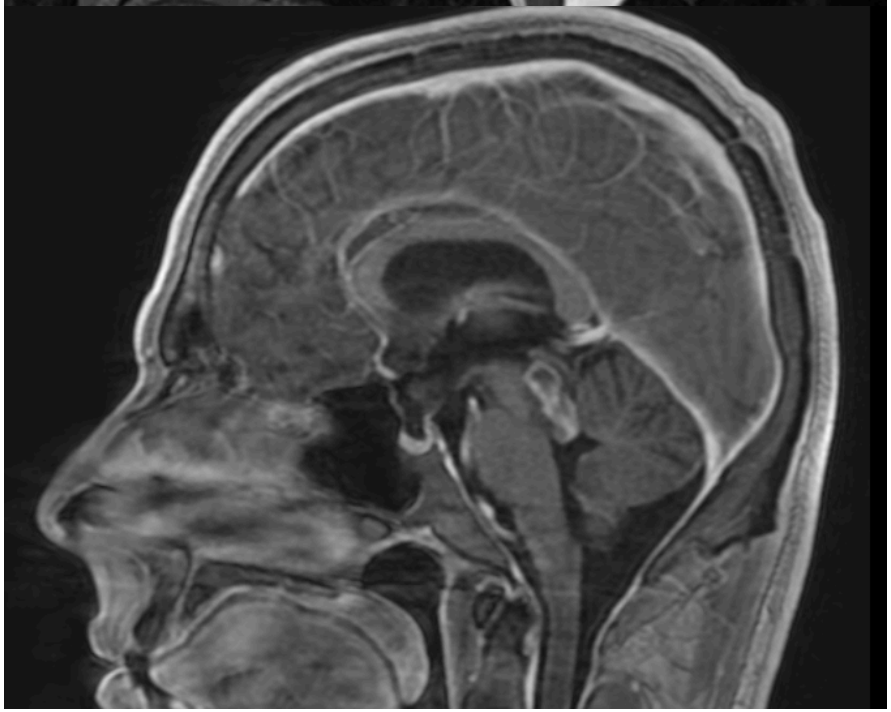
# Midbrain lesions I

- Tegmental tumors
  - extension of diencephalic or pontine tumors
  - Pure tegmental lesions
  - Lesions involving the aqueduct
- Pathology Include low (I, II) + high grade (III, IV) gliomas
  - May be ependymomas, gangliogliomas, oligo's, & PNETS
- May produce obstructive HCP, CN and long tract signs
- Diagnosis – when part of diencephalic tumor or have an aqueductal component - Bx (endoscopic / stereotactic)
- Treatment – ETV / VPS for HCP (VPS may be preferred for severely compromised third vent )
- Tx as per epicenter tu:
  - ChTx ± Rx for diencephalic lesion (according to pathology)
  - Rx for pontine originating tumors (as per DPG)
  - Surgery – for selected, well delineated lesions reaching pial / ependymal surfaces

- Male
- Obstructive HCP
- Tegmental / aqueductal / tectal tumor
- ETV + endoscopic Bx (GBM)
- Resection + Radiation





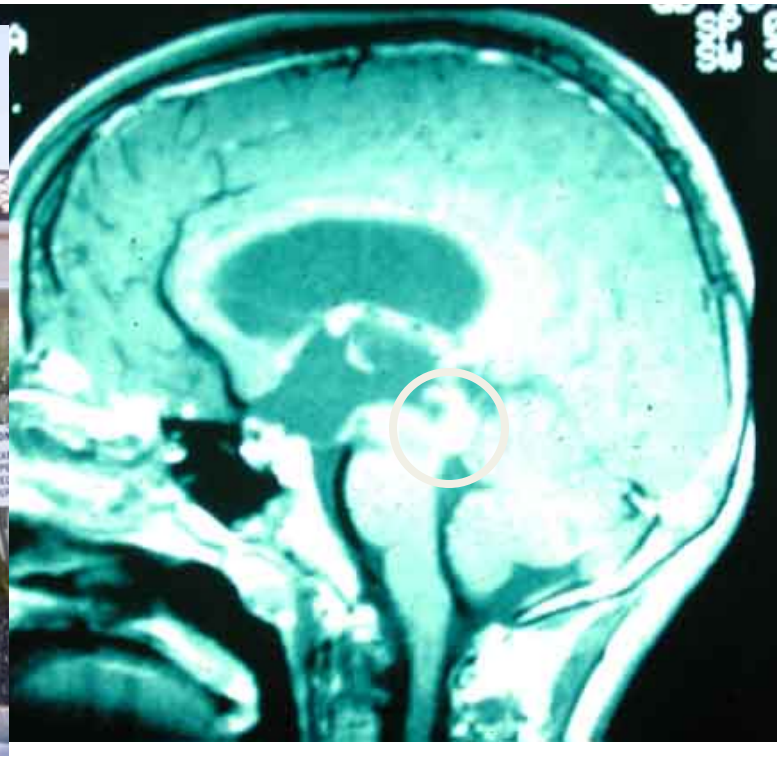


Film KM

# Midbrain lesions II

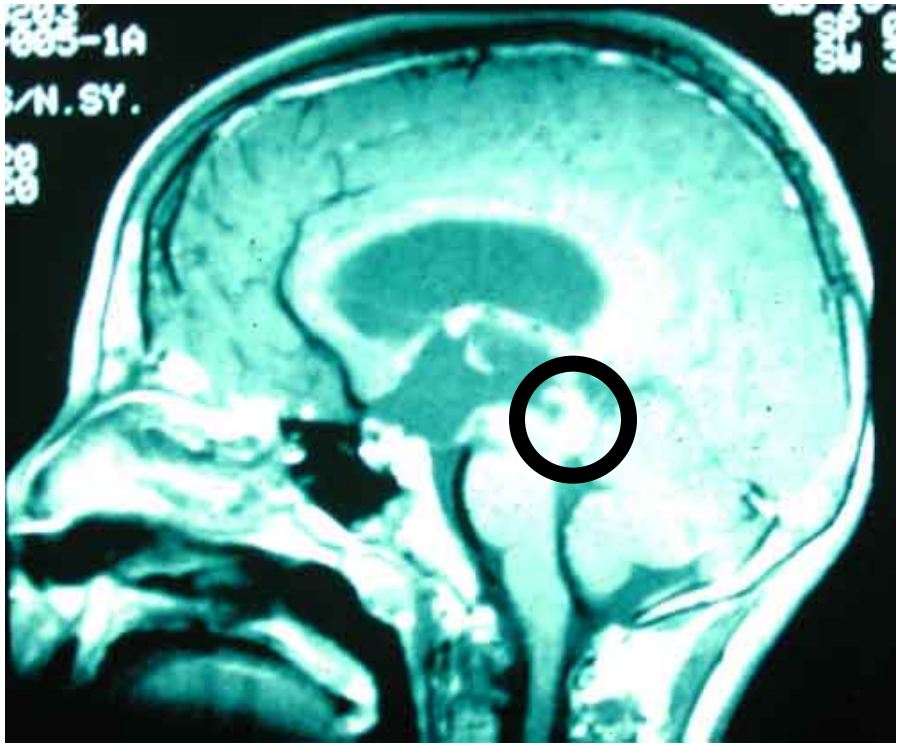
- Tectal lesions
  - Mostly low-grade gliomas.
    - Never undergo malignant transformation
  - Present mostly with obstructive HCP
  - Diagnosis – radiological (MR) No need for biopsy
  - Treatment – ETV for HCP, follow lesion
  - If tumor grows, or, undergoes enhancement changes – consider to operate or focally irradiate
    - (chemo for infants)

# Combining technology with understanding of biology

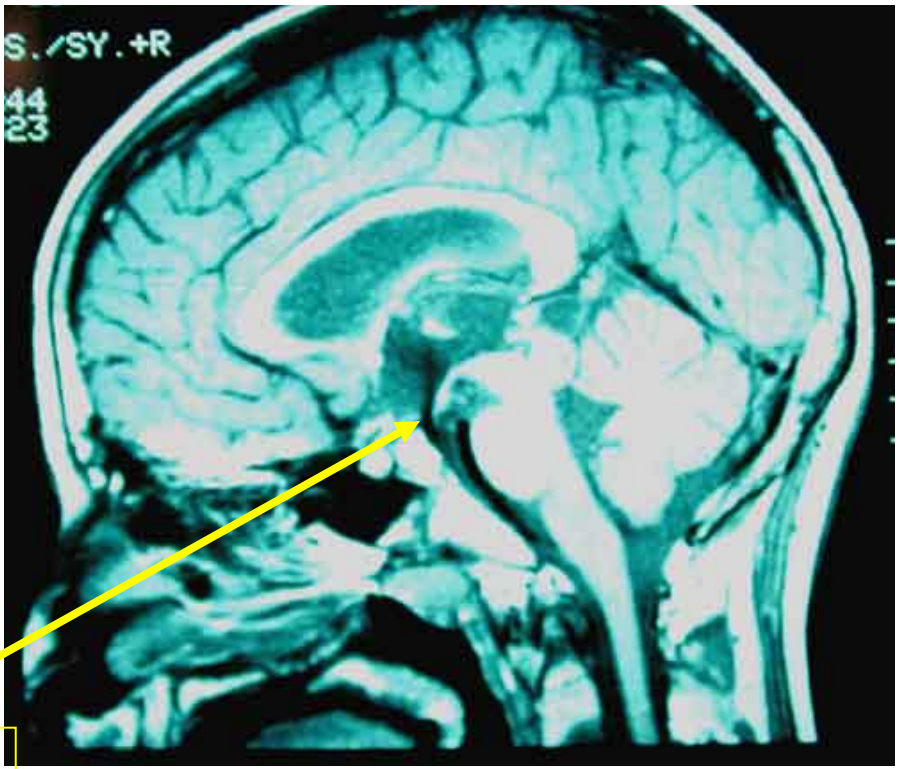
**15 y.o. male w/ tectal Tm**
**1994: ETV…… cured….**

# 15 y.o. male tectal Tm 1994
# 2012- tumor never changed



Pre-ETV

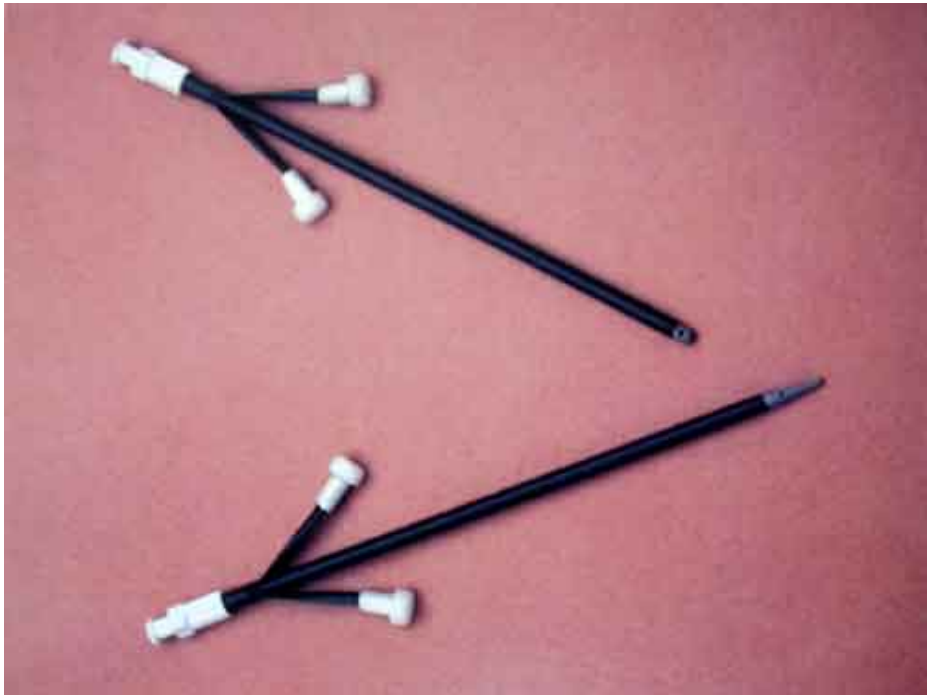
Post-ETV



*Flow void*

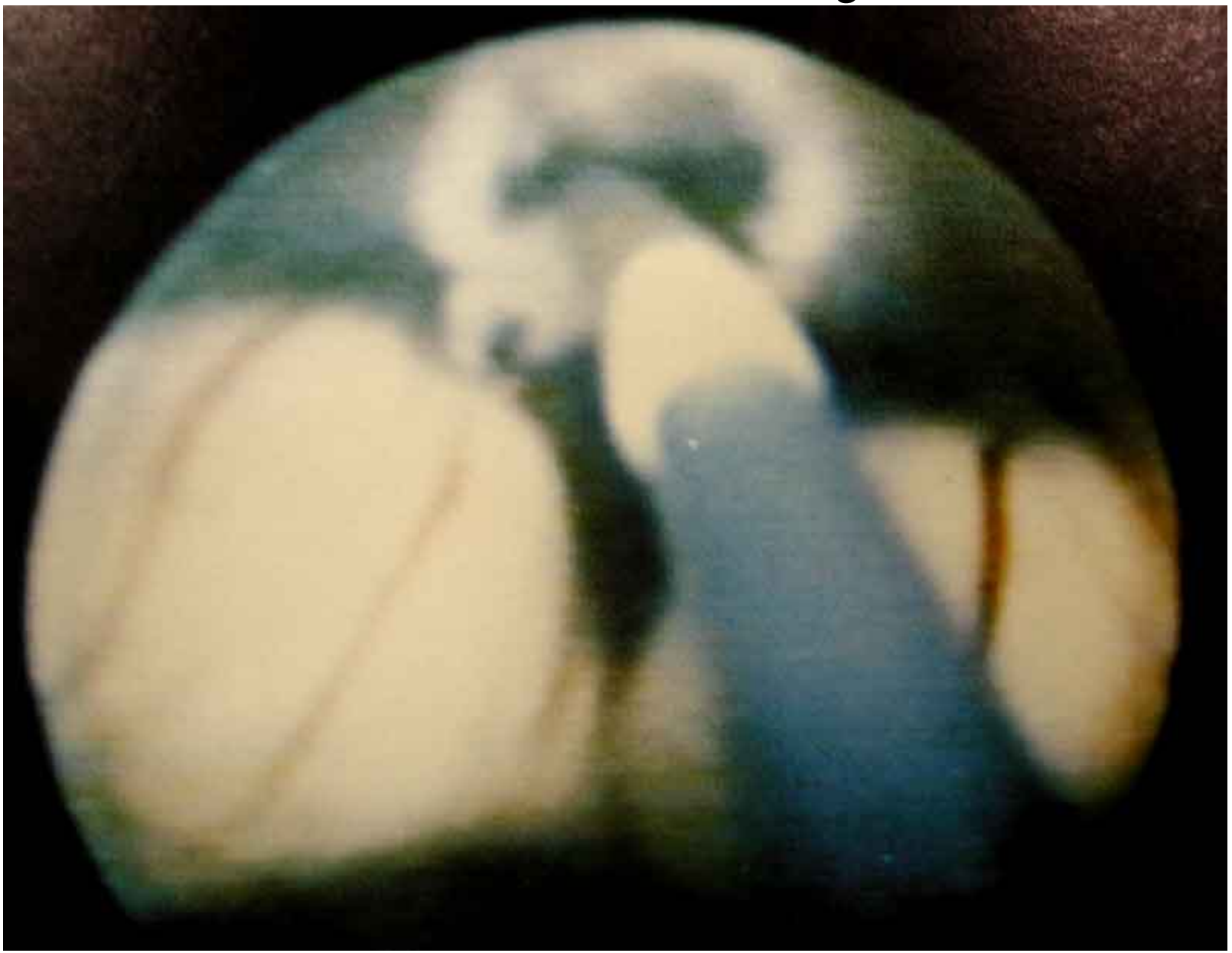
# ETV Setup

**Minimal shaving**



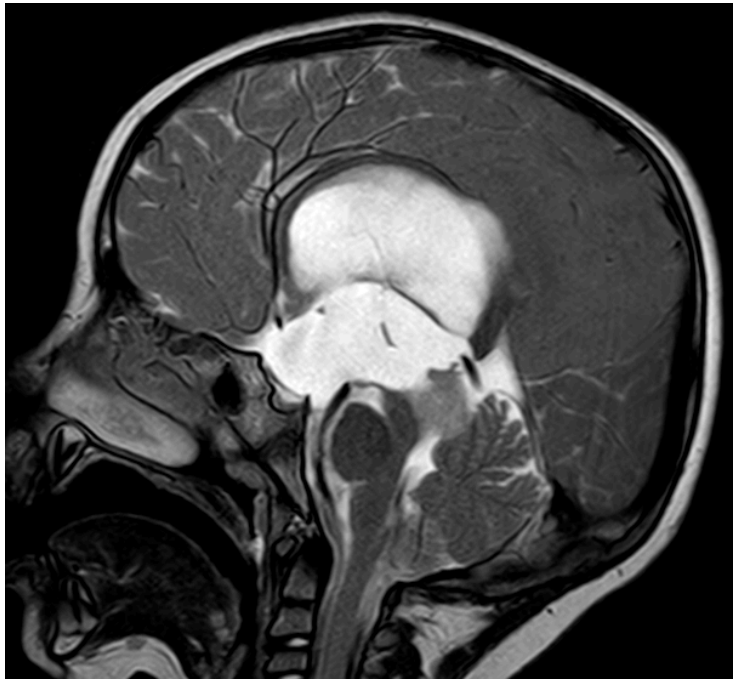
**A peel-away guide**

# Ventriculostomy site

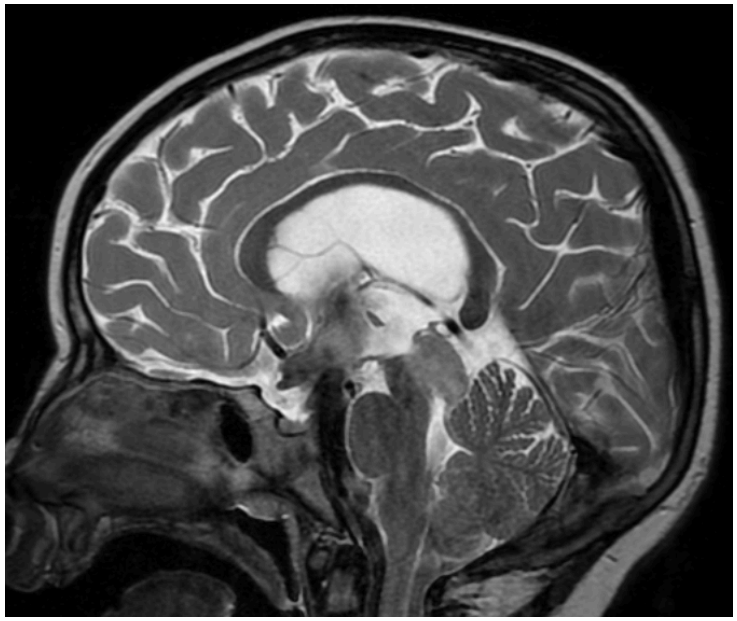


- 5 yo boy
- Obstructive HCP
- Tectal tumor no enhancement
- ETV, follow

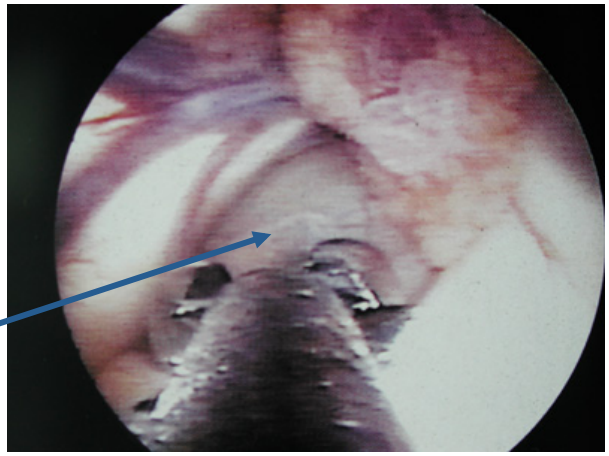
Preop



Postop
Note Flow-void

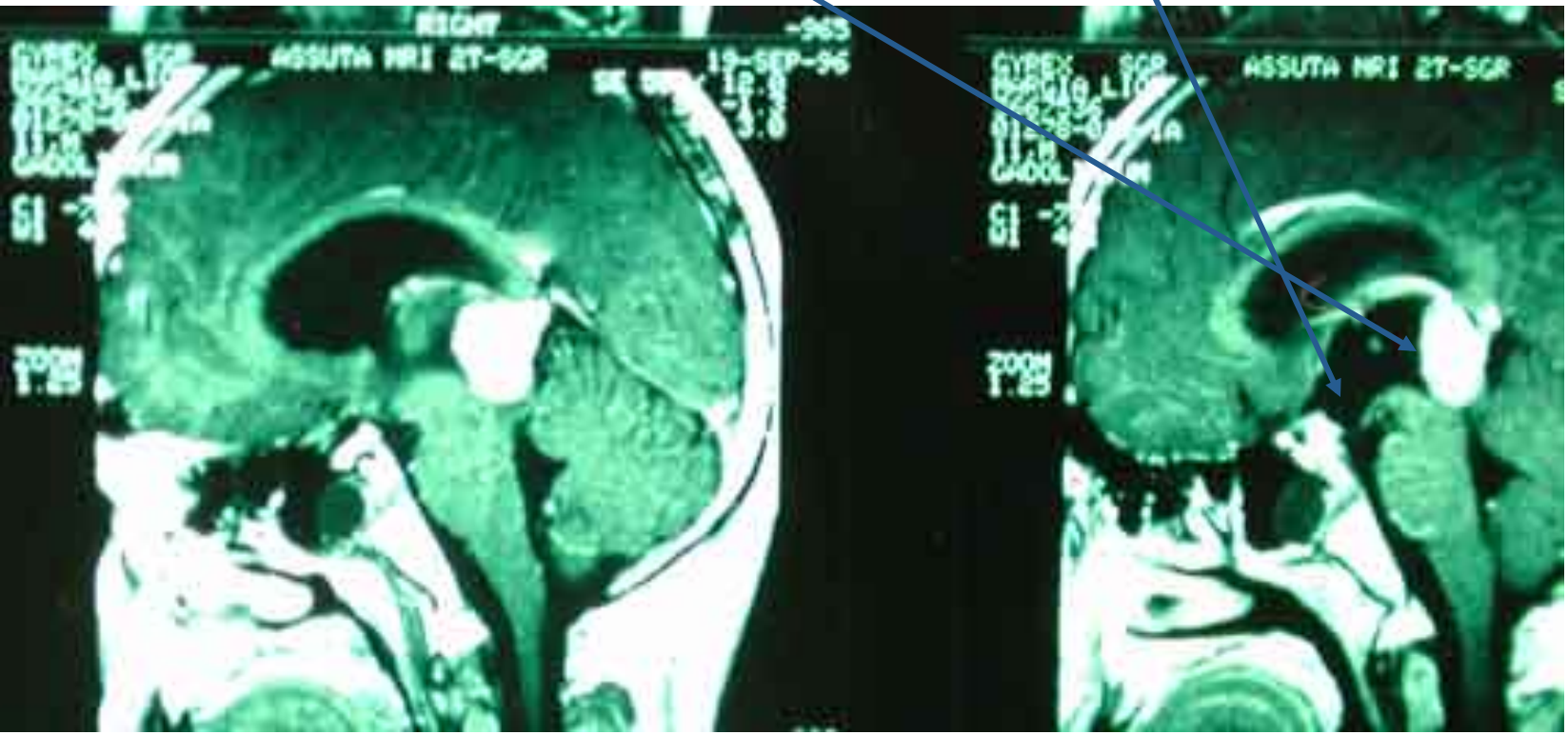


# Easy to differentiate:
# Pineal Tumor (Not a BST)
# Germinoma



**Biopsy**

**ETV**

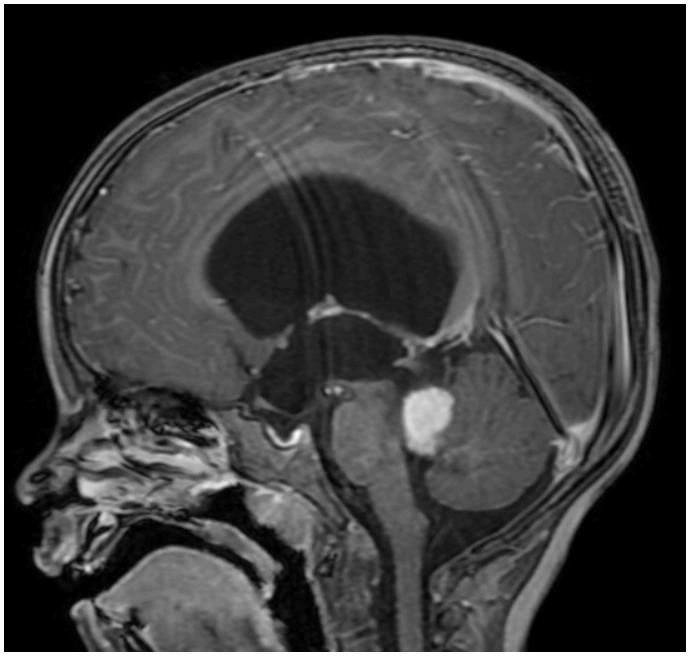


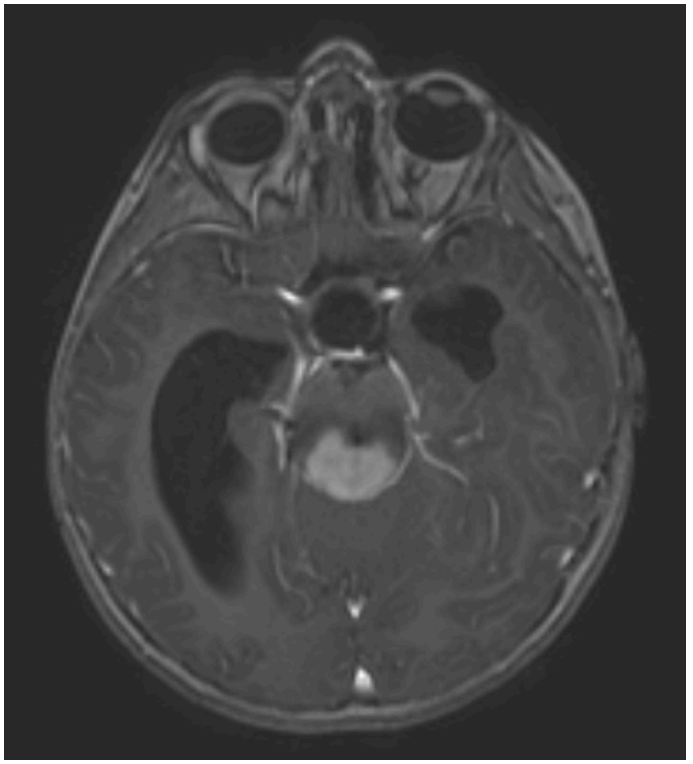
# Midbrain lesions III

- Dorsal exophitic tumors
  - Usually low-grade
  - Present with HCP, incidental
  - Typical in NF 1
  - Diagnosis – Biopsy?  Occasionally to follow
  - Treatment – resection, Chemotherapy, Radiation*

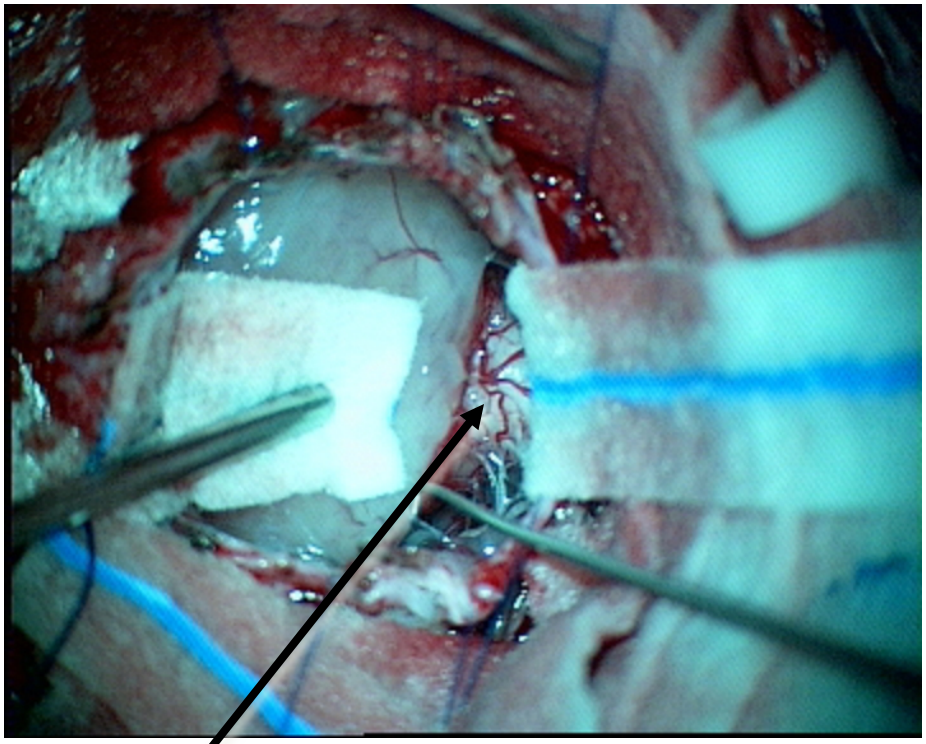
  - * the optimal type of radiation is not determined
    - Proton Beam, fractionated should be considered in young children

- 4 yo boy
- Obstructive HCP
- ETV + endoscopic Bx (JPA)
- Resection (trans 4V)

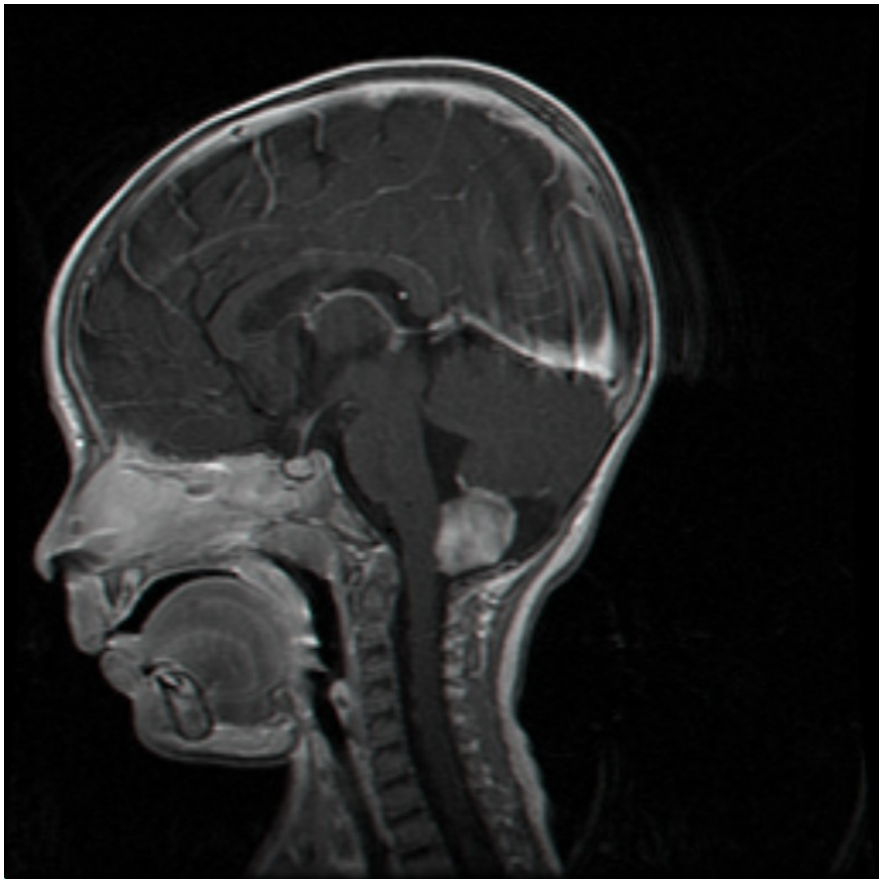




10m old: since 3m:
Severe FTT, Some vomiting, 4Kg
4 hospitals: massive GE workup

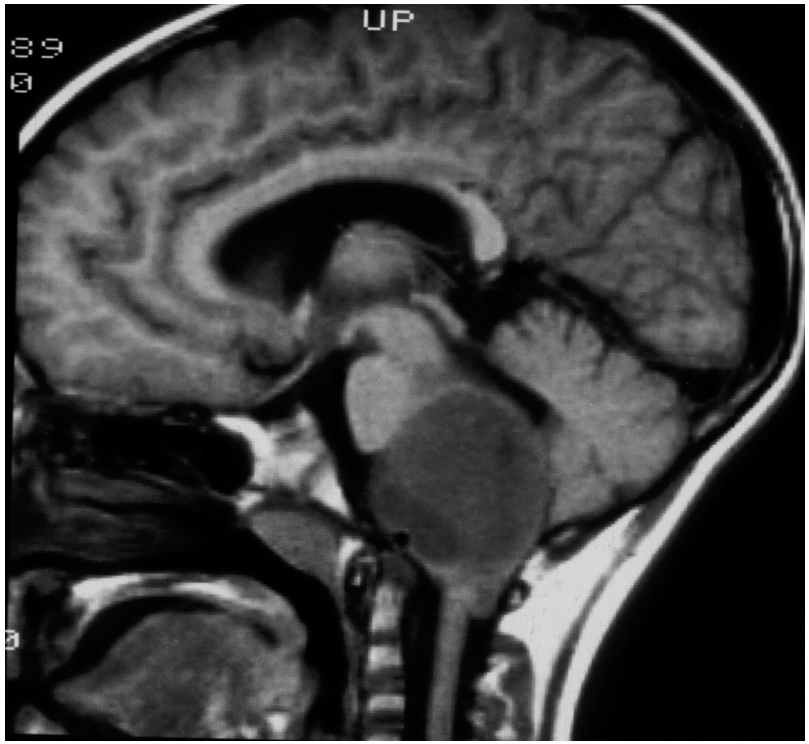


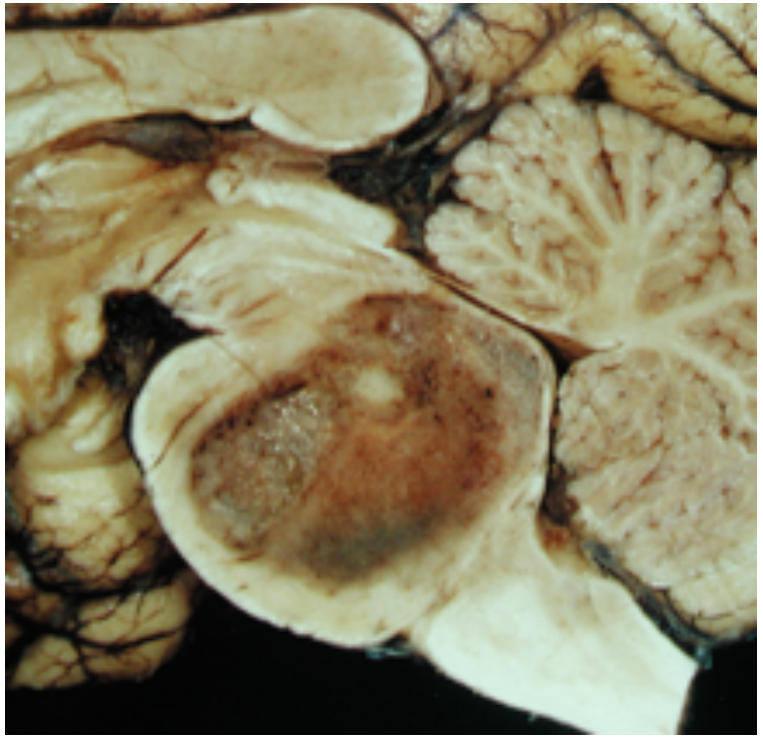
Infiltrated Obex



GTR: Pathology: JPA

# Diffuse Brainstem tumors



The only step forward we have made is: No biopsy required

# Pontine tumors DPG

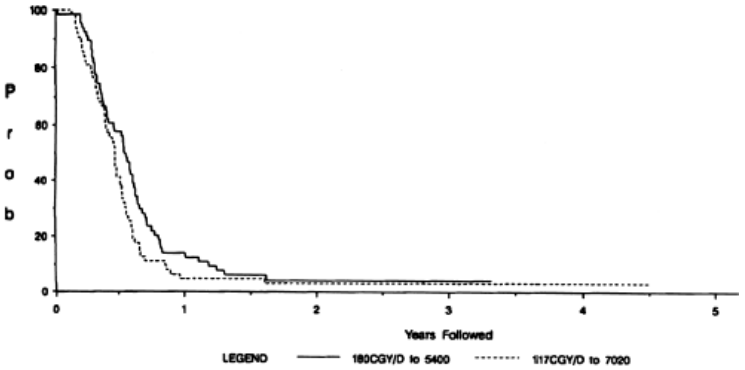
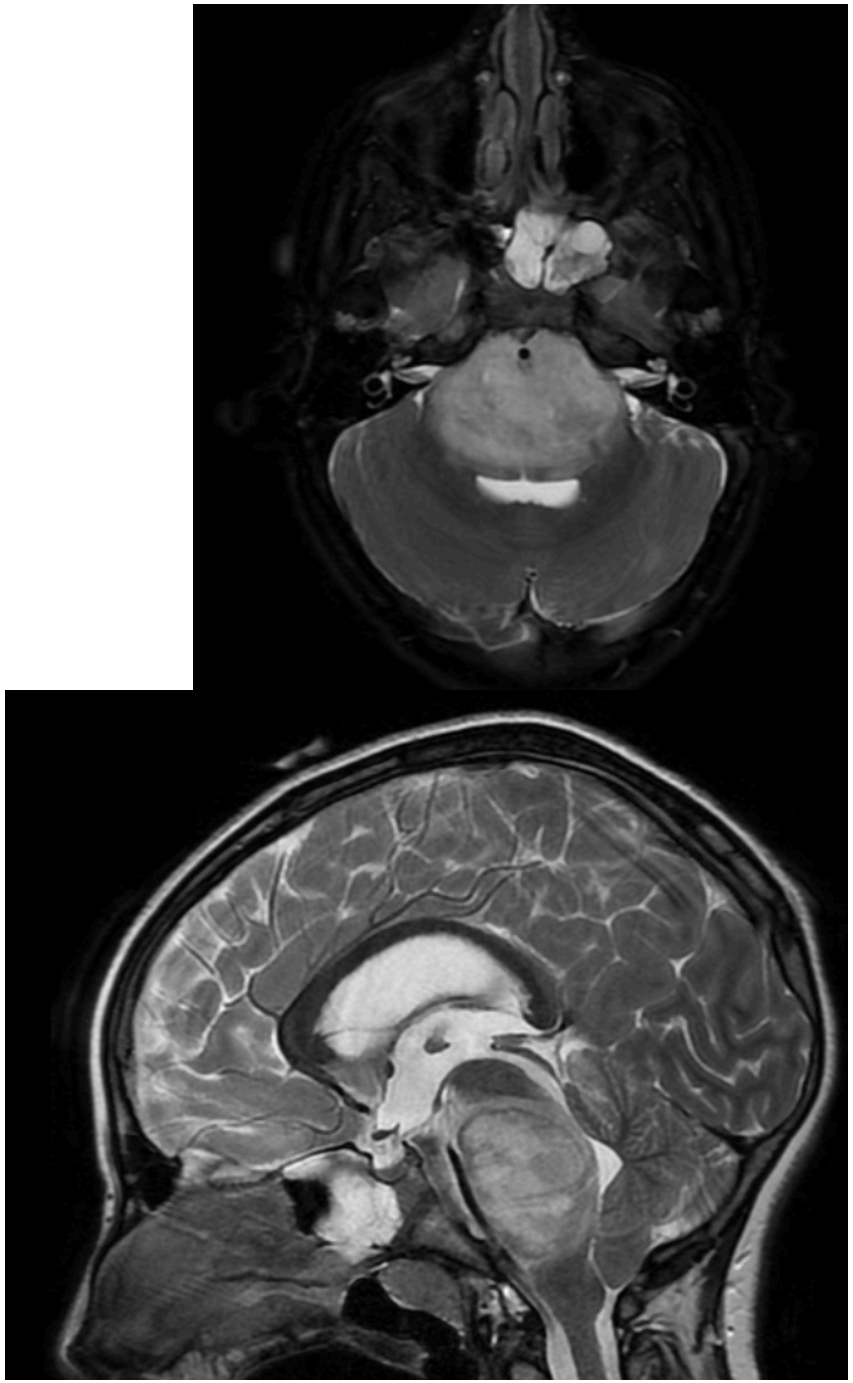


Fig. 1. Event-free survival (arm 1, 66 patients; arm 2, 65 patients).

- Diffuse pontine glioma (DPG)
  - Highly malignant, poorly responsive tumor
  - Mean survival about 1 year
  - Age group – mostly 5-10 years old
  - Pathology may include grade II, III and IV
  - Typically presents with CN deficits (esp CN VI and VII), long tract and cerebellar signs common too
  - May present with HCP
  - Diagnosis
    - Radiological diffuse (> 50-66%) pontine involvement (T2 hyper intensity), inconsistent enhancements, basilar artery often engulfed by tumor
    - Bx – debatable if radiology is typical, has a role in atypical cases (eccentric tumors). May have a sampling error, and does not represent tumor biology even if grade II
  - Treatment
    - HCP – VPS  ETV has limitations in this situation
    - Radiation  Has chemotherapy a role? Is it MGHT dependent?

- 10 yo girl
- Headaches
- CN6 palsy
- Imaging typical for DPG, also HCP
- VPS
- radiation



# *Molecular characterization of pediatric brain stem infiltrative gliomas*

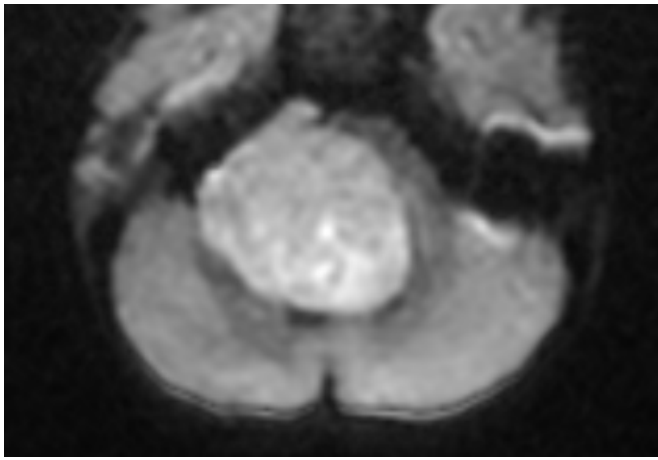
Stéphanie Puget, Cathy Philippe, Bastien Job, Thomas Roujeau, Pascale Varlet, Catherine Richon, Chris Jones, Christian Sainte-Rose, Jacques Grill (Paris, France)

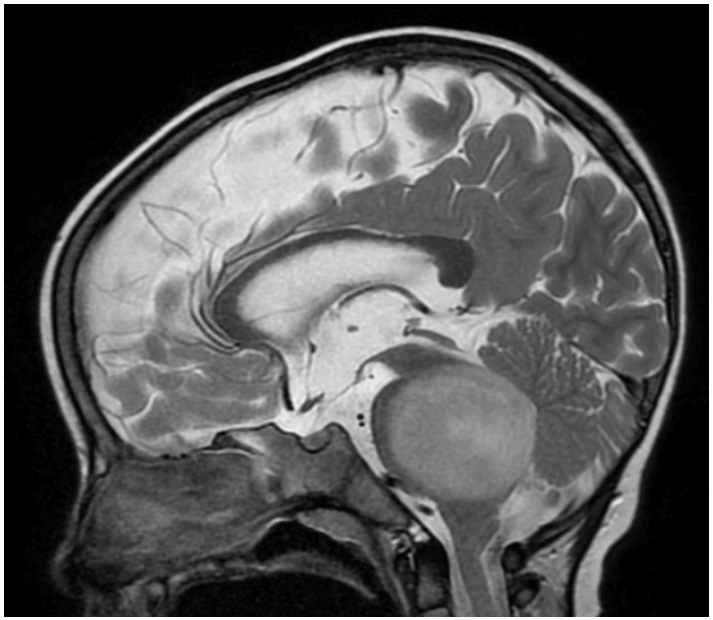
- Stereotactic biopsy in 60 children with typical MRI for BSIG
- Mean age 6.8 years - Median overall survival 10 months
- 3 patients suffered transient deficit
- Diagnostic yield: 100%
- 59 patients diagnosed with BSIG:
  - 6 cases not graded
  - 14 were grade II
  - 20 were grade III
  - 19 were grade IV
  - 1 pilocytic astrocytoma (excluded)
- Grade and MRI features not associated with survival
- 38 patients with frozen samples: 32 of them array-CGH and gene expression profiles
- 3 patterns identified in the a-CGH unsupervised clustering:
  - gain of 1q (100% of cases)
  - no or very few aberrations
  - many losses (the most frequent ch14q in 38% of cases and 17p
  - clusterisation poorly correlated with survival but showed a significant association with tumors grades (P=0.01)
  - amplification of PDGFRa in 4 samples demonstrated and some mutations for this gene found

# Biopsy is not justified out of study

# Atypical DPG that should undergo Bx

- 2 yo boy
- Gait instability
- Eccentric pontine lesion, restricted diffusion
- Bx- PNET
- Died despite Chemotherapy



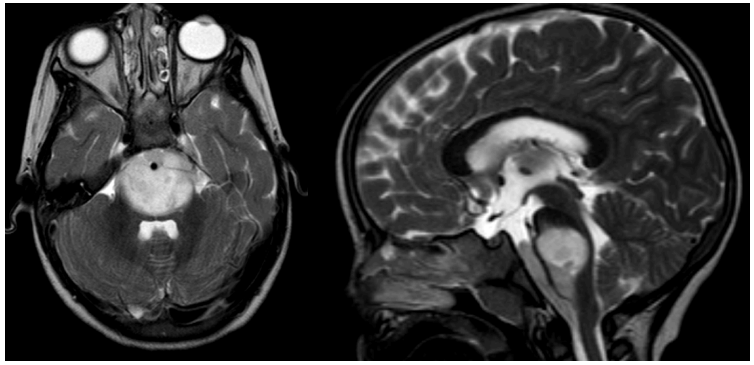


- Watch for inflammatory processes

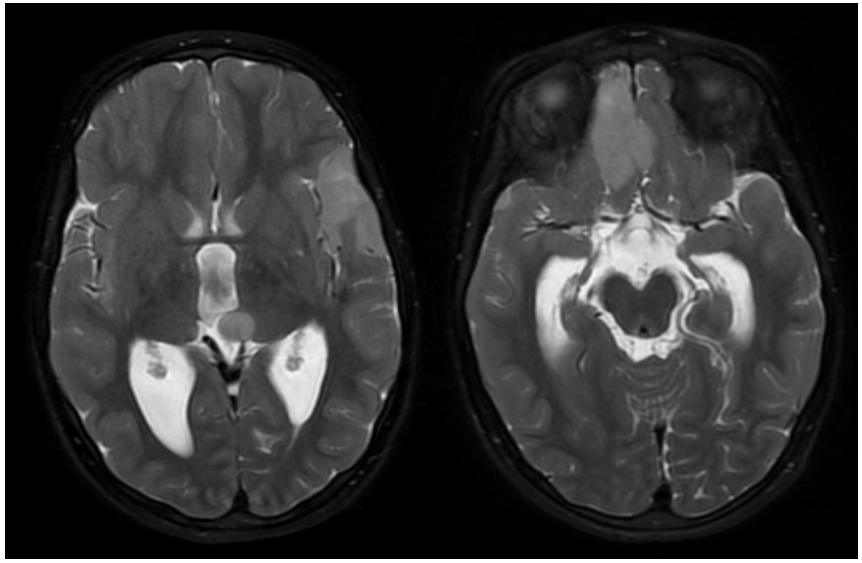
- 15 y girl
- Brainstem encephalitis

- 4 yo girl
- Tiered, decreased appetite
- CN7 and long tract signs
- On MRI – lesion has an exophitic component reaching the foramen magnum
- Bx – grade II astrocytoma
- ChTx + Rx
- 1 year later, multiple tumor focci, pt died

On presentation



1 year later

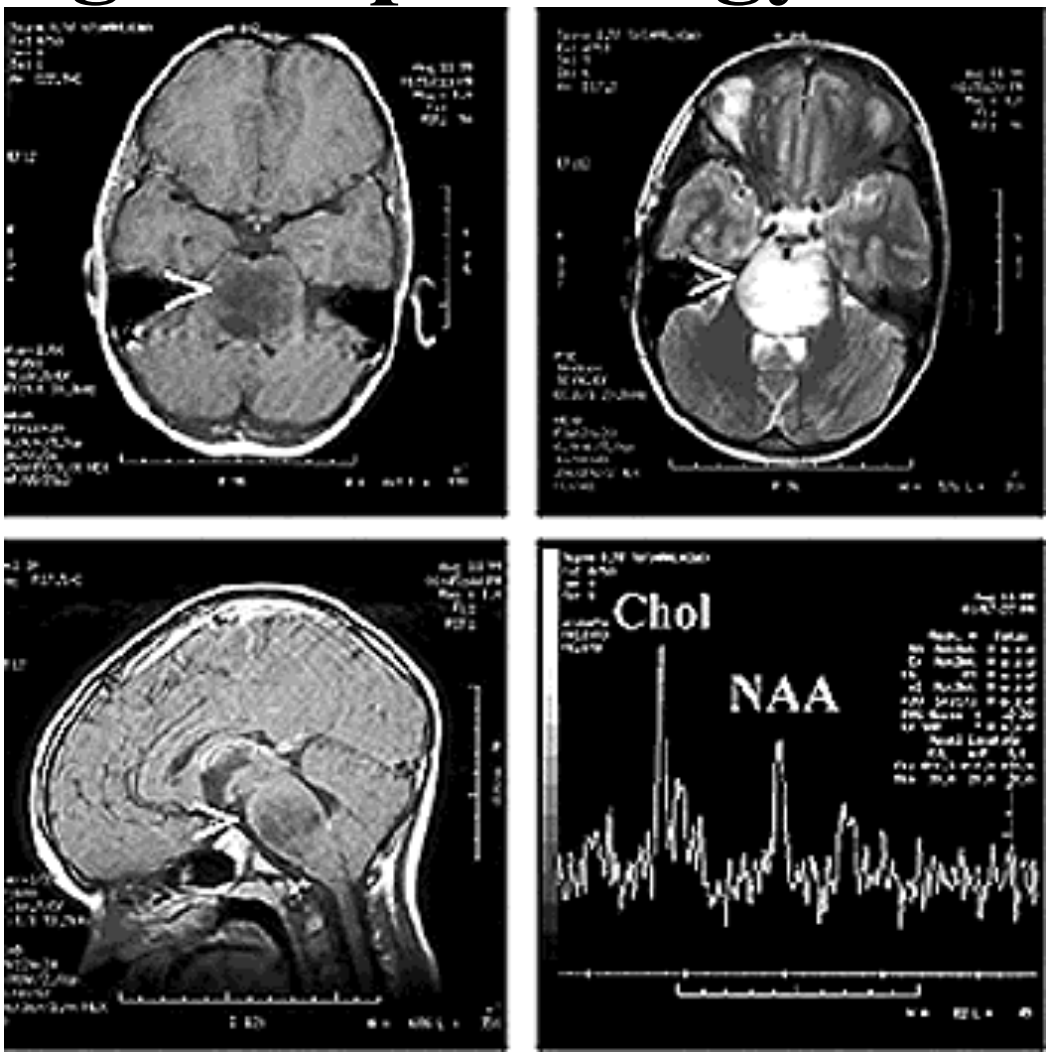


- 22 yo male
- Diplopia, headaches
- Radiation

# MR Spectroscopy: defining histopathology?

*Clinical significance?*

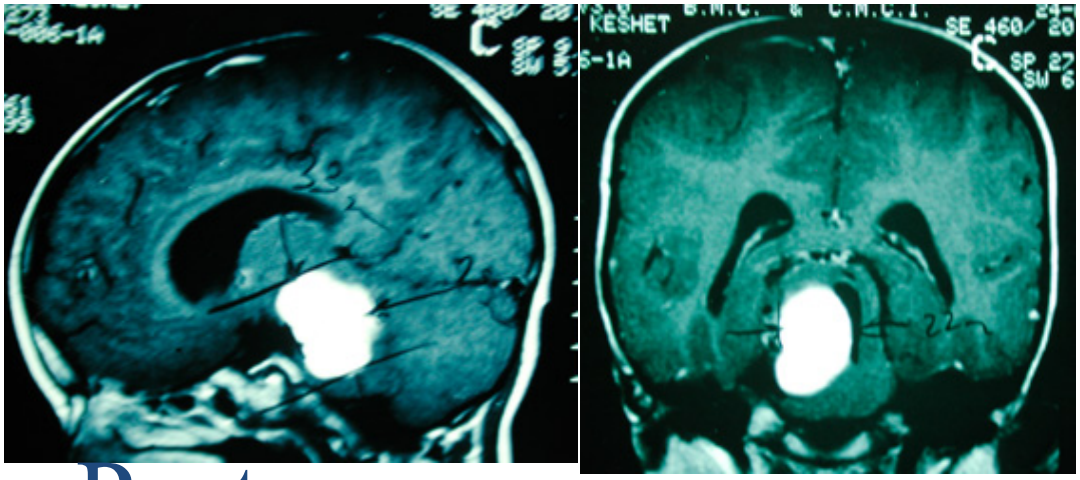
**Not reliable enough to be used for tumor differentiation**



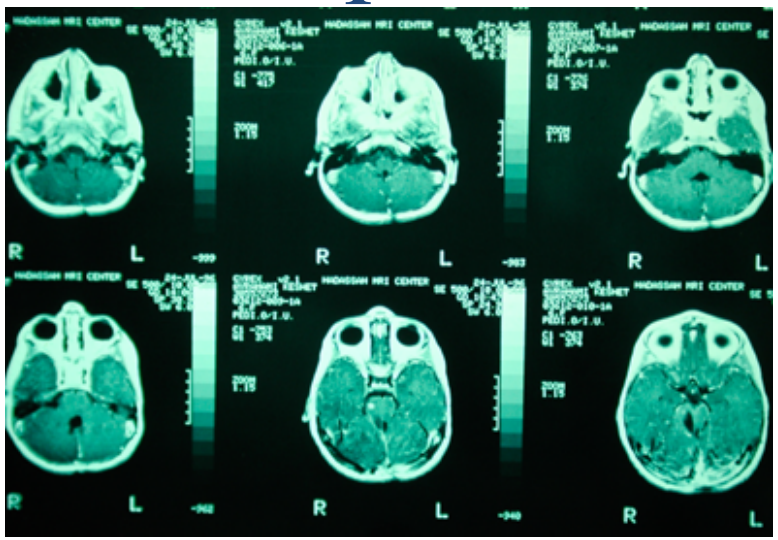

***Patient with diffuse pontine glioma: no need for Bx?***

# Focal Brainstem tumor-JPA

1994 **1994: Surgery GTR:** 2003




Postop



**Today:**

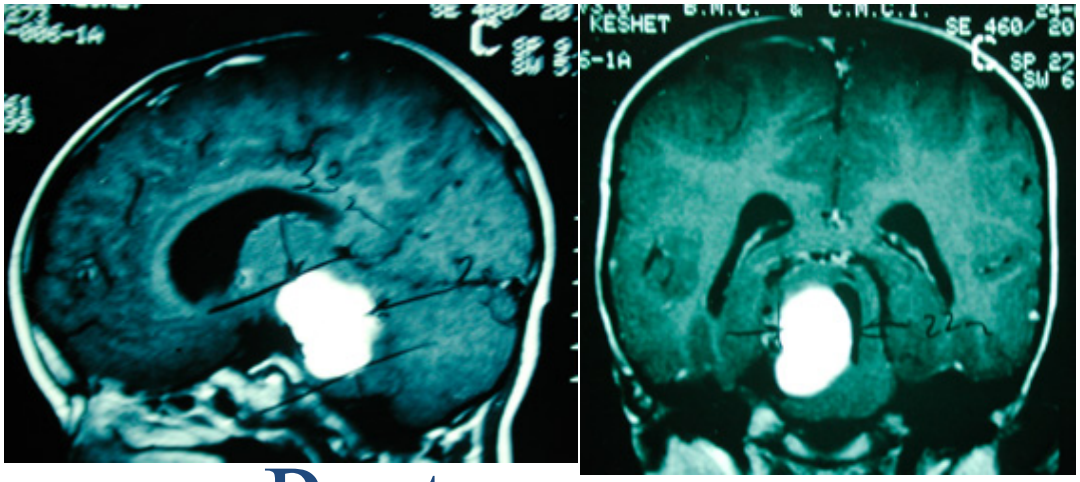
**SP Rxt**

**SP Chemo (soft)**

**Role of multi-modality treatment**

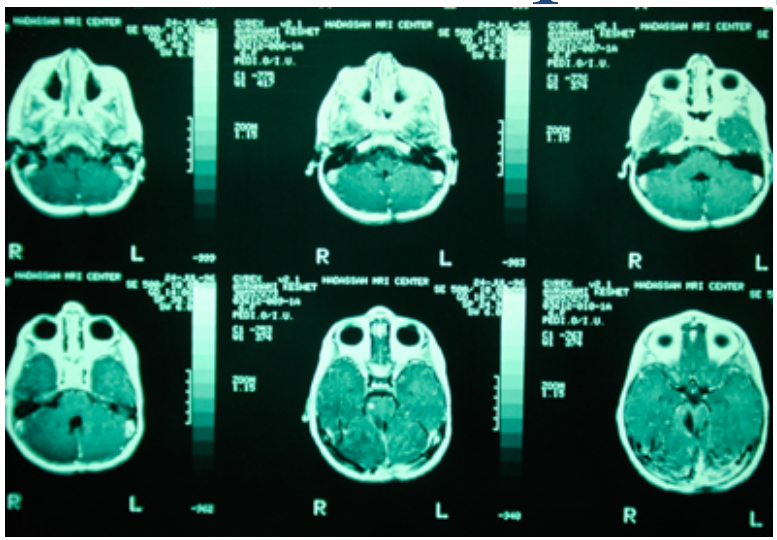
# Focal Brainstem tumor-JPA

1994




2010

Postop



**Today**

**SP Rxt**

**SP Chemo**

**(soft)**

# Multi-modality treatment for low-grade astrocytomas

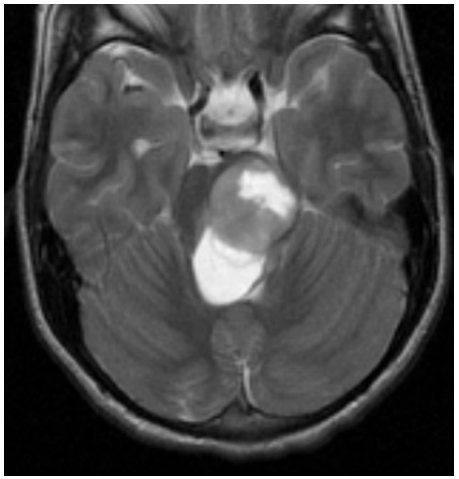
- Surgery
- RxT
- Chemotherapy
- Nothing

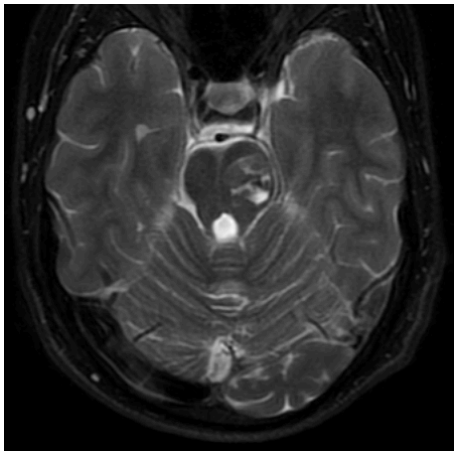
***How to combine them***

***Challenge: QOL!***

# Focal pontine tumor

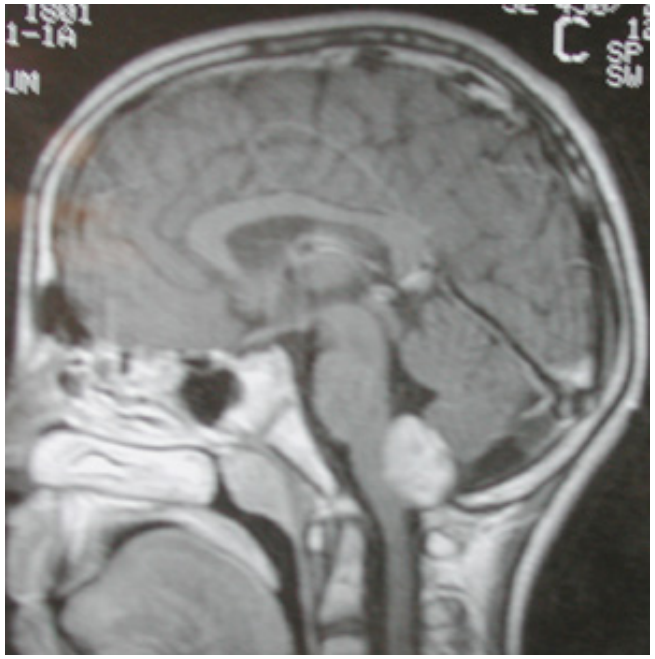
- 15 yo male
- Chronic complaint of dyplopia
- Recent right hemiparesis
- Partial resection (2005)
- Pathology – JPA
- Followed by soft chemotherapy
- Recent MRI (2011) steady
- Clinically doing very well

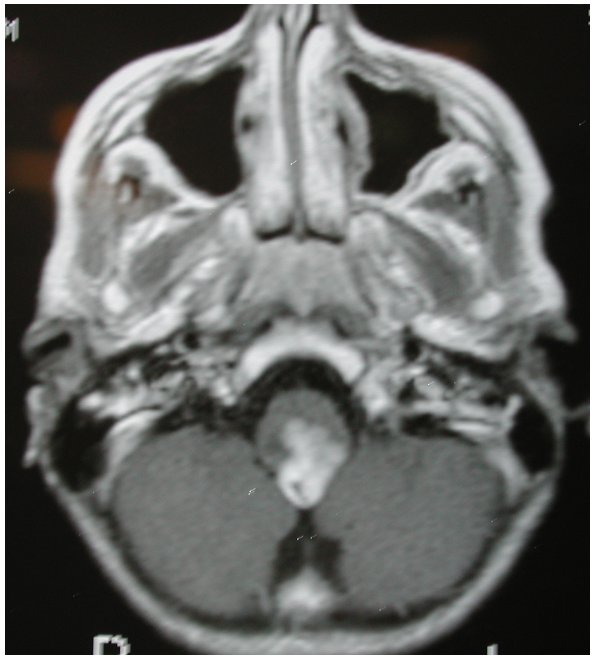




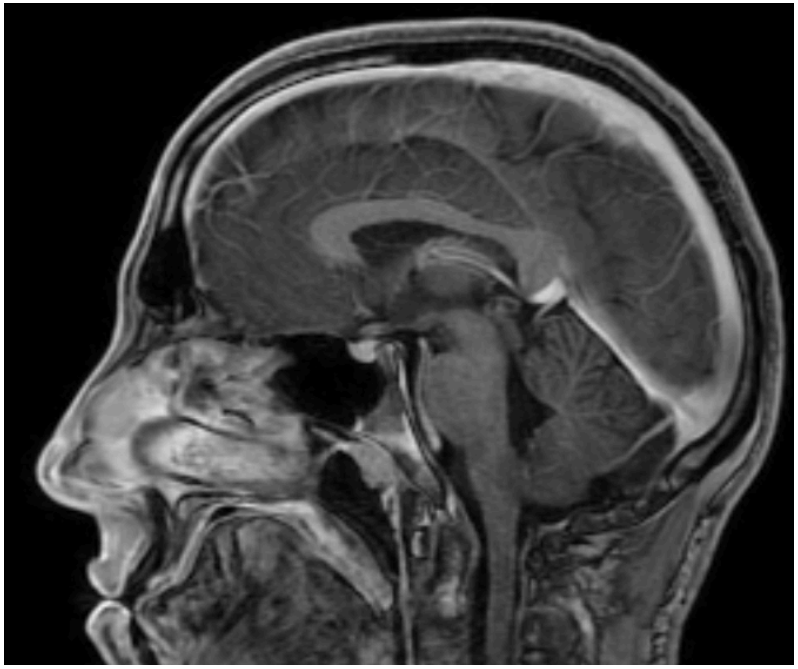
# Exophitic medullary tumor

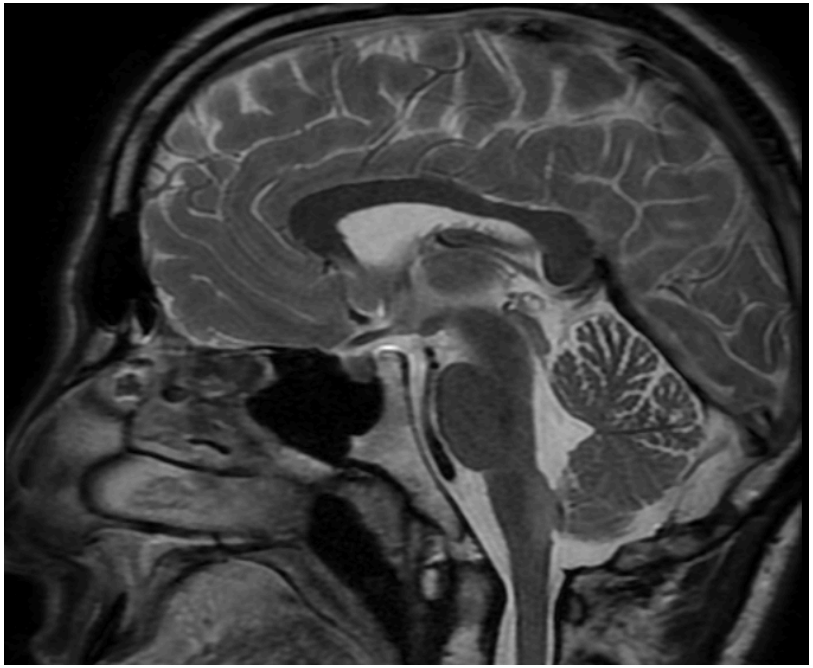
- 13 yo boy
- Nausea, weight loss, no neurological deficits



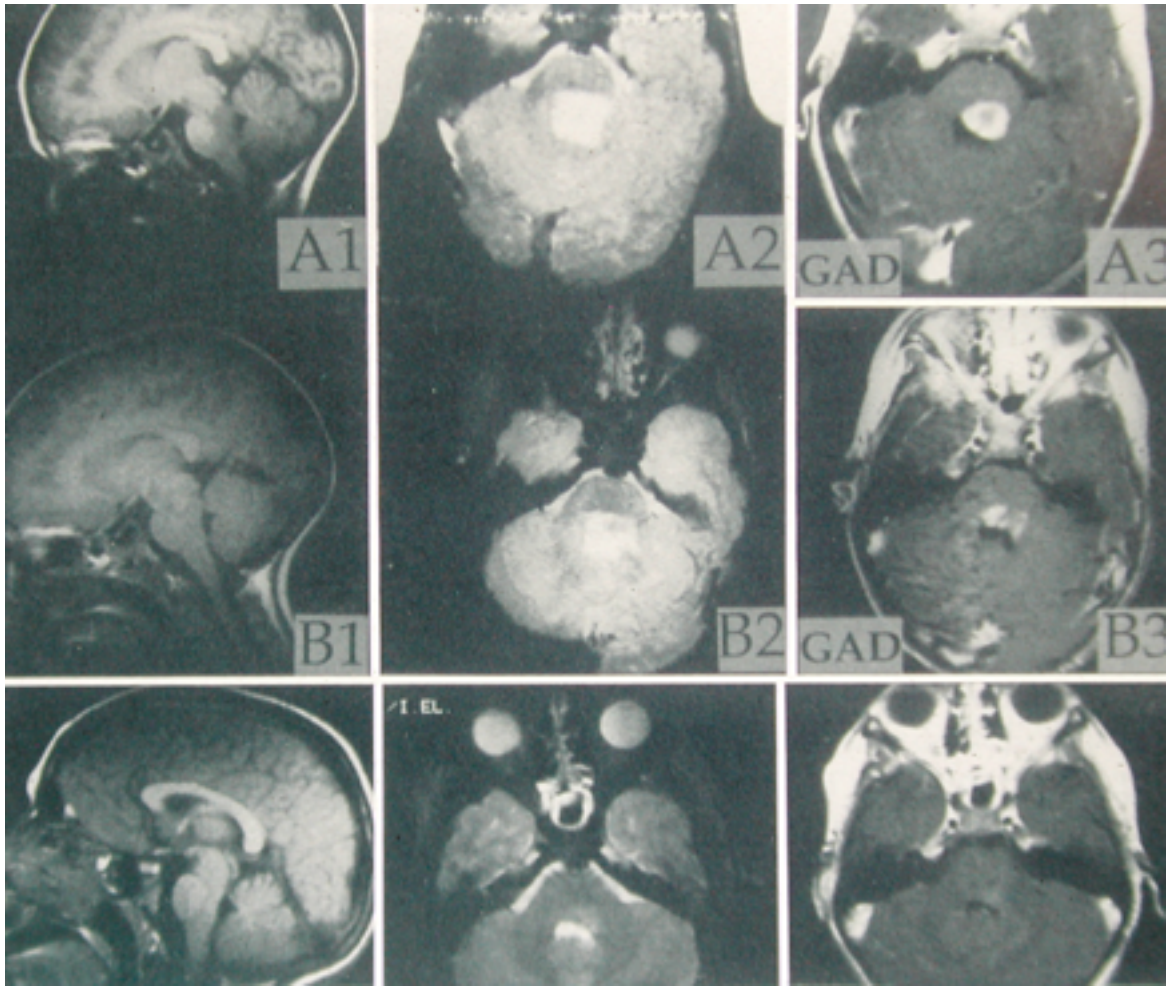


- Underwent GTR – JPA (2001)
- Prolonged ventilation (8d's)
- Rt Hypoglossal palsy, stable
- Stable postoperative tissue changes (2012)





# Focal brainStem tumor: Spontaneous involution: no treatment

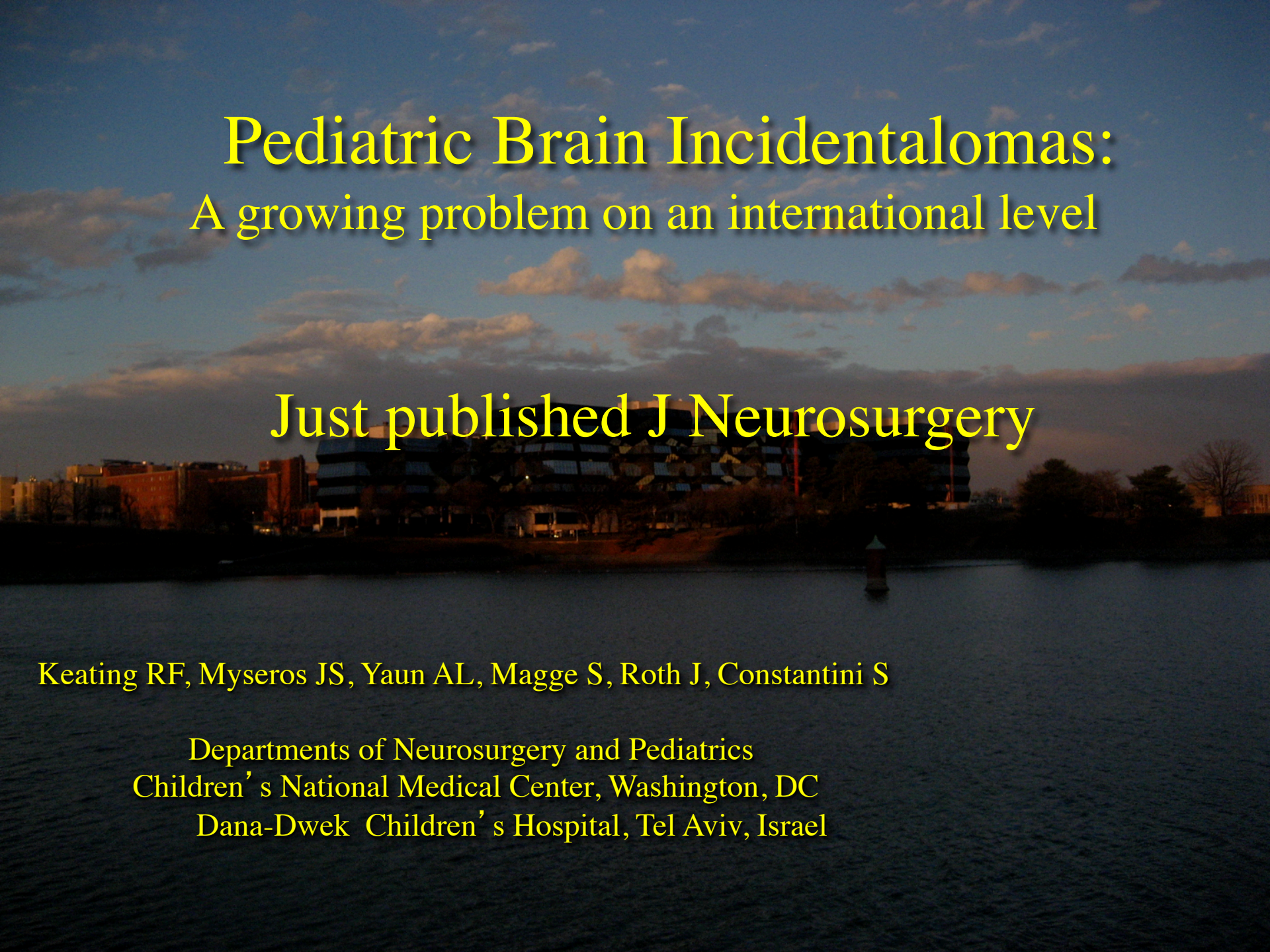



1988

1990

1992

S. Rao, S. Constantini, M. Gomori, F.J. Epstein, T. Siegal
Spontaneous involution of an intra-axial brainstem tumor : a case report.
Pediatric Neurosurgery 23(5):279-281, 1997



# Pediatric Brain Incidentalomas:
## A growing problem on an international level

## Just published J Neurosurgery

Keating RF, Myseros JS, Yaun AL, Magge S, Roth J, Constantini S

Departments of Neurosurgery and Pediatrics
Children's National Medical Center, Washington, DC
Dana-Dwek Children's Hospital, Tel Aviv, Israel

# Pediatric incidental brain tumors: a growing treatment dilemma

Clinical article

**Jonathan Roth, M.D.,[1] Robert F. Keating, M.D.,[2] John S. Myseros, M.D.,[2] Amanda L. Yaun, M.D.,[2] Suresh N. Magge, M.D.,[2] and Shlomi Constantini, M.D., M.Sc.[1]**

*[1]Department of Pediatric Neurosurgery, Dana Children's Hospital, Tel-Aviv Medical Center, Tel-Aviv, Israel; and [2]Departments of Neurosurgery and Pediatrics, Children's National Medical Center, Washington, DC*

*J Neurosurg: Pediatrics / July 20, 2012*

# Surgery tips BST's I

- Study anatomical variation very carefully
  - Potential relationship to peduncles and C nuclei

- Mostly from the back
  Midline or side depending on location
  Most would do prone
    - Sitting is possible for supra-cerebellar approaches

- Trans-occipital and Parietal inter-hemispheric app
  For very superior lesions

- Trans or sub-temporal for anteriorly located lesions

# Surgery tips  BST's II

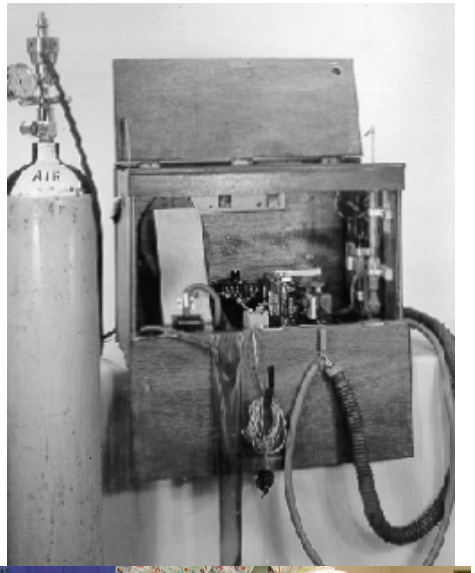
- Consider opening of Foramen magnum
- Consider a ventricular catheter in those with HCP
- Watch for occipital sinus in infants
- Avoid large vermian splitting
- Consider navigation in truly intrinsic tumors
- Enter 4$^{th}$ V in safe zones with monitoring
- Work from inside-out  Always use CUSA
- Be very modest in Medulla
- Informed consent should include (beyond specific points)
  - Sensory deficits Including position
  - Diplopia
  - Mutism

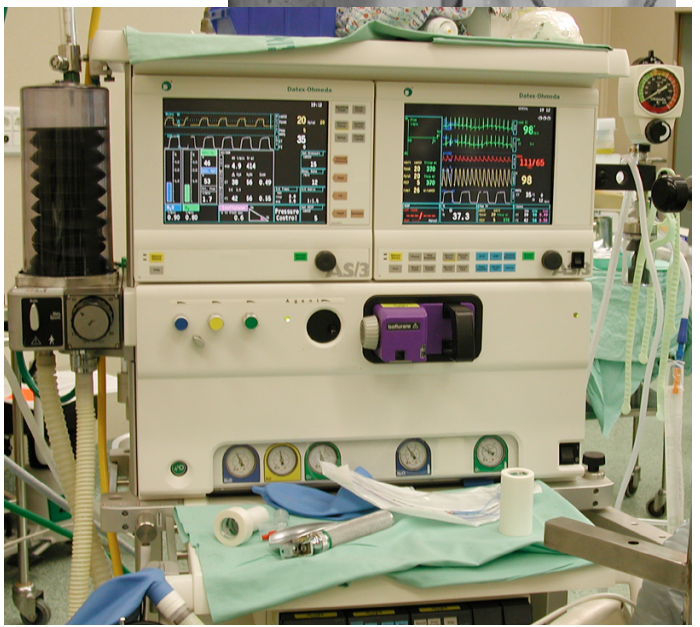
# Revolution in anesthesia/ICU

## Especially important in BS Surgery


prototype inhaler


wire masks



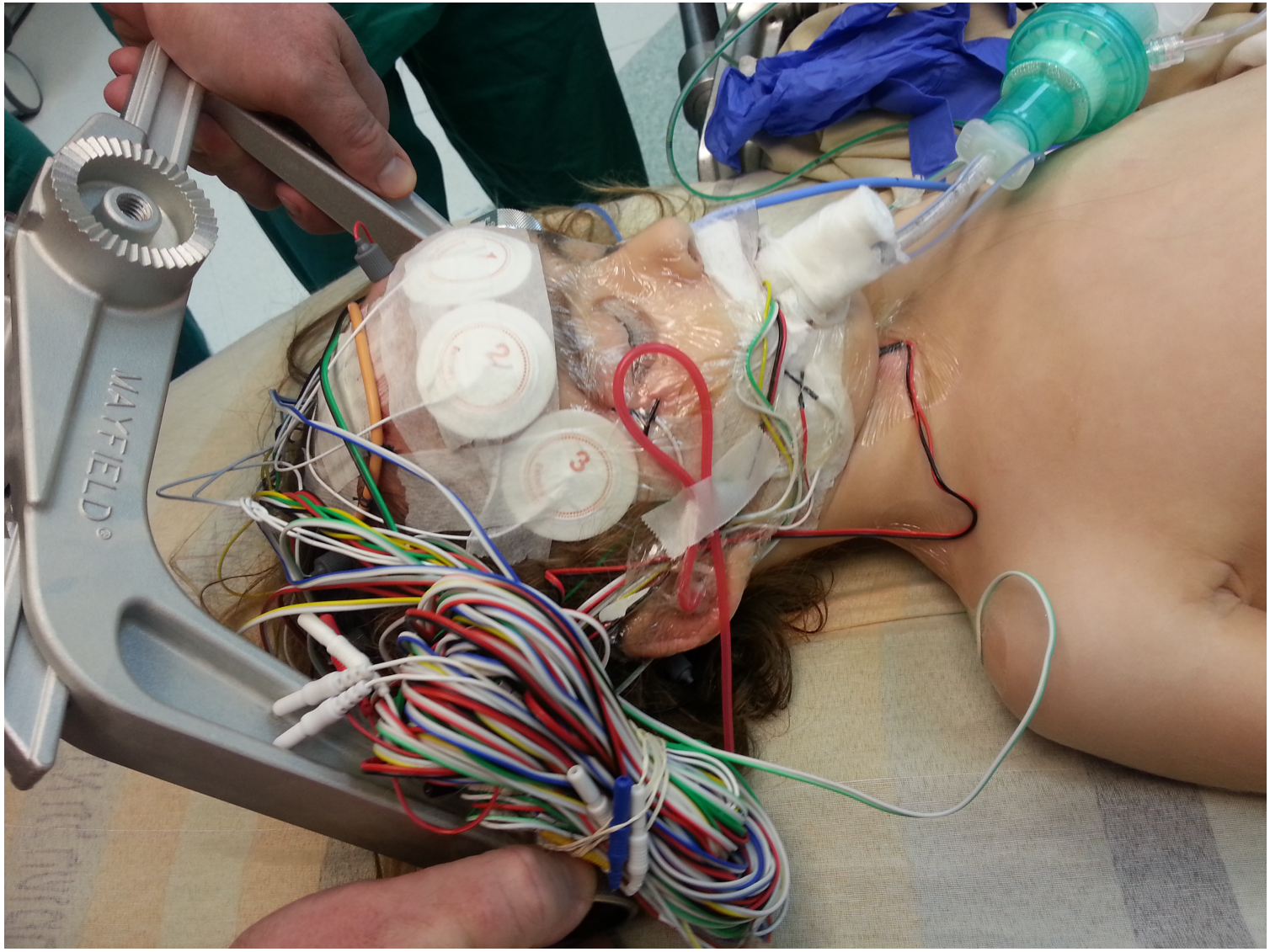



*Long OR*
*Relaxed brain*
*Blood replacement*
*Metabolic control*

Changes in pulse and BP are VERY relevant!

# The setup!

# Intra-operative Monitoring in Brain Stem tumor surgery

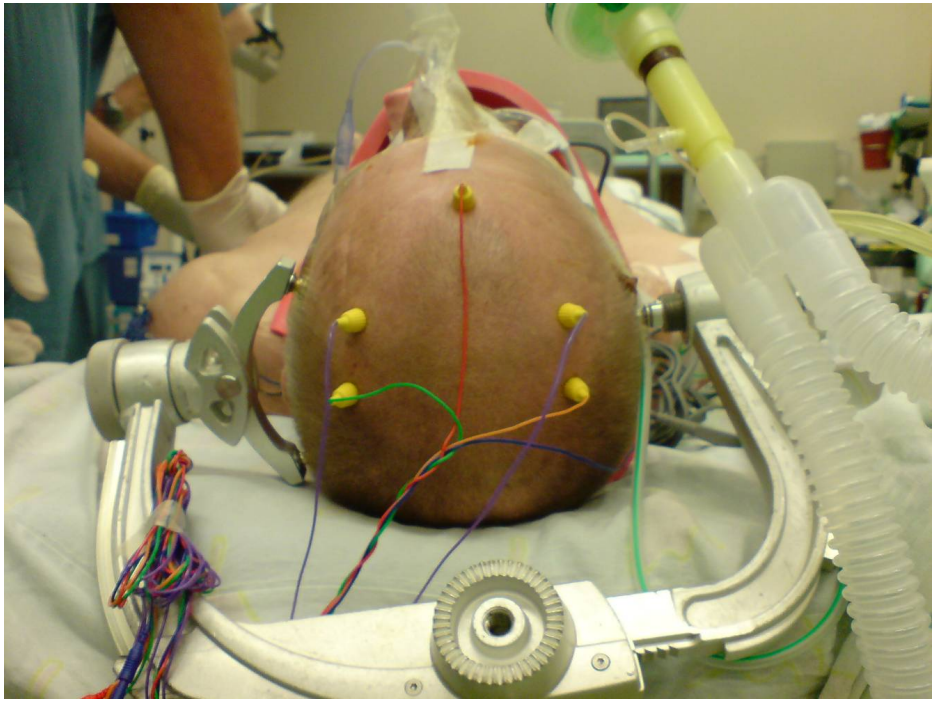


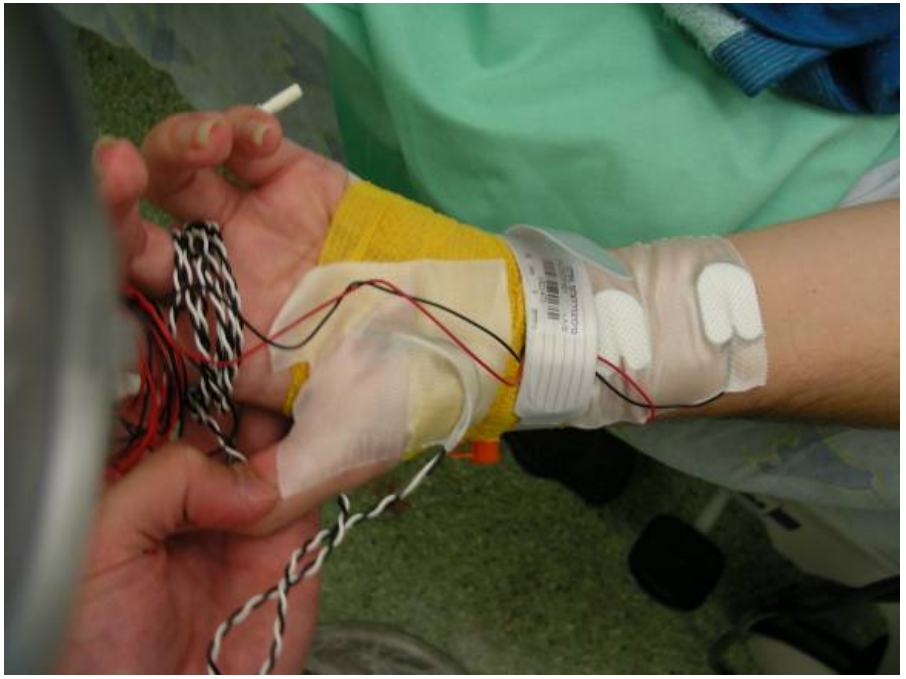
# Structures at Risk

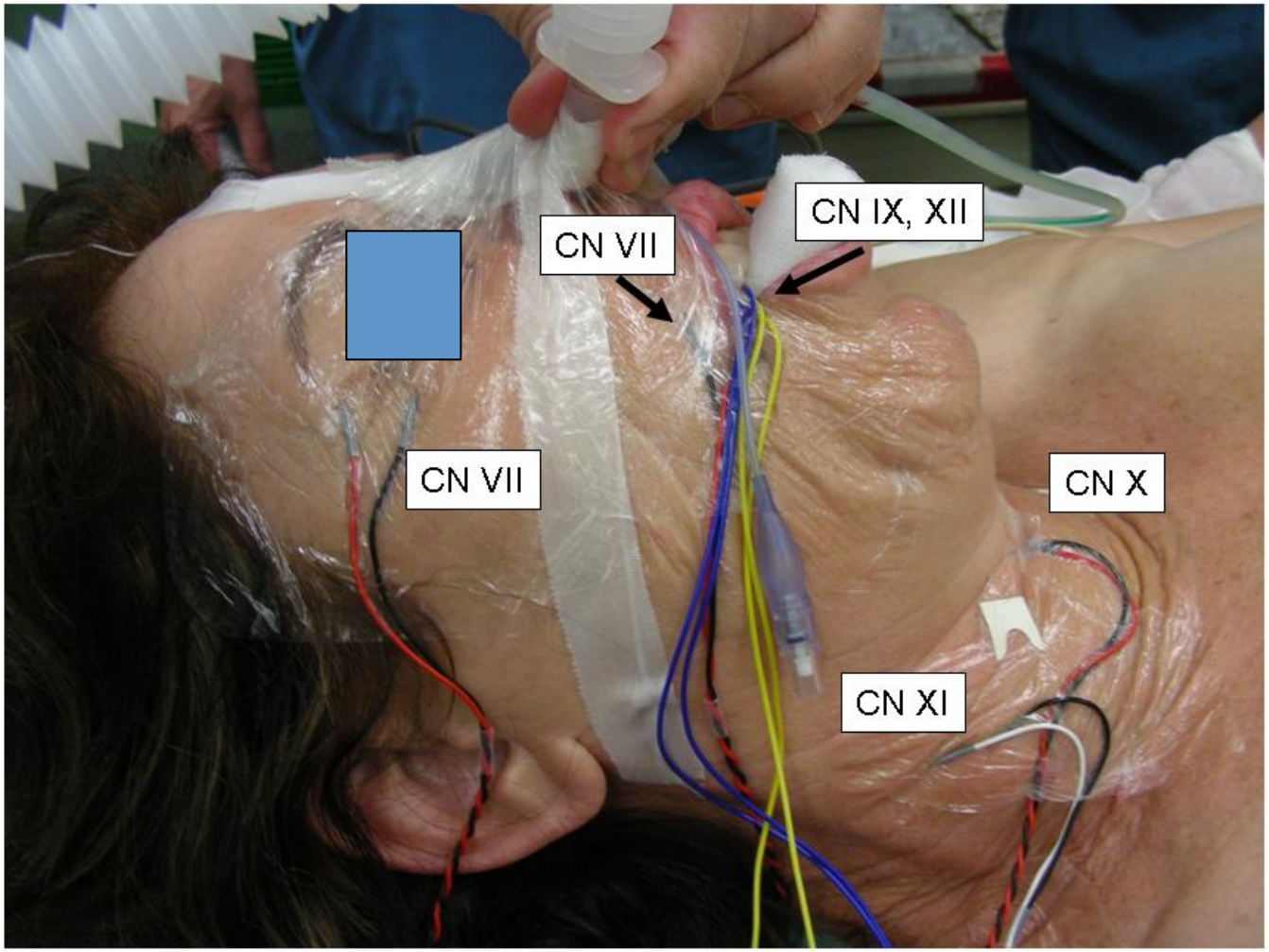
- Corticospinal tracts (MEP)
- Sensory tracts (SSEP)
- Cranial nerves (EMG, tEMG)
- Brainstem Nucleii (tEMG)

- Reticular formation (??)  Not yet…..

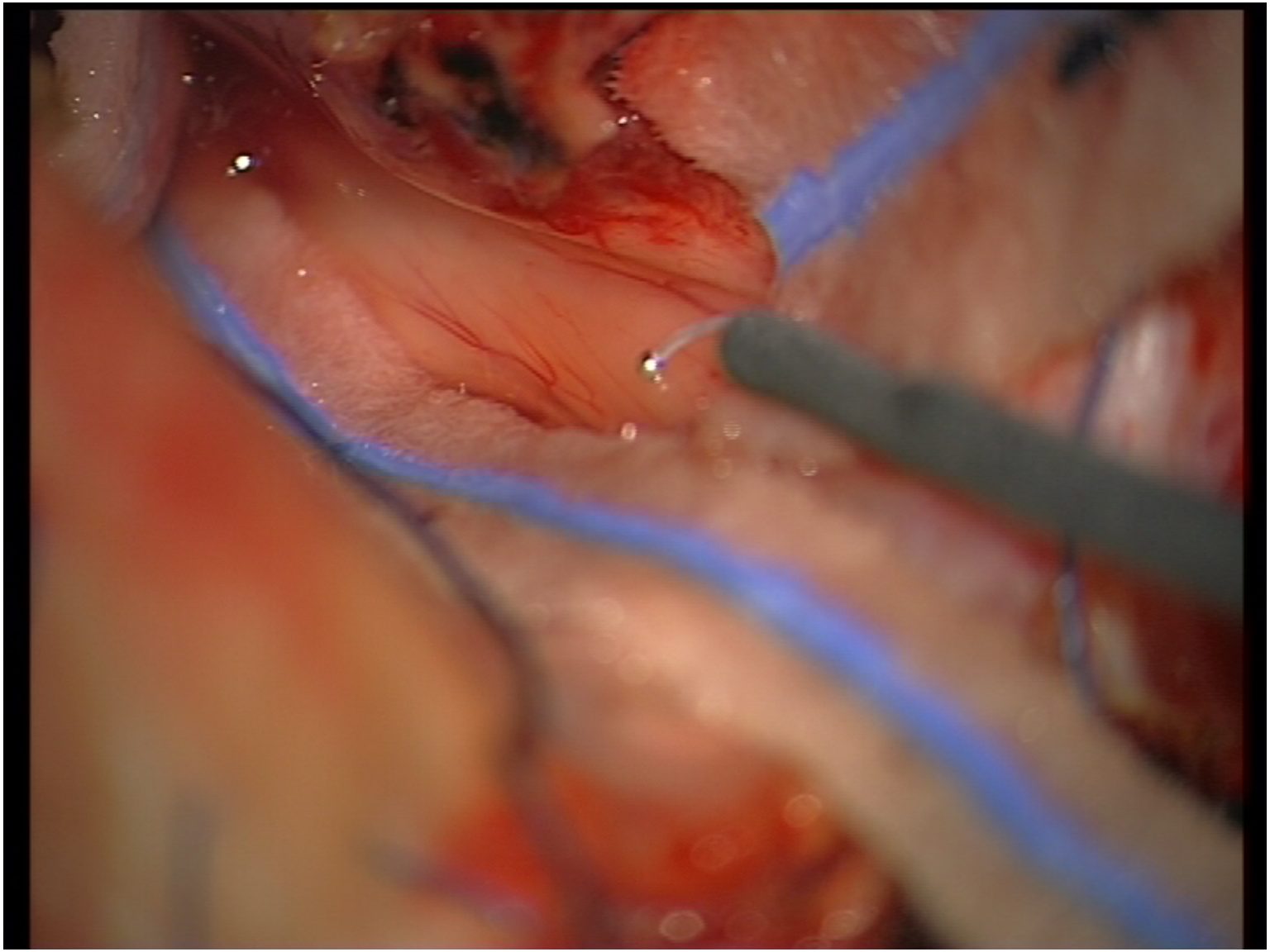
# Standard MEP stimulation & SSEP recording setup






CN IX, XII
CN VII
CN VII
CN X
CN XI

# 4th V floor stimulation



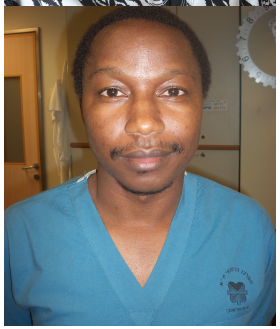
# References
# see also attached word file

F. Epstein, S. Constantini
Practical Decisions in the Treatment of Pediatric Brain Stem Tumors.
Pediatric Neurosurgery 24:24-34, 1996

S. Constantini, F. Epstein
Surgical indication and technical considerations in the management of benign brain stem gliomas.
Journal of Neuro-oncology 28: 193-205, 1996

# International department





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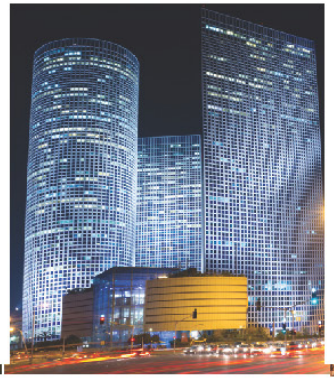
# EANS Annual Meeting 2013

## EANS Tumor Section
## AANS/CNS Section on Tumors
## Annual International Neuro-Oncology Updates

## Tel Aviv, Israel, 11-14 November, 2013



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**www.kenes.com/eans2013**

# Common-sense

**Technology!**

Compassion!

Collaboration!

Competition!

# Thank you!

# Addendum

# Clinical presentations

# Clinical Presentation
# Diffuse Brainstem Tumors

- Triad of cranial neuropathy, long tract signs and cerebellar signs
- Sensory changes rare
- Isolated cranial nerve involvement good prognostic factor

# Clinical Presentation
# Midbrain Tumors

- CNIII, IV
- Insidious presentation
- Long history of localising findings
- Increased ICP symptoms

# Ventral Midbrain

- Cerebral peduncle involvement
- Medial - dysarthria, dysphagia, facial and upper extremity weakness
- Lateral- pain and temperature sensory loss on the trunk and extremities
- Red nuclei, superior cerebellar peduncles and MLF- choreoathetosis, ataxia, internuclear ophthalmoplegia

# Ventral Midbrain

- Descending sympathetic tracts - Horner's syndrome
- Medial geniculate ganglia – auditory dysfunction

# Dorsal Midbrain

- Neuroophthalmologic abnormalities
- Ivth nerve palsy, vertical gaze abnormalities
- Tinnitus/auditory alterations from inferior colliculi
- Reticular formation: consciousness disturbance

# Midbrain Syndromes

- Parinaud's syndrome
- Top of Basilar syndrome

# Pontine lesions

- V, VI, VII, VIII
- Facial pariesis
- Hearing loss
- Long tract findings
- Poorer prognosis

# Anteromedial pontine lesions

- Corticobulbar – dysarthria, dysphagia, facial palsy
- Corticopontocerebellar - ataxia, pathologic laughter, pariesis/dysarthria
- Medial lemnisci – vibration sense, deep sensation from contralateral extremities

# Anterolateral pontine lesions

- Weakness and loss of position sense

# Lateral Pontine Lesions

- Inferior and middle cerebellar peduncles and pontocerebellar fibers: contralateral ataxia
- Contralateral extremity loss of pain and sensation
- V nuclei – motor deficits in mastication, corneal sensory loss
- VI nuclei and fascicular involvement – ipsilateral facial pariesis

# Dorsolateral Pontine Lesions

- Lateral leminiscus or cochlear nucleus – reduced auditory acuity and sound localisation
- Superior cerebellar peduncles – ataxia
- Locus ceruleus involvement – Parkinsonian symptoms
- Vth nerve – jaw jerks

# Tegmental lesions

- Rare
- Disturbance of consciousness
- Severe ataxia
- Skewed eyed deviation
- One and half syndrome
- Vertigo

# Bilateral pontine lesions

- Pseudobulbar syndrome: locked in syndrome – fascicles of abducens nerves, paramedian pontine reticular formation

# Pontine syndromes

- Millar- Gubler's syndrome- ipsilateral VI and VII palsy with contralateral hemipariesis
- Raymond syndrome – ipsilateral VI pariesis with contralateral hemipariesis
- Dejerine's syndrome – rare. Distal occlusion of vertebral artery. Contralateral arm and leg pariesis, facial, hypoglossal pariesis. Position sense and vibratory sense compromise in contralateral extremities. Preserved pain and temperature

# Medulla

- IX, X, XI, XII
- Changes in voice
- Swallowing difficulty
- Pneumonia
- Absent gag reflex and tongue assymetry

# Medullary syndrome

- Unilateral: Contralateral hemipariesis, contralateral hemisensory loss, ipsilateral horner's syndrome, ipsilateral ataxia, ipsilateral facial sensory loss, ipsilateral tongue pariesis, dysarthria, nausea vomiting
- Bilateral: flaccid quadriplegia, loss of deep sensation, respiratory failure, IX failure