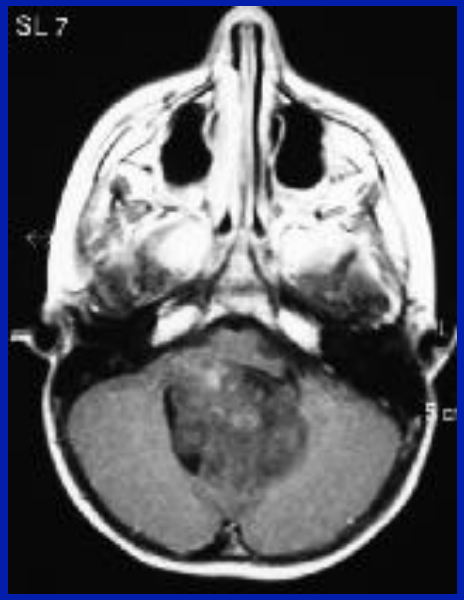
DIAGNOSIS AND MANAGEMENT OF MIDLINE POSTERIOR FOSSA TUMORS IN CHILDREN



INTRODUCTION

- Medulloblastoma
- Ependymoma
- Astrocytoma
- Brainstem glioma
- Choroid plexus papilloma
- Dermoid

Medulloblastoma

- Bailey and Cushing in 1925 first used the term medulloblastoma.
- One of the most common tumors of posterior fossa (20 – 25 % all pediatric brain tumors)
- 5 –7 yrs – median age of diagnosis.
- 2 – 4 and 6 –8 yrs : two peaks in children

Medulloblastoma

Histologic subtypes:

Classical medulloblatoma →

Desmoplastic medulloblastoma

Medullomyoblastoma

Melanotic medulloblastoma

Large-cell medulloblastoma: Very poor outcome

Medulloblastoma….origin

- Debatable:
  - Origin from remnant of cells of the external granular layer of the cerebellum.
  - Transformation of normal undifferentiated progenitor cells of superior medullary velum which migrate to the external granular layer.

Medulloblastoma….Clinical

- Hydrocephalus : Raised ICP
  - Behavioral change, listlessness, irritability, vomiting, and decreased social interactions.
  - Headache, especially in the morning.
  - Double vision.
  - Head tilt : tonsillar herniation below the foramen magnum. (Can result from trochlear nerve palsy caused by direct tumor compression)

Medulloblastoma….Clinical

- Cerebellar symptoms
- Brain stem involvement
- Leptomeningeal dissemination

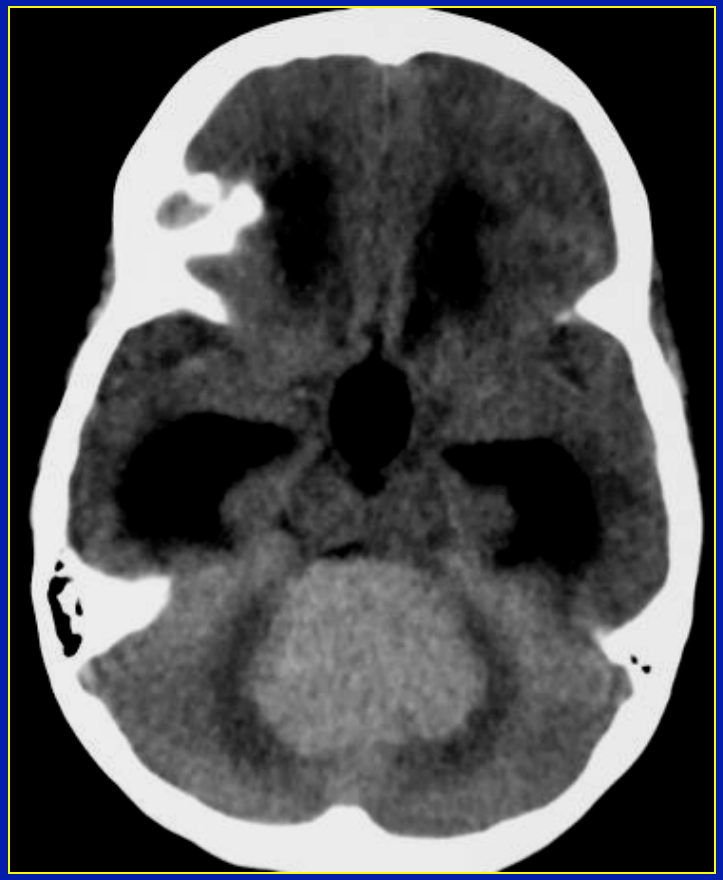
Medulloblastoma….Clinical

- Physical:
  - Increasing head circumference , full anterior fontanalles with widely split cranial sutures.
- Fundus examination
  - Papilledema can be present in as many as 90% of patients.

Medulloblastoma….Clinical

- Extraocular examination
    - Diplopia and lateral gaze paresis
    - Fourth cranial nerve palsy (should be considered in any patient with a head tilt)
    - Nystagmus
- Cerebellar signs (ataxia > unilateral dysmetria)

Radiology…….CT



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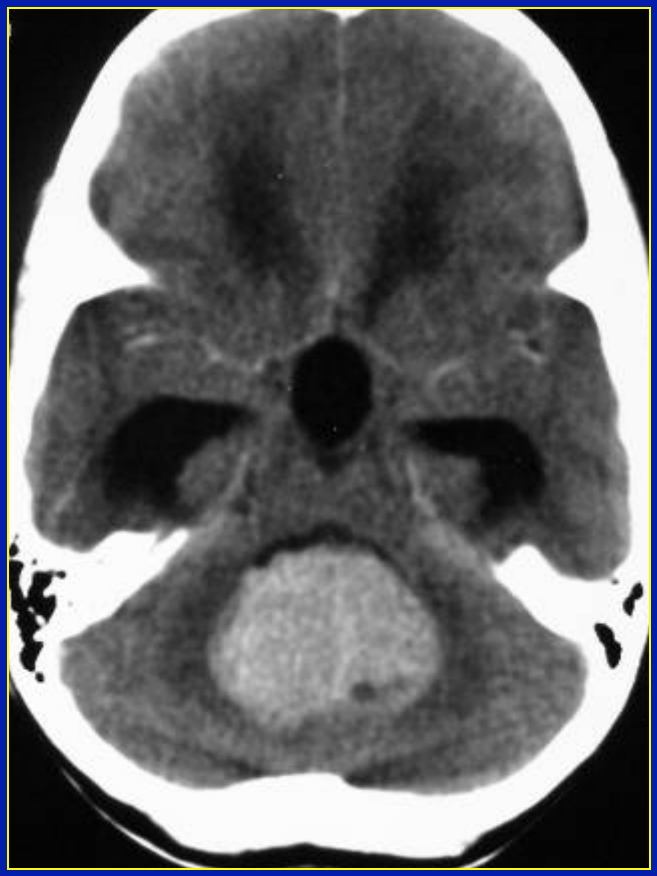
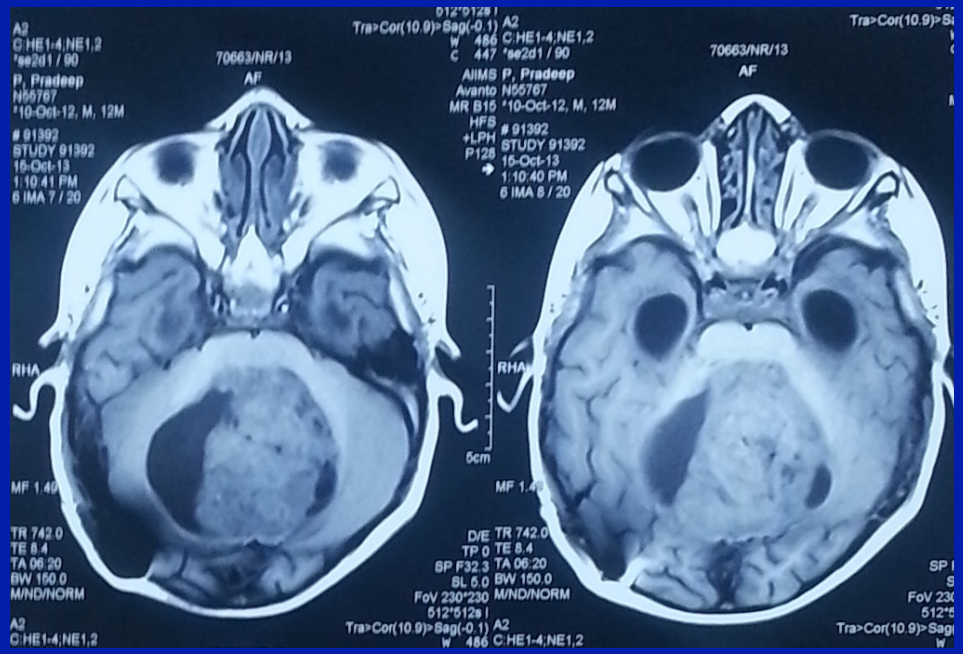


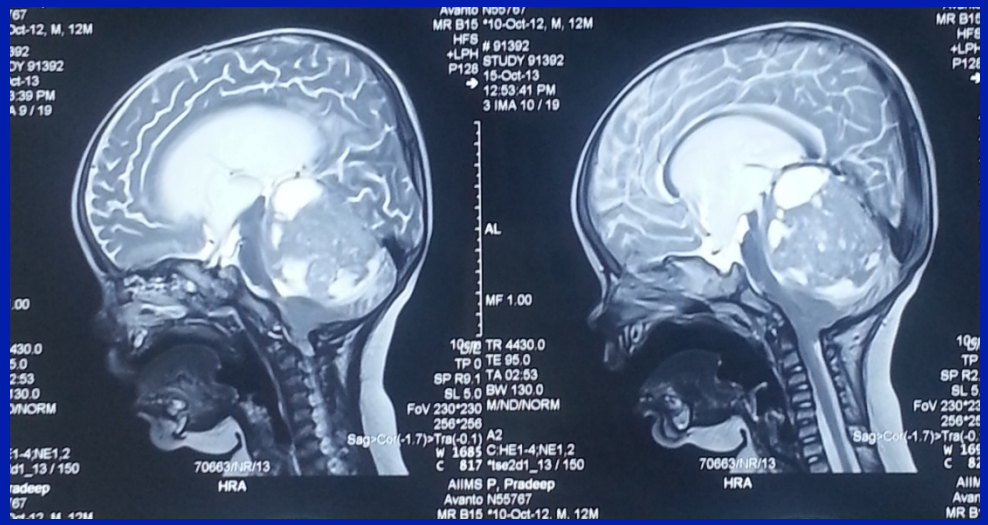
CECT

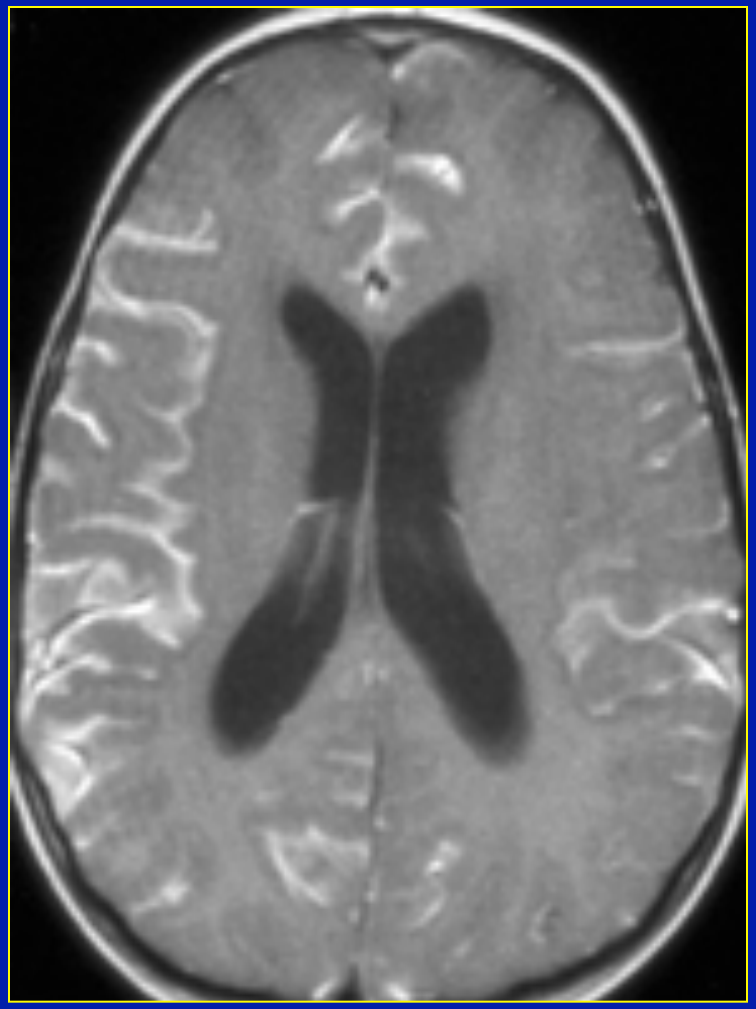
Radiology……MRI

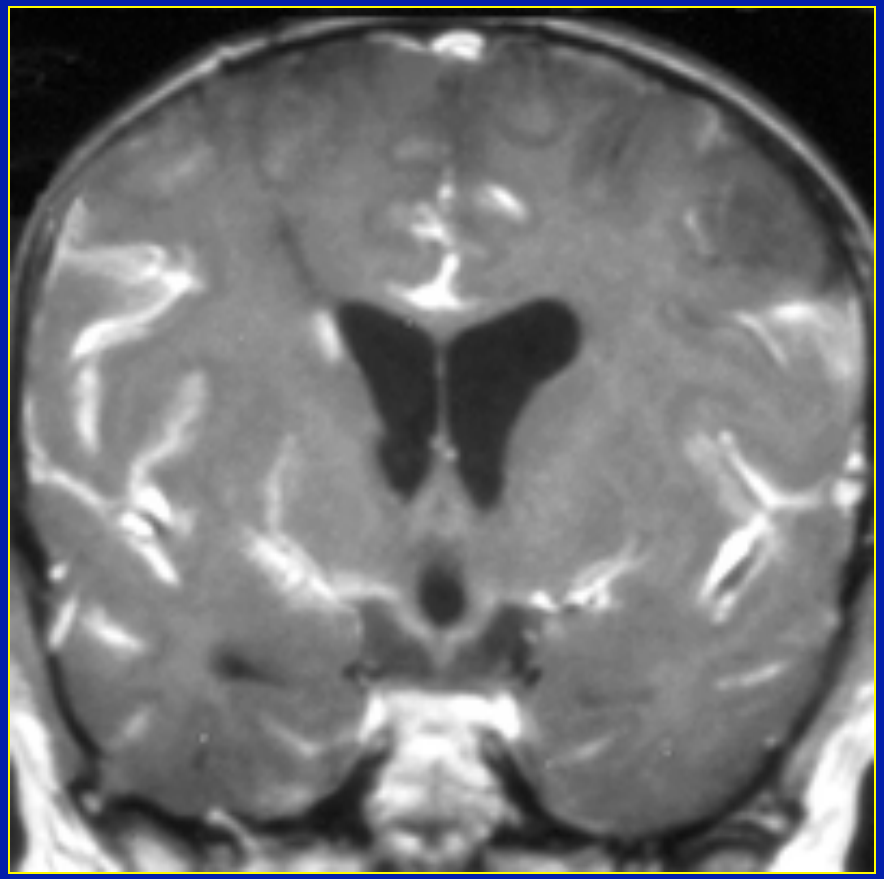
- Homogeneous enhancement (may be absent in about 15 – 20 %)
- DWI shows restricted diffusion with increased ADC.
- MRI spine : Should be done at time of diagnosis.
- BEST : prior to surgery. If not possible Should be delayed for at least 2 weeks after surgery.

MEDULLOBLASTOMA









Leptomeningeal Dissemination

Radiology…….

- Skeletal imaging
  - Metastasis to the bone must be considered in any child with medulloblastoma and bone pain.
  - A skeletal survey helps elucidate lytic or sclerotic lesions.

Diagnosis …..CSF cytology

- No standardized method: HOW and WHEN ??
  - **Lumbar puncture**
  - **Ventricular drain**
  - **Cisterna magna at the time of surgery from the for cytologic analysis**.

Stage	Feature
Tumor stage	
T1	Less than 3 cm diameter; limited to vermis, roof of fourth ventricle, or hemisphere
T2	More than 3 cm diameter; invades one adjacent structure or partially fill fourth ventricle
T3a	Invades two adjacent structures or completely fills fourth ventricle with extension into cerebral aqueduct, foremen of Luschka, or foramen of Magendie
T3b	Arises from floor of fourth ventricle or brain stem; fourth ventricle completely filled
T4	Spreads to involve cerebral aqueduct, third ventricle, midbrain, or upper cervical spinal cord
Metastasis stage	
M0	No evidence of metastasis
M1	Tumor cells in CSF
M2	Gross nodular seeding of brain CS)' spaces
M3	Gross nodular seeding of spinal CSF space
M4	Extraneural spread

Modified Chang's Staging for medulloblastoma

Staging…….

- Within 48 hours of surgery, a Gd MRI.
  - Staging.
  - Assess residual tumor size prior to the onset of enhancing reactive gliosis.
- Staging is dependent upon :
  - extent of resection,
  - radiographic evidence of tumor spread,
  - and CSF cytology.

Current staging of medulloblastoma

- Standard Risk

- Posterior fossa
- No metastasis
- < 1.5 cm^2 residual
- Undifferentiated

- High Risk

- Posterior fossa with intracranial or spinal dissemination.
- Extra neural metastasis
- > 1.5 cm^2 residual
- Differentiated

Diagnosis….genetics

- Routine use : Controversial.
- Correlation between aneuploid DNA content and a better prognosis.
- 17qi an isochromosome : Most common
- C-ERB2 – poor outcome
- Neurotropin growth factor receptor (TrkC) expression: associated with better outcome.

Risk factors associated with outcome for medulloblastoma

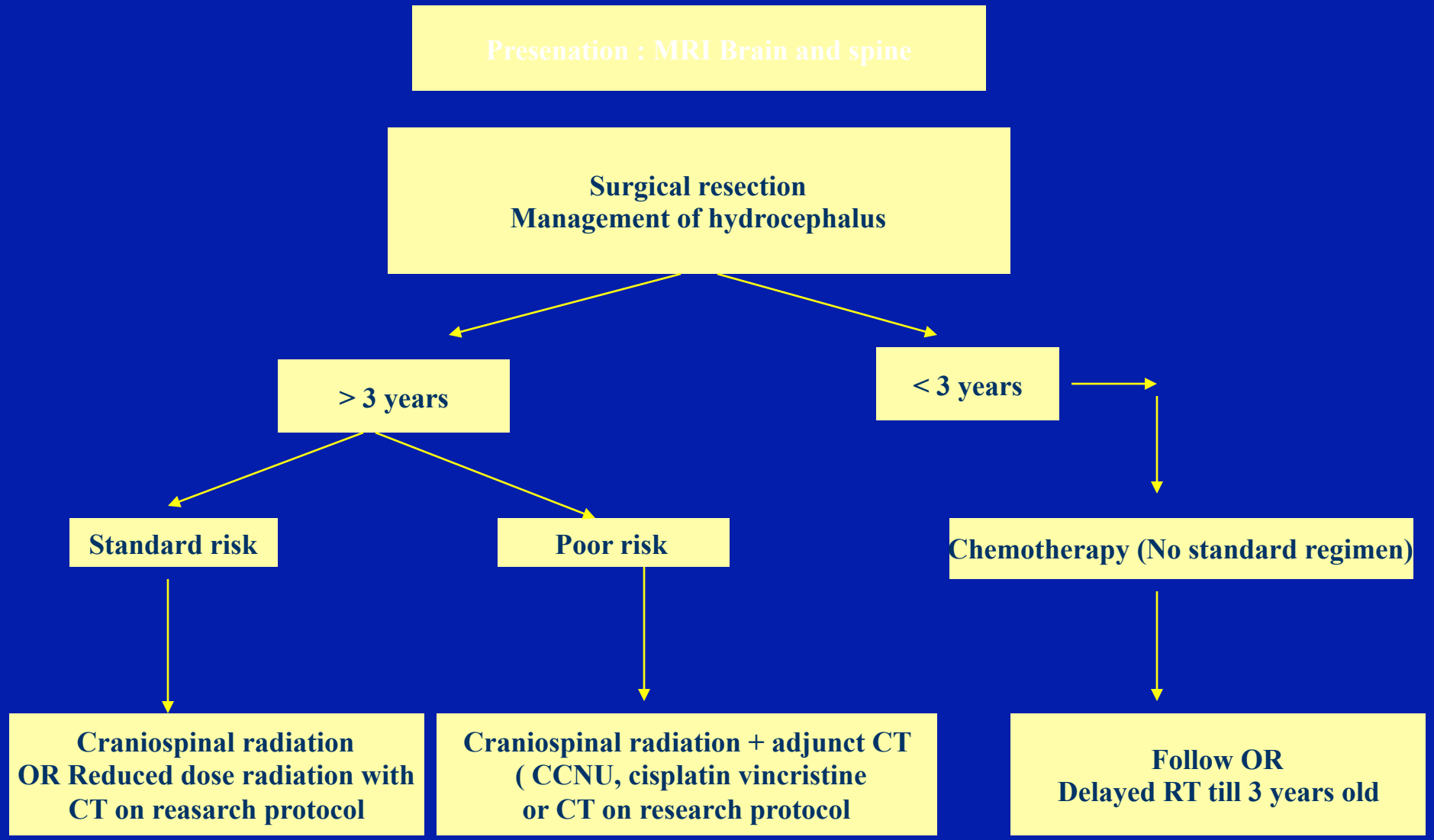
- Good Prognosis

- Females Sex
- Gross total resection
- No metastasis
- Desmoplastic histology
- Increased apoptosis index
- Hyperdiploidy
- High TRKC expression

- Poor Prognosis

- Younger age
- Subtotal resection
- Metastasis
- Large-cell anaplastic histology
- Elevated Ki-67/MIB index
- Aneuploidy
- Elevated ERB2 expression
- Isolated 17p LOH
- Elevated expression and amplification of MYCC
- Up regulation of PDGFR
- Over expression of calbindin-D28k

Fisher PG etal. Biologic Risk Stratification of Medulloblastoma: The Real Time Is Now. J Clin Oncol 2004;22; 971-74



Management algorithm for medulloblastoma

Hydrocephalus

- The majority of children with posterior fossa tumors have hydrocephalus at the time of presentation.
- There is no consensus regarding the management of HC in these children

Hydrocephalus

- Treatment options:
  - Ventriculoperitoneal shunt
  - Perioperative EVD
  - Endoscopic third ventriculostomy
  - Direct surgical resection

Hydrocephalus……..

- Recent studies have shown that ultimately 17 to 40% of children have uncontrolled hydrocephalus and require shunt placement during the postoperative period; and that this predominantly occurred within the 1st postoperative month.

- An expectant policy in these subgroup who ultimately require a shunt place them at risk of developing intracranial hypertension ,an increased rate of CSF leakage, and pseudomeningocele formation, prolonged hospitalization.

Hydrocephalus …….Factors predicting patients at risk of requiring placement of a shunt postoperatively

- Younger age at diagnosis
- The severity of hydrocephalus prior to resection of the tumor
- Midline localization
- Incomplete tumor removal
- Use of substitute dural grafts during closure
- CSF infection
- Persistent pseudomeningocele

- An analysis of factors determining the need for ventriculoperitoneal shunts after posterior fossa tumor surgery in children.
  - **Neurosurgery 34:**402-408, 1994
  - **Pediatr Neurosurg 20:**240-247, 1994

Management……. Surgery

- Gross Total Resection, if possible.
- Brainstem damage should be avoided.
- Resolution of natural CSF pathways.
- Tumor adheres to the floor of the fourth ventricle, precluding gross total resection.(1/3 rd of cases)
- Sugar coating – subarachnoid spread.

Management……. Radiotherapy

- SURGERY alone : NOT CURATIVE
- RADIOTHERAPY : cornerstone of adjuvant therapy.
- 54 to 58 Gy to the primary site with 35Gy to the entire craniospinal axis

Institution of presymptomatic craniospinal radiation therapy is probably the single most important factor responsible for the improved survival rates

Management……. Radiotherapy

Complications of radiotherapy :

- lowered intelligence quotient (IQ),
- small stature, endocrine dysfunction,
- behavioral abnormalities,
- secondary neoplasms
- white matter necrosis.
- Reduction in IQ and neurobehavioral function.

Radiotherapy and chemotherapy trials

SIOP and the (German) Society of Paediatric Oncology (SIOPII) Bailey et al. Med Pediatr Oncol 25:166--178, 1995	Patients with low-risk medulloblastoma were randomized to receive or not receive CT as well as randomized to reduced- or standard-dose neuraxis RT treatment groups.	Patients receiving a reduced craniospinal axis dose of 2500 cGy had a worse mean survival rate when compared with those treated with a dose of 3500 cGy (5-year event-free survival [EFS] 55.3% and 67.6 respectively; p = 0.07). In a subgroup analysis, the addition of a chemotherapy regimen produced a negative effect on survival in patients who received reduced doses of craniospinal axis radiation (p = 0.0049).
French Society of Pediatric Oncology Journal of Clinical Oncology 23,4726-34;2005	Standard-Risk Medulloblastoma Treated by Adjuvant Chemotherapy Followed by Reduced-Dose (25 Gy) Craniospinal Radiation Therapy	The overall survival rate and 5-year recurrence-free survival rate were 73.8% ± 7.6% and 64.8% ± 8.1%, respectively
CCG multicenter randomized trial (CCG-921) Zeltzar et al. J Clin Oncol 17:832--845, 1999	Compared the 8-in-1 chemotherapy regimen both before and after radiotherapy with a combination of vincristine, CCNU, and prednisone (VCP) after radiotherapy	Chemotherapy with VCP was superior to the 8-in-1 regimen in patients with medulloblastoma, with a 5-year PFS rate of 63% compared with 45%, respectively (p = 0.006).
CCG and Pediatric Oncology Group Deutsch et al. Pediatr Neurosurg 24:167--177,	Standard-risk patients were randomized to receive standard dose of craniospinal axis radiation (3,600 cGy in 20 fractions) or reduced dose (2,340 cGy in 13 fractions).	The study was closed before patient accrual was complete because of an increased number of recurrences in the low-dose treatment group (31% compared with 15% recurrence, respectively, at 16 months)

Management….. Hyperfractionated radiotherapy

- Delivery of higher doses of radiation without increased toxicity.
- The typical hyperfractionated radiotherapy schedule consists of twice-daily fraction sizes of 100 to 120 cGy to a total dose of 7200 to 7800 cGy.
- In practice hyperfractionated therapy has shown no advantage over the standard RT.

Management…… Chemotherapy

- Delay the onset of radiation therapy in young children (< 3 years)
- Increase in survival rates in high-risk children with medulloblastoma
- Patients with recurrent or advanced disease
- Reduction in the RT dose to the neuraxis in patients with nondisseminated disease

Management……. New studies

- Sensitizing the tumor to irradiation with the concomitant use of chemotherapy.
- Presurgical chemotherapy to treat patients prior to surgery.
- Intraventricular administration of cytotoxic agents,
- Newer drug combinations, and
- Immunotherapy based on genetics analysis

Management……. Recurrent Medulloblastoma

- Recurrences : 30 to 40% of patients

- Chemotherapy : limited due to chemo resistance in those patients who have previously undergone CT

- Redosing with RT avoided due to radiation necrosis. (Local RT using stereotactic techniques can be used can palliative)

Management……. Recurrent Medulloblastoma

- High-dose chemotherapy with autologous SCR or autologous BMR : subject of intense investigation.

  Stem cell rescue involves harvesting autologous bone marrow or preferably, peripheral stem cells by using pheresis techniques and subsequently reinfusing them after provision of high-dose myeloablative chemotherapy.

  - Int J Legal Med. 2001;114(6):331-7

Substantial toxicity :

Death, serious infection, and venoocclusive disease.

Management……. Recurrent Medulloblastoma

- Though data suggests longer EFS. (In the absence of RCT, the interpretation of the results remains limited)

- locally recurrent disease (not involving the brainstem) and without evidence of dissemination.

Management……. Prognosis

- 5 - year recurrence-free survival rates : 55% - 67%.
- Even after a good response to surgery and radiation, recurrence is common.
  - Most common site : PRIMARY TUMOR SITE
- Bone : most common site of systemic metastasis; followed by regional lymph node.

AIIMS Protocol

Surgical resection
Management of hydrocephalus

CSF - VE

Cranial RT –
56Gy / 30# / 6 wks.
(36 Gy/20# followed by a boost of 20Gy /10 #)
Spinal RT – 30 Gy / 20# / 4 wks.
Concurrently with cranial RT)

CSF +VE

Dose of spinal RT
36Gy/30#/6 weeks

Cerebellar Mutism

- Cerebellar mutism was first reported in 1979 by Hirsh after a posterior fossa tumor resection.
- Also known as posterior fossa syndrome
- Approximately 10 -1 5 % of children undergoing posterior fossa surgery for tumor.

Cerebellar Mutism

- Decreased or absent speech, irritability, hypotonia, ataxia.
- Onset : Immediate or delayed.
- Virtually all cases of mutism will occur within the first week of surgery (50% within the first two days)
- Most cases resolves in a week or two.(longest 52 months) with return of functional speech.

Factors associated with the development of mutism

- Posterior fossa surgery for tumor.
- Children
- Midline tumor location
- Cerebellar vermal incision
- Large tumor size (> 5cm)
- Medulloblastoma

Cerebellar Mutism…. Pathophysiology.

- UNKNOWN. However not emotional.

- Focal decreased cerebral and cerebellar blood flow leading to decreased cell functioning in particular areas, dentate-thalami-cortical pathway causing dysfunction. SPECT studies have lead support to this theory

Cerebellar Mutism…. Outcome

- Speech almost always returns.
- The speech is virtually always becomes functional for communication, however it may not be the same as before surgery.

Cerebellar Mutism…. intervention

- Speech therapy
- Assisting in some form of nonverbal communication
- Reassurance : usual course of cerebellar mutism and what to expect in the recovery.
- Practicing tongue and lip movements before speech returns

Brain Stem Gliomas

- Brainstem tumors comprise 10–20% of all pediatric central nervous system tumors.
- Once considered uniformly fatal ; the perspective has changed now.

Clinical hallmark

- Bilateral long tract signs
- Bilateral multiple contiguous cranial nerve palsies.
- Horner's syndrome
- Inter Nuclear Ophthalmoplegia

BSG……Classification

- The most recent classification system by Choux et al based on both CT and MRI imaging

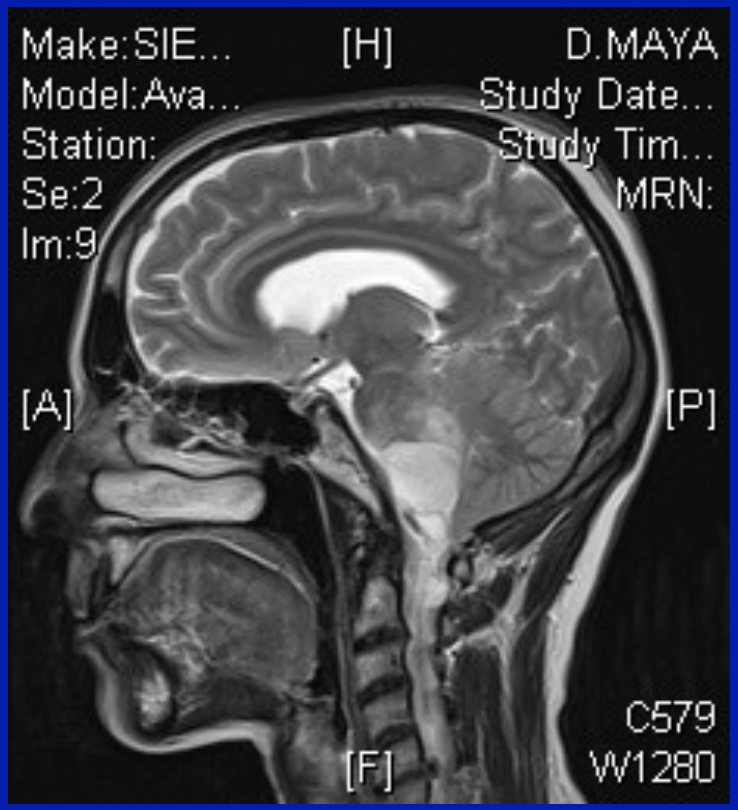
  - Type I – Diffuse
  - Type II – Intrinsic, focal
  - Type III – Exophytic, focal
  - Type IV – Cervicomedullary

  - Pediatric Neurosurgery. New York, Churchill Livingstone, 2000, pp 471–491.

BSG……

- Type I : Diffuse brainstem gliomas
- Appro. 75% of all tumors
- Hypointense on CT
- No significant enhancement on MRI.
- Characterized by diffuse infiltration and swelling of the brainstem.
- Typically, are malignant fibrillary astrocytomas (WHO grade III or IV).

Diffuse Brainstem Glioma



T2W

BSG……

- : Focal intrinsic tumors (cystic/solid)
- Sharply demarcated from surrounding tissue on MRI and are associated with less brainstem edema.
- Majority of these lesions are low grade gliomas (WHO I or II).
- Contrast enhancement : variable

BSG……

- Type III : Exophytic tumors that arise from the subependymal glial tissue of the fourth ventricle and mostly grow dorsally or laterally.

- MRI characteristics similar to type II lesions, and histologically, these lesions are usually low-grade lesions (WHO I or II) like type II lesions.

BSG……

- Type IV lesions are cervicomedullary brainstem gliomas.
- Imaging, histology and behavior : similar to intramedullary spinal cord gliomas.
- Majority are low-grade, non-infiltrative tumors.

BSG….Clinical

- Repeated vomiting with failure to thrive.
- School-aged children : a decline in school performance.
- Cranial neuropathies can develop and produce subtle changes.
- A history of dysphonia or changes in voice pitch and tone.
- Frequent upper-respiratory infections

BSG…..Management

- Biopsy : only for indeterminate lesions as no therapeutic benefit is gained by sampling lesions that behave and appear like diffuse gliomas.
- Stereotactic biopsy: can provide diagnostic tissue.
- Not without risk:
- Damage to the cranial nerves and long tracts .
- The HPE may not necessarily correlate with clinical prognosis. (Tissue heterogeneity)

Management

- A patient with a clinical presentation and imaging consistent with a diffuse glioma : NO BENEFIT from surgery.

Corticosteroids/ RT may provide temporarily benefit.

- A large phase III trial demonstrated no benefit for the use of hyperfractionated radiation in children newly diagnosed with diffuse brainstem glioma .

- Mandell LR, Int J Radiat Oncol Biol Phys 1999; 43: 959–964.

Management...Focal BSG

Location	Approach
Dorsal midbrain (tectum mesencephali)	Supracerebe llar infratentorial
Ventral midbrain	Pterional trans-Sylvian
Lateral midbrain	Subtemporal transtentorial
Ventrolateral pons (cerebellopontine angle)	Retromastoid re tros igmoid
Dorsal pons and medulla oblongata	Midline suboccipital transventricular (through the fourth ventricle)
Lower medulla oblongata and cervicomedullary junction	Midline suboccipital and C1 laminectomy

Management……..Postoperative Course

- Postoperative treatment and monitoring : on the location
- Patients who have had a CSF diversion procedure : monitor for reemergence of signs and symptoms of hydrocephalus.
- Tumors of the pons carry the worst prognosis because the majority are diffuse gliomas. (survival rates are low with a 1-year survival of 35–46% and 3- year survival of 11–17%.

Pediatr Neurosurg 1996; 24: 9–23.

Management……..Postoperative Course

- The postoperative course of focal medullary neoplasms depends on the tumor type.
- Dorsal exophytic tumors treated with surgery have an excellent prognosis with a 92% long-term survival some series.
  - Pediatr neurosurg 1994; 20: 2–10
- Pollack et al. reported a long-term survival of 94% in their series of 18 patients.
  - J Neurosurg 1993; 78: 859–863.

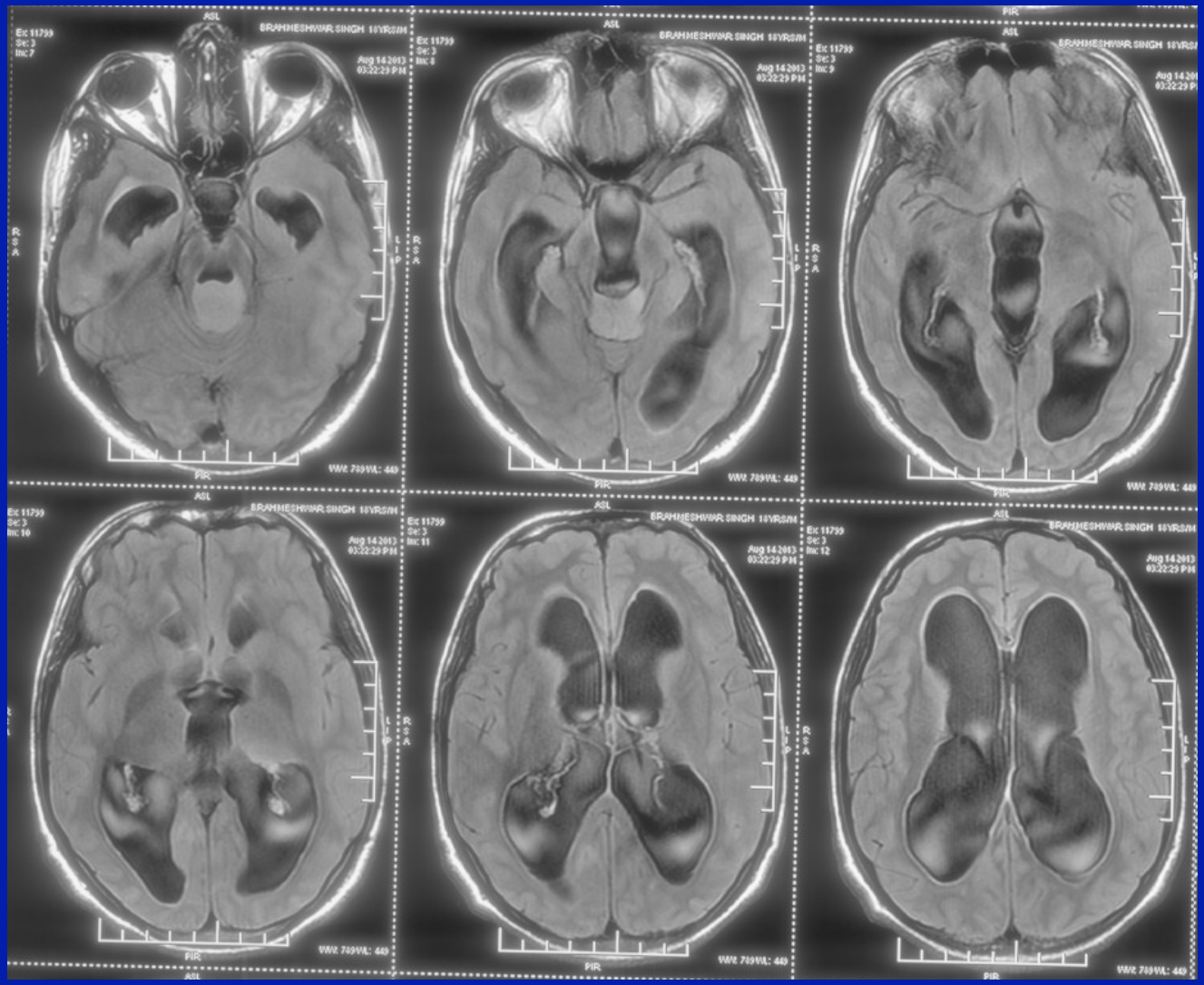
Management……..Postoperative Course

- However, significant lower cranial nerve dysfunction can occur and may need prolonged postoperative ventilation or a feeding gastrostomy postoperatively.

Tectal plate gliomas

- Unique subset of brainstem gliomas.
- Presents with late onset obstructive hydrocephalus that can be confused with benign aqueductal stenosis.
  Tectal gliomas are believed to be low-grade astrocytic tumors that usually follow a benign clinical course.
  VP shunts or ETV for CSF diversion.

MRI



AIIMS Protocol

Radical Radiotherapy with concurrent chemotherapy.

60 Gy/30#/ 6 wks.

Ependymoma

- Ependymomas are glial tumors that arise from ependymal cells within the CNS.

- WHO grade I : Myxopapillary ependymoma and subependymoma;
- WHO grade II : Ependymoma (with cellular,papillary and clear cell variants)
- WHO grade III : Anaplastic ependymoma.
- Who grade IV : Ependymoblastomas

Ependymoma

- In children : 90% of ependymomas are intracranial, majority of these occuring in the posterior fossa usually arising from the roof of the fourth ventricle

- In adults : 75% of ependymomas arise within the spinal canal, with a significant minority occurring intracranially in the supratentorial compartment.

Ependymoma ……. Imaging

CT : Typically isodense with heterogenous enhancement

Calcification : common (can be seen in one half of cases)

Ependymoma…..MRI

- On MRI, heterogeneous secondary to necrosis, hemorrhage and calcification.
- Heterogenous contrast enhancement
- Plastic ependymomas.
- Extension to the cerebellopontine angle is characteristic of ependymomas
- Commonly found intraventricularly
- Calcification common (appro.45% of cases)

Ependymoma…..

- **Staging:** No conventional staging criteria.

- Postoperative MRI is recommended within 48 hours of tumor resection to assess presence of residual tumor and to facilitate adjuvant treatment planning.

Ependymoma…..Surgery

- Most significant factor associated with increased survival in almost every large series of pediatric ependymoma.
  - Aggressive primary resection,
  - Immediate second look surgery if a post-operative residual tumor is identified and
  - Re-surgery at time of recurrence.

Ependymoma…Role of Radiotherapy

- Post-operative radiation recommended for patients older than 3 years.

- Stereotactic radiosurgery : therapeutic option in patients with residual, unresectable or recurrent tumor.

Ependymoma…Role of Chemotherapy

- May be useful < 3 years : Delay cranial radiation.
- Childhood intracranial ependymomas : in general chemo-resistant

over-expression of the multi-drug resistance-1 gene and the 06-methylguanine-DNA methyl transferase.

Children cancer group (CCG) 942: the only randomized trial, which compared survival after radiation alone, and survival after CT + RT did not show improved outcome

Med Pediatr Oncol 1996;27:8-14

AIIMS Protocol

Low Grade

CSF -VE

Surgery

Radiotherapy
56Gy / 28# / 5.5 wks
(50 Gy followed by a boost of 6 Gy)

High grade

CSF + VE

Surgery

Surgery followed by CSI and 6 cycles chemotherapy.

Pilocytic astrocytoma

- Pilocytic astrocytoma is the most common pediatric central nervous system glial neoplasm
- Exceptional benign biologic behavior : extremely high survival rate 94% at 10 years
- Most patients present in the first 2 decades
- Surgical resection is the treatment of choice.

Pilocytic astrocytoma….MRI

Four predominant imaging patterns :

Mass with a nonenhancing cyst and an intensely enhancing mural nodule (21%)

Mass with an enhancing cyst wall and an intensely enhancing mural nodule (46%)

Necrotic mass with a central nonenhancing zone (16%), and

Predominantly solid mass with minimal to no cystlike component (17%)

Pilocytic astrocytoma….

- Surgical resection of cerebellar pilocytic astrocytomas is considered the treatment of choice.

- Radiation therapy is strictly avoided, given its risk of causing significant morbidity in children younger than 5 years of age.

Pilocytic astrocytoma….

- k Resection of the cyst wall : Controversial ??
  since the surrounding cyst occurs as a simple reactive change in most cases.

NO STATISTICAL DIFFERENCE IN SURVIVAL has been noted in patients who have undergone resection of the cyst wall compared with those in which the cyst is left alone.

Pilocytic astrocytoma…. Prognosis

- EXCELLENT: 10-year survival rate : up to 94%

- In contrast to the generally poor outcome (for patients with an infiltrating brainstem glioma (WHO grade II), those with Pilocytic astrocytoma has a much better prognosis, with stable neurologic status and long term survival.

Pilocytic astrocytoma….Recurrence

- Can occur many years after surgery
- Repeat surgery : Desired treatment
- Radiotherapy can be avoided if complete resection possible.
- Residual / Unresectable recurrence : RT preferably SRS.

Choroid Plexus Papilloma

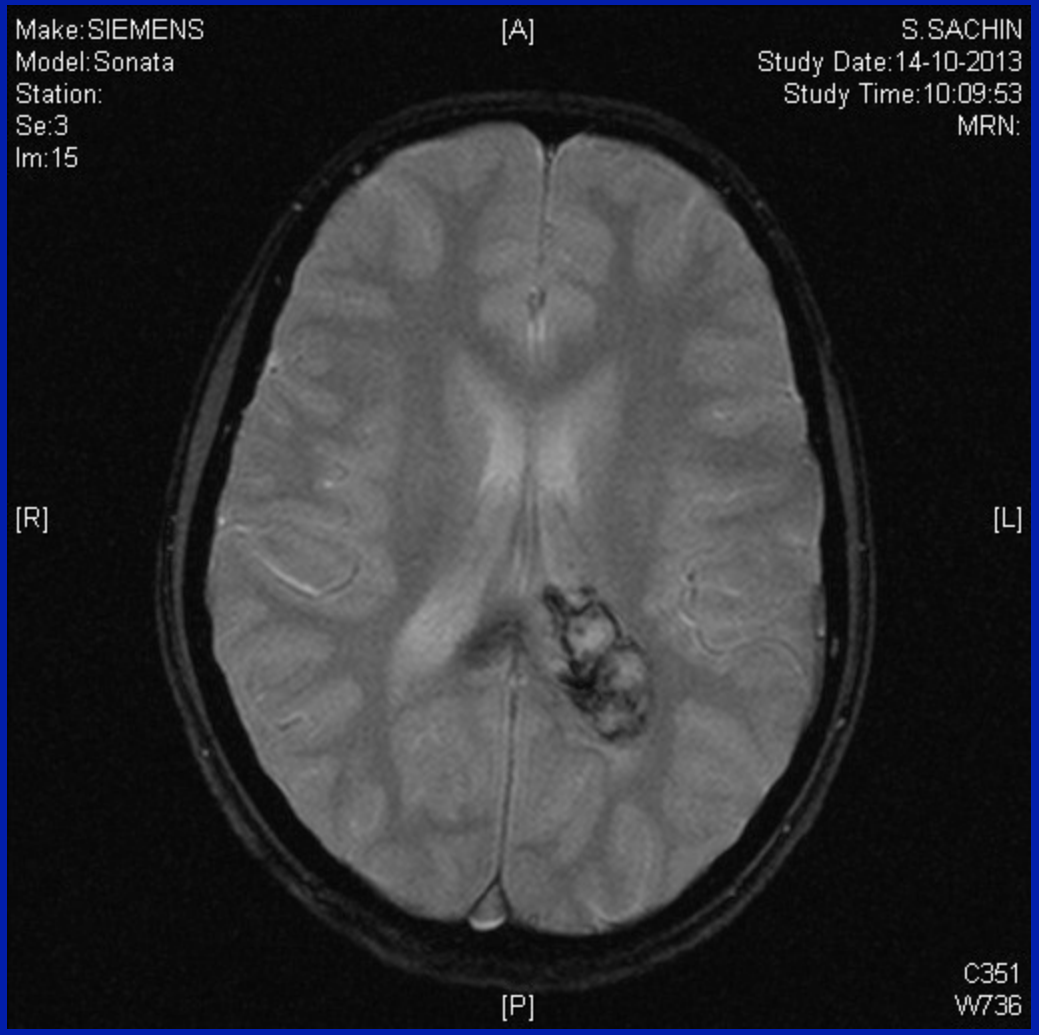
- CPP are benign neoplasms of the choroid plexus.
- Lateral ventricles : most common location in children.
- 4-6% of the intracranial neoplasms in children younger than 2 years.
- 12-13% of intracranial neoplasms in children younger than 1 year.

Choroid Plexus Papilloma…..Clinical

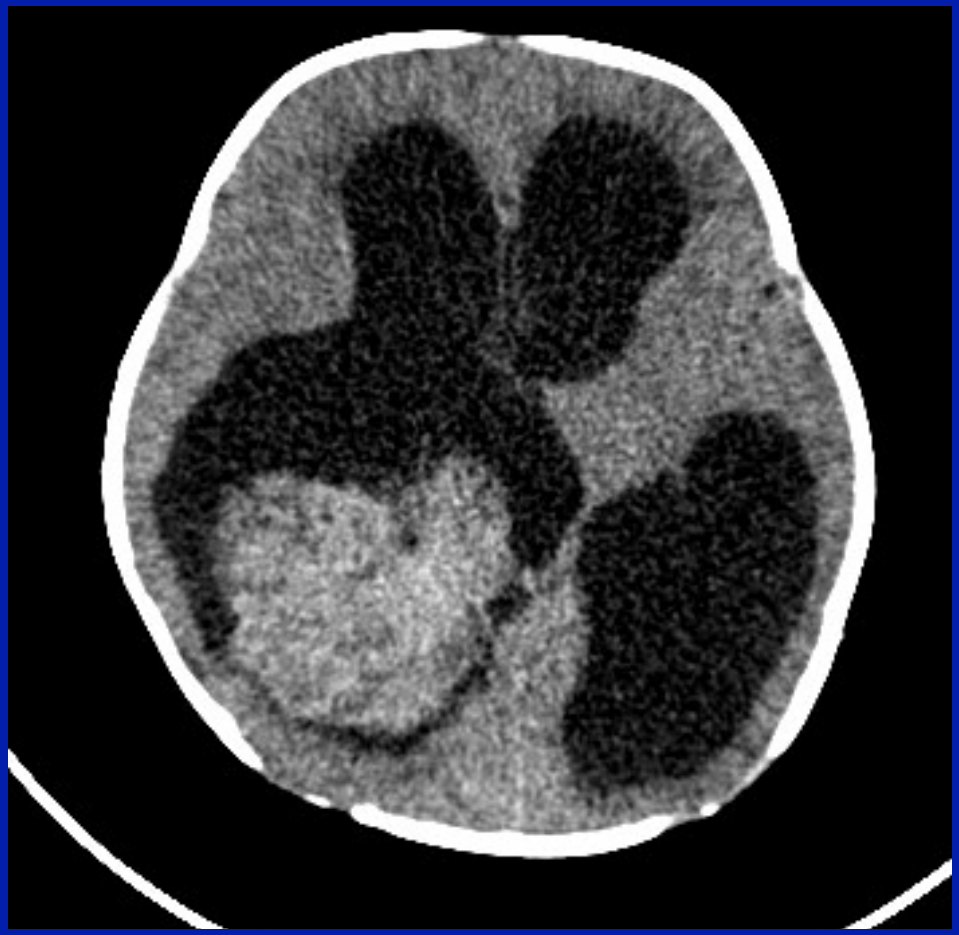
- Hydrocephalus and raised ICT

- The tumor itself can cause mass effect
- possibly because of derangement of reabsorption mechanisms or blockage at other sites in the ventricular system.

Choroid Plexus Papilloma



Choroid Plexus Papilloma…..Radiology



NCCT

Choroid Plexus Papilloma…..Radiology

On MRI : intermediate-to-strong intensity on both T1- and T2 - weighted images with dense enhancement.

Choroid plexus carcinoma appears more heterogeneous than the papilloma and often shows adjacent parenchymal invasion or surrounding edema.

Choroid Plexus Papilloma…Management

- Treatment of hydrocephalus must be considered both before and after any surgical procedures.
- An acute increase in ICP : V P Shunt.
- Hydrocephalus often resolves following removal of the mass.

Choroid Plexus Papilloma…Management

- Total surgical resection is the goal.
- Complete removal: generally curative in CPP.
- Even in choroid plexus carcinoma, total resection leads to the best possible outcome.
- Adjuvant CT and RT have been demonstrated to increase survival in the treatment of choroid plexus carcinoma, although gross total resection remains the primary treatment.

Dermoid cyst

- Congenital ectodermal inclusion cysts.
- Extremely rare, constituting fewer than 0.5% of primary intracranial tumors .
- Midline sellar, parasellar, or frontonasal regions : most common sites.
- Posterior fossa (vermis or within the 4^{th} ventricle)

Dermoid cyst

- Origin : inclusion of ectodermally committed cells at the time of neural tube closure (3rd–5th week of embryogenesis.)
- Glandular secretion and epithelial desquamation.
- Growth can lead to rupture of the cyst contents, causing a chemical meningitis that may lead to vasospasm, infarction, and even death.

Dermoid cyst

- Well - defined, lobulated, “pearly” mass of variable size.
- Characteristically,the cyst contains thick, disagreeable, foul-smelling, yellow material due to the secretion of sebaceous glands and desquamated epithelium.
- The cysts may also contain hair and/or teeth

CONCLUSIONS

- Pilocytic astrocytoma bears the best outcome.
- Management of hydrocephalus still remains controversial.
- Though surgery and RT remains the treatment of choice for medulloblastoma; optimal cranispinal radiation dose remains debatable.
- Outcome for brainstem gliomas remains dismal.