Clinical Application of Pathology

BRAIN TUMOURS V – Choroid Plexus & Embryonal Tumours

Co-authors: Clinical Professor Lesley Cala and Clinical Associate Professor Peter Robbins

<table>
<thead>
<tr>
<th>CHOROID PLEXUS tumours</th>
<th>WHO gr I</th>
<th>WHO gr II</th>
<th>WHO gr III</th>
<th>WHO gr IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Choroid plexus papilloma</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atypical Choroid plexus papilloma</td>
<td></td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Choroid plexus carcinoma</td>
<td></td>
<td></td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>

EMBRYONAL

| MEDULLOBLASTOMA (Mb) - classic                    | +        |
| Mb – desmoplastic/nodular                        | +        |
| Mb – extensive nodularity                        | +        |
| Mb – large cell/anaplastic                       | +        |
| Mb – NOS – 9470/3                                | +        |
| Mb – genetically defined – 4 types               | +        |
| CNS neuroblastoma                                | +        |
| CNS ganglioneuroblastoma                         | +        |
| Embryonal tumours with multilayered rosettes -NOS and C19-MC altered | +        |
| Medulloepithelioma                               | +        |
| Atypical teratoid/rhabdoid tumour                | +        |
| CNS embryonal tumour with rhabdoid features – 8508/3 | +        |

Friday, December 16, 2016
CHOROID PLEXUS TUMOURS

CHOROID PLEXUS PAPILLOMA – 9390/0

Choroid plexus tumours are believed to originate from the epithelium of the choroid plexus. Both benign (choroid plexus papilloma) and malignant (choroid plexus carcinoma) choroid plexus tumours are recognized, though distinction between these two is not always straightforward. Choroid plexus papilloma is classified as WHO grade I, atypical choroid plexus papilloma – WHO grade II and choroid plexus carcinoma is WHO grade III.

Sites: Choroid plexus tumours arise in sites where choroid plexus is normally found. Common sites are the lateral ventricles, fourth ventricle and lastly the third ventricle.

Incidence: choroid plexus neoplasms are uncommon CNS tumours but they account for a significant proportion of paediatric CNS tumours and particularly those that present in the first 12 months of life. Account for 3% of intracranial neoplasms in children and 0.4 – 0.6% of all brain tumours in adults. The choroid plexus papilloma is more common than the carcinoma.

Age: peak age of incidence is 6 years.

Gender: male preponderance.

Immunohistochemistry: Expression of pancytokeratin and vimentin is a consistent feature of choroid plexus papillomas, whereas staining for S100 protein, glial fibrillary acidic protein (GFAP), transthyretin, and synaptophysin is more variable (see the image below courtesy of Koeller KK, Sandberg DG. Radiographics, 2002 ; 22 (6) ). Epithelial membrane antigen (EMA) is usually negative, as is carcinoembryonic antigen (CEA)

Expression patterns may vary by tumour location and grade and patient age For example, S-100, transthyretin, and GFAP are all less likely to be positive in choroid plexus carcinomas compared with choroid plexus papillomas. S-100 expression tends to be greater in choroid plexus tumours arising in the fourth ventricle, whereas transthyretin expression by these tumours may be higher in patients
older than 20 years. Any combination of positivity for CK7 and CK20 may be encountered. It is the limited focal staining of choroid plexus tumours with these markers that is useful in discriminating them from metastatic carcinomas. Most CPPs express CK7 but CK20 positivity is less common.

Similar to CPPs, choroid plexus carcinomas are generally immunopositive for cytokeratin; but s100 and transthyretin are less consistently positive. Synaptophysin, GFAP, CA19-9, and EMA may all be focally expressed, whereas CEA staining is quite unusual. MIB-1 (Ki67) proliferative index is typically brisk in choroid plexus carcinomas and the majority show nuclear positivity for p53.

**Differential diagnosis using markers:** Several markers may be helpful in distinguishing choroid plexus neoplasms from other primary central nervous system (CNS) and metastatic tumours. For example, membranous positivity for excitatory amino acid transporter-1 (EAAT-1) is present in a significant proportion of choroid plexus tumours, whereas EAAT-1 is typically negative in metastatic adenocarcinoma, urothelial and small cell carcinomas, and endolymphatic sac tumours (which may quite closely mimic choroid plexus tumours).

HEA-125 and Ber-EP4 are negative in most choroid plexus neoplasms, whereas these markers are positive in most metastatic carcinomas.

Synaptophysin may also be useful in distinguishing choroid plexus neoplasms from metastatic papillary carcinomas, as synaptophysin is frequently demonstrable in choroid plexus neoplasms but lacking in the latter.

CA19-9 and CEA, which are positive in some metastatic carcinomas, are also occasionally positive in choroid plexus carcinomas. Although not useful in distinguishing choroid plexus neoplasms from metastatic carcinoma, both of these markers can be detected in peripheral blood and may be efficacious as follow-up tumour markers following treatment.

The inwardly rectifying potassium channel Kir7.1 and stanniocalcin-1 have been found to be both sensitive and specific markers for choroid plexus neoplasms when compared with other primary brain tumours and metastases.

Laminin and collagen IV, highlight the basement membrane in almost all choroid plexus papillomas and can therefore effectively separate these lesions from papillary ependymomas, which lack these basement membranes. Basement membrane stains may not be quite as useful in choroid plexus carcinomas in which fragmentation of the basement membrane is quite common.

E-cadherin is positive in many choroid plexus tumours and may be useful in distinguishing them from ependymomas, as ependymomas are typically negative. Podoplanin is positive in almost all choroid plexus tumours, but it is also frequently positive in ependymomas and some other primary brain tumours. Lastly, nuclear INI-1 reactivity is retained in choroid plexus carcinomas, but this finding is absent in atypical teratoid/rhabdoid tumors (AT/RTs), aiding in differentiation between these two neoplasms.

**Genetics:** Choroid plexus papillomas are frequently hyper-diploid; gains of chromosomes 5, 7, 8, 9, 12, 15, 17, 18, 20, and 21 and losses involving chromosomes 10 and 22q have all been documented. Choroid plexus carcinomas have likewise been found to harbor numerous regions of chromosomal gain (chromosomes 1, 4, 8q, 9p, 12, 14q, 20q, and 21) and loss (chromosomes 3p, 5, 9q, 10q, 13q, 18q, 22q). Comparative genomic hybridization studies confirm genetic differences between CPP and CPC, and also suggest that there are genetic distinctions between adult and paediatric choroid plexus tumours.
With regard to specific genetic alterations observed in choroid plexus tumours, VHL allele loss may be seen in those choroid plexus papillomas arising in the context of von Hippel-Lindau disease. Activation of the Notch signalling pathway may also play a role in the formation of choroid plexus papillomas, with nuclear translocation or overexpression of one or more Notch receptors (Notch 1, 2, and 3) identified in some choroid plexus papillomas.

Although many choroid plexus carcinomas and few choroid plexus papillomas show positive staining for p53 by immunohistochemistry, corresponding TP53 mutations are quite uncommon. Chromosome 22q loss and INI1 alterations have been described for some choroid plexus carcinomas; but, immunohistochemical studies have indicated that INI1 protein expression remains intact in choroid plexus carcinomas, including those with a "rhabdoid morphology.”

Lastly, platelet-derived growth factor (PDGF) receptors may be overexpressed or amplified in some choroid plexus carcinomas. PDGF receptor signalling has been suggested as a potential therapeutic target.

**Imaging:** CT scan shows hyperdensity and the tumour intensely enhances. The tumour is very lobulated ‘cauliflower-like’ and is within a ventricle. Sometimes it grows by direct extension into an adjacent CSF-containing space and drop metastases can occur. This can make a decision difficult as to whether the tumour is benign or not. Stippled calcification can also occur.

The image below is a post contrast CT scan of a newborn infant showing a choroid plexus papilloma in the third ventricle (uncommon location) – see arrows - and gross hydrocephalus. It is reproduced with permission from Anderson DR, Falcone S, Bruce JH, Mejidas AA, Donovan Post MJ. Radiologic-Pathologic correlation of congenital choroid plexus papillomas. AJNR 1995 Nov; 16 : 2072-2076.

We are indebted to Professor JG Smirniotopoulos, for permission to use the next 3 images taken from MedPix TM of the Uniformed Services University of the Health Sciences, Bethesda, Maryland. The first two images are axial post contrast CT images of a 2 year old child with a large head, showing hydrocephalus and a hyperdense, lobulated mass in the trigone of the left lateral ventricle.

Hydrocephalus is due to increased CSF production and may have a contribution from ventricular outflow obstruction.
The next image is the same patient, MRI T1W and post contrast – sagittal view. Usually the mass will show characteristic central branching vascular flow voids but not here. There is no associated vasogenic oedema and no evidence of invasion of the parenchyma.

**Microscopic:** histologically characterized by a well-developed papillary architecture. Papillary stromal cores of fibrovascular tissue are lined by a monolayer of relatively uniform cuboidal or columnar epithelial cells. Accelerated mitotic activity, invasion of brain parenchyma and tumour necrosis are absent.

The example below shows long papillae (see arrows), with stromal cores and a monolayer of lining cells.
CHOROID PLEXUS CARCINOMA

**Macroscopic:** are typically heterogeneous in appearance and usually invade the adjacent brain parenchyma passing through the ventricular wall and stimulating the onset of vasogenic oedema. There may be foci of calcification in the mass best seen on CT scan. A frontal, occipital or temporal horn of the involved ventricle becomes encysted in more than 80% of cases.

We are grateful to the Geneva Foundation for Medical Education and Research for the example that follows under imaging below, reproduced from the Archives of the AFIP, Cerebral Intraventricular Neoplasms, Radiologic-Pathologic Correlation,. Koeller and Sandberg, 22 (6) : 1473 Fig 22 (A-D) Radiographics.

CT scan shows a lobulated, hyperattenuated, intraventricular mass within the posterior portion of the lateral ventricle. There is surrounding vasogenic oedema (arrows).
MRI T1W axial shows the lobulated mass with heterogeneous signal intensity.

MRI axial T2W image – below - shows the mass is slightly hyperintense compared with the white matter. The vasogenic oedema is more obvious than on the CT scan. Circumferential marked hypointensity – see arrowheads – suggests haemosiderin deposition.

MRI T1W post contrast shows intense but heterogeneous enhancement within the mass.
Choroid plexus tumours may be bilateral, involving both lateral ventricles — see below — courtesy of Koeller KK, Sandbert DG. Radiographics 2002;22 (6).

MR spectroscopy shows increased levels of choline (Cho) with a decreased amount of N-acetylaspartate (NAA), and a mildly elevated peak of lactate (Lac). These features favor a malignant neoplasm. Peak at 3.6 ppm is likely secondary to inositol (Ino).

Microscopic appearance: choroid plexus carcinoma is much less well differentiated than choroid plexus papilloma and is often characterized by frank anaplasia.

The neoplastic cells have malignant cytologic features, there is often loss of papillary architecture, evidence of brain parenchymal invasion, high mitotic rates, areas of hypercellularity and tumour necrosis.

Choroid plexus carcinoma is exceptionally rare in adults and is essentially a diagnosis of exclusion, which should only be made after excluding the possibility of an intraventricular metastatic deposit from a primary carcinoma arising outside the CNS.

Some choroid plexus neoplasms have borderline features and may be difficult to accurately categorize as either papilloma or carcinoma. These are categorized as atypical choroid plexus papilloma – 9390/1 and are WHO grade II.

The example below of choroid plexus carcinoma, shows sheets of markedly atypical cells and almost a complete loss of papillary architecture.

At surgery, the ventricular wall was transgressed by the mass.
Choroid plexus carcinoma can resemble primitive medulloblastoma, containing a monotonous population of malignant cells with a small round blue cell morphology (H & E. (courtesy of Dr Christine Fuller. Medscape Nov 4, 2015).

![Image]

**Treatment:** may have embolization prior to surgery as reducing the blood supply to the tumour will also reduce the amount of CSF production which directly relates to the presence of hydrocephalus. Unfortunately, it is not enough on its own, so permanent CSF diversion is still required in the post-operative period.

**Prognosis:** The extent of resection and histologic grade are the most important prognostic factors determining recurrence-free and overall survival in choroid plexus tumours, and surgical resection remains the first-line therapy for these patients. **Choroid plexus papillomas** may be cured by gross total resection alone, and, even in cases with recurrent disease, the outcome is often still favourable (5-y survival rates of 80-100% following gross total resection and approximately 68% following subtotal resection). A small percentage of choroid plexus papillomas undergo malignant progression, but this is an extremely rare occurrence.

**Choroid plexus carcinomas** are more aggressive, with a tendency for leptomeningeal dissemination and/or recurrence and a survival rate around half of that seen with choroid plexus papillomas. Choroid plexus carcinomas may have a favourable outcome when gross total resection is combined with adjuvant chemotherapy and/or local radiotherapy.

Cranio-spinal irradiation may be helpful in those cases of choroid plexus carcinoma with subtotal resection and/or disseminated leptomeningeal disease at presentation. Whereas elevated Ki-67–labelling indices are associated with a less favourable postoperative outcome, a more favourable clinical course may be encountered in those patients whose choroid plexus carcinomas have chromosome 9p gain or 10q loss.

**Atypical choroid plexus papillomas** - WHO grade II -fall somewhere between WHO gr I and III in terms of their biologic behaviour with a good prognosis but with a greater risk of local recurrence than conventional choroid plexus papillomas. Increased mitotic activity is the only histologic feature identified to be independently associated with recurrence; choroid plexus papillomas with increased mitoses carry nearly 5 times the risk of recurrence compared with less proliferative papillomas.
Additional histologic features suggesting a poor prognosis include decreased S-100 protein expression (< 50% of cells strongly positive for S-100), lack of immunoreactivity for transthyretin, brain invasion, lack of marked stromal oedema, and the presence of necrosis.

Ref: Dr Christine Fuller, Medscape Nov 4, 2015.

**EMBRYONAL TUMOURS – all types are WHO grade IV**

**MEDULLOBLASTOMA (Mb) – classic (previously called cerebellar PNET)**

It is a primitive neuroectodermal and invasive embryonal tumour of the cerebellum, often involving the vermis or roof of the 4th ventricle and 70% occur in children. It is predominantly neuronal in differentiation and has a predilection to metastasize via CSF-containing pathways and is classified WHO grade IV.

Those arising in other CNS locations are cerebral neuroblastoma.

Primitive neuroepithelium develops into medullary epithelium. At that point the cerebellar medulloblastoma and the supratentorial medulloblastoma arise. The medullary epithelium gives rise separately to the precursor neuronal cell “neuroblast” and the putative precursor glial cell “glioblast” or “spongioblast which progress down a pathway of further differentiation.

In the 2016 WHO Classification update medulloblastomas can be classified according to molecular characteristics in addition to histopathological features. Both molecular and histopathologic classifications are discussed in detail below. Molecular classification is finding increasing clinical utility, but histopathologic classification also provides important prognostic information, and is important when molecular studies are not feasible or available.

**The 2016 WHO Classification update** is intended to encourage ‘integrated’ diagnoses incorporating both molecular information and histopathologic classification wherever possible, but recognizes that detailed molecular studies may not be available in all reporting centres.

**Viz. Medulloblastoma, histologically defined:**

- Medulloblastoma, classic
- Desmoplastic/nodular Medulloblastoma
- Medulloblastoma with extensive nodularity
- Large-cell/anaplastic Medulloblastoma

**Medulloblastoma, genetically defined:**

- Medulloblastoma, WNT-activated
- Medulloblastoma, SHH-activated and TP53-mutant
- Medulloblastoma, SHH-activated and TP53-wildtype
- Medulloblastoma, non-WNT/non-SHH

**General features of the Medulloblastomas:**

- May grow rapidly and cause hydrocephalus, invade subarachnoid space and 4th ventricle early
- 5% metastasize systemically, commonly to bone
- 5 year survival is 75% with surgery/radiation
May arise from primitive cells of external granular layer of cerebellum
Large cell / anaplastic. More aggressive.

**Macroscopic:** Well circumscribed, gray-pink, soft/friable; involves surface of cerebellar folia and infiltrates leptomeninges. Image courtesy of Dr Nat Pernick. PathologyOutlines.com, 27th Nov 2013

**Microscopic:** Classic medulloblastoma

The example below shows sheets of primitive cells with high rates of mitotic and apoptotic activity. See cells within the circle.

In another example see a diffuse pattern of tumour growth with poor cellular differentiation, nuclear molding and minimal indistinct cytoplasm.

**Incidence:** 20% of brain tumours annually are medulloblastoma. Occurs in 5 persons/million. Is second in frequency to pilocytic astrocytoma of the cerebellum.

**Race:** no predilection for any one race.

**Gender:** aged 0-14 years is 6.1/ million for boys and 4.5 / million for girls.

**Age:** Peak age of incidence is 3-5 years. Approximately 80% of patients are diagnosed in the first 15 years of life. Can affect adults in their 20’s. Rare after 35 years

**Clinical presentation:** Although 70-90% of patients with medulloblastomas present with a history of headaches, emesis, and lethargy, these symptoms are generally intermittent and subtle. Duration of symptoms for 3 months or more before diagnosis is common.

Early symptoms are secondary to increased intracranial pressure (ICP). The classic triad consists of morning headaches, vomiting, and lethargy. Headache consists of head pain present upon arising that is relieved by vomiting and gradually lessens during the day.

Cushing triad (hypertension bradycardia, and hypoventilation), an uncommon finding in children with increased intracranial pressure, usually indicates impending herniation.

Initial signs of increased ICP are usually subacute, nonspecific, and nonlocalizing. School-aged children may complain of vague intermittent headaches and fatigue. They may demonstrate declining academic performance and personality changes. Infants may present with irritability, anorexia, and developmental delay.

With increasing tumour size and invasion into the surrounding brain tissue, more characteristic symptoms appear. One symptom is progressively worsening ataxia involving the lower extremities, often with relative sparing of the trunk and upper extremities.
Tumour infiltration of the brain stem or increased ICP may result in diplopia and multiple other cranial nerve findings, such as facial weakness, tinnitus, hearing loss, head tilt, and stiff neck.

Uncommonly, patients may present with back pain or leg weakness secondary to spinal metastasis.

**Physical exam:** The earliest signs are non-localized and caused by increased ICP. Later signs are generally due to tumour invasion of the surrounding tissue.

Funduscopic evaluation reveals papilledema or optic pallor in infants. Palsy of cranial nerve VI resulting in the inability to abduct one or both eyes is common. Infants may have the "setting sun" sign. This is demonstrated by impaired upward gaze and seemingly forced downward deviation of the eyes.

Measurement of head circumference in infants with open cranial sutures also may reveal macrocephaly.

Localized deficits in truncal steadiness, upper extremity coordination, and gait are common.

Invasion into the brain stem may cause loss of conjugate gaze (gaze palsy) or the inability to adduct one eye on attempted lateral gaze. This is observed most commonly in combination with deficits of cranial nerves V, VII, and IX. Invasion into the cerebellopontine angle results in facial weakness and hearing loss, often with associated unilateral cerebellar deficits.

**Associated conditions:** Medulloblastoma is associated with recessively inherited Turcot syndrome. Turcot syndrome is a rare inherited disorder characterized by the association of benign adenomatous polyps in the mucous lining of the gastrointestinal tract with tumours of the central nervous system. Also medulloblastoma is associated with ataxia-telangiectasia syndrome.

As many as 5% of patients with autosomal dominant nevoid basal cell carcinoma (Gorlin) syndrome develop medulloblastoma. These tumours demonstrate loss of heterozygosity at band 9q22-q23, the region containing the PTCH tumour suppressor gene associated with Gorlin syndrome.

**Pathophysiology:** The histogenesis of medulloblastoma remains controversial.

One view suggests that the cell of origin derives from the external granular layer of the cerebellum. This is supported by the finding that the proliferation of precursor neurons in this layer is controlled by sonic hedgehog (shh), whose receptor PTCH is mutated in a subset of sporadic medulloblastomas.

Other studies have shown that overexpression of the oncogenes ERBB2 and MYCC are associated with worse outcome, and that MYCC can induce the potentially more aggressive large cell/ anaplastic variant of medulloblastoma. Finally, amplification of the oncogene OTX2 has been most recently described in association with medulloblastoma.

As the tumour grows, obstruction of cerebrospinal fluid (CSF) passage through the fourth ventricle generally occurs, resulting in hydrocephalus. The tumour may spread contiguously, to the cerebellar peduncle and/or the floor of the fourth ventricle; anteriorly, to the brainstem; inferiorly, to the cervical spine; or superiorly, above the tentorium. It also may spread via the CSF intra-cranially or to the leptomeninges and spinal cord.

Of all the pediatric CNS neoplasms, medulloblastoma has the greatest propensity for extra-neural spread, especially to bone and bone marrow; however, the rate of such events is less than 4%.
**Molecular /Genetic:** 40-50% of patients have a deletion of the short arm of chromosome 17, implicating the presence of a tumour suppressor gene that maps to 17p, which is distinct from the *p53* gene. Alternatively, a gene on 17q may be related to transformation because of increased copy number.

The most common cytogenetic change found in medulloblastomas is loss of chromosome 17p, which is frequently accompanied by duplication of the long arm, resulting in an isochromosome 17q. One of the candidate tumour suppressor genes on 17p is *KCTD11* that inhibits a sonic hedgehog (SHH) signalling pathway known to regulate cerebellar granule cell proliferation during development. During normal brain development, SHH protein secreted from Purkinje cells inhibits a cell-surface receptor (encoded by the *PTCH* gene on chromosome 9), thus promoting proliferation of cerebellar external granule layer (EGL) cells. The EGL cells give rise to internal granule cells, which are the most abundant neurons of the brain.

Patients with the nevoid basal cell carcinoma syndrome (NBCCS) (Gorlin syndrome) have germline mutations of *PTCH*, a tumour suppressor gene. When active, *PTCH* inhibits Smoothened (SMO), a cell surface protein that regulates a cell proliferation pathway that includes several intracellular downstream effectors such as GLI1 and MYCN. Inactivating *PTCH* mutations in patients with NBCCS presumably release susceptible cells from *PTCH*-mediated inhibition of cell proliferation, with resulting neoplasia.

*PTCH* mutations (allelic losses) have been identified in about 10-18% of medulloblastomas, especially the desmoplastic type, but such mutations are much less common in the most common classic variant. Copy gain and aberrant expression of *FOXG1*, a downstream effector of SHH signalling with a putative role for maintaining a persistent undifferentiated state in neuroepithelial stem cells, has also been reported to be a frequent event in medulloblastoma.

Some patients with germline mutations of the adenomatous polyposis (APC) gene may develop medulloblastoma in addition to their predisposition to colon cancer (familial adenomatous polyposis [FAP]). The APC protein is an inhibitor of the WNT pathway. Turcot syndrome describes the subset of patients with FAP that develop medulloblastoma.

More recently, there has been emerging evidence that neural stem or progenitor cells may give rise to embryonal tumours of the nervous system.

**Based on combined data emerging from gene expression profiling, CGH array, and cytogenetic studies and their correlation with clinical outcome, medulloblastomas have been divided into 4 clinical subgroups, depending on the predominantly activated signalling pathways in a tumour. These include 2 groups with predominant wnt (group A) or Sonic hedgehog (SHH) (group B) pathway activation, respectively, and have a better prognosis. The other two groups, C and D, are biologically aggressive and noted to overexpress either *MYCN* (group C) and/or *OTX2* and *FOXG1* (groups C and D).

In addition, some specific genetic events serve as signatures for each of the subgroups. The group A tumours are more likely to show a loss of chromosome 8, *CTNNB1* mutations, rarely metastatic, show classic histology, occur in older children, and have a good prognosis.

Group B tumours are more likely to show a 9q deletion, *PTCH/SMO/SUFU* mutations, MYC amplification, and a desmoplastic histology. They are seen in infants and adults, rarely metastasize and have a good prognosis.
Group C and D tumours often show i(17q), 1X, -18, and MYC amplification. FOXG1 upregulation may be seen in both groups but more frequently seen in the group C. They are often metastatic, associated with the aggressive large cell anaplastic histology, seen in children and have intermediate (group D) and poor (group C) prognosis. The slightly better prognosis of the group D tumours correlates with their higher expression of neuronal and photoreceptor markers.

Combining subgroup and cytogenetic biomarkers with established clinical biomarkers substantially improves patient prognostication, even in the context of heterogeneous clinical therapies. The prognostic significance of most molecular biomarkers is restricted to a specific subgroup. There is a small panel of cytogenetic biomarkers that reliably identifies very high-risk and very low-risk groups of patients. These biomarkers are a tool for selecting patients for therapy intensification and therapy de-escalation in future clinical trials.

**Differential diagnoses:** astrocytoma, paediatric ependymoma, paediatric aseptic meningitis and bacterial meningitis. Note ependymoma arises from the floor of the 4th ventricle.

**Biochemistry and haematology tests:**
- The routine pre-treatment laboratory evaluation for medulloblastoma includes FBC count, electrolytes, liver and renal function tests.
- Baseline thyroid function studies and viral titres are recommended.

**IMAGING; CT scanning**

A CT scan of the head with and without contrast has more than 95% sensitivity for the detection of brain tumours. On CT scans, prominent hydrocephalus and a solid, homogeneous, iso-dense to hyper-dense, contrast-enhancing, midline cerebellar mass are characteristic of (although not diagnostic of) medulloblastoma.

Image is a non-contrast CT scan, courtesy of Dr Mohammad Taghi Niknejad, Radiopaedia.org, RID: 32692, shows a hyperdense mass in the right side of the posterior fossa – black arrow - which is displacing and rotating the 4th ventricle – yellow arrow. There is dilatation of the temporal horns – white arrow - which is an early sign of hydrocephalus.

**MRI - Head and spinal MRI** with and without gadolinium should be performed in all patients with CT or clinical findings consistent with medulloblastoma.

Other midline posterior fossa tumours, such as cerebellar astrocytoma and ependymoma, may have a similar appearance on CT.
MRI can be useful in such instances by better demonstrating the anatomic origin and extent of tumour (see the image below, courtesy of Dr Toby J MacDonald, Medscape Nov 26, 2014)). The tumour is in the floor of the 4th ventricle which is unusual.

MRI T2W axial and coronal T1 post contrast, showing a cerebellar vermian midline mass with contrast enhancement and obstruction of the 4th ventricle. Courtesy of Dr Adekunie Adesina, Medscape Jan 14, 2015.

Preoperative and postoperative MRI is required for detection and measurement of residual disease following surgical resection. Postoperative MRI evaluation should be performed within 72 hours of surgery to delineate residual tumor from the postsurgical inflammatory changes that are visualized on MRI at this time.

**Spinal MRI** is the most sensitive method available for detection of spinal cord metastasis.

**Bone scan**: Because medulloblastoma can metastasize outside the CNS, especially to bone, a bone scan with plain film correlation may be useful in symptomatic patients.

**Audiology**: A baseline hearing test or brainstem auditory-evoked response (BAER) is recommended because of the potential toxicity from radiation and chemotherapy treatment.

May require **additional tests**, such as echocardiography, pulmonary function tests, or other more specific tests, for the purposes of monitoring treatment-related toxicity.
**Lumbar puncture**: CSF cytologic examination is useful for the detection of microscopic leptomeningeal tumour dissemination. However, neither clinical symptoms nor negative CSF cytologic findings can be relied on to indicate the presence of nodular spinal cord disease. As many as 50% of patients with positive spine MRI studies are asymptomatic and have negative cytologic results.

**Funduscopic examination (or CT or MRI)** must be performed before lumbar puncture to rule out the presence of hydrocephalus.

In known cases of medulloblastoma, lumbar puncture is generally deferred until 2 weeks post-operation to avoid the presence of tumour cells that have disseminated as a result of surgery.

**Bone marrow aspirate and biopsy**: Medulloblastoma rarely metastasizes to bone marrow. These tests should be reserved for patients who demonstrate abnormal peripheral blood findings that have no clear etiology.

**Microscopy**: Medulloblastomas are undifferentiated embryonal neuroepithelial tumours of the cerebellum. They are highly cellular, soft, and friable tumours composed of cells with deeply basophilic nuclei of variable size and shape, little discernible cytoplasm, and often abundant mitoses (see Image below courtesy of Dr Nat Pernick. PathologyOutlines.com. 27th Nov 2013).

There is a fibrillary nature to the tumour cells. Occasional Homer Wright rosettes may be seen.

This section displays a typical medulloblastoma, composed of undifferentiated cells with deeply basophilic nuclei of variable size and shape and little discernible cytoplasm.

These characteristics give the microscopic appearance of a small, round, blue cell tumour. Image courtesy of Dr Nat Pernick. PathologyOutlines.com. 27th Nov 2013.
Homer-Wright rosettes (ringlike accumulations of tumour cell nuclei around a neuropil-containing or fibrillary core) – see arrow and pseudorosettes are variably present.

Immunohistochemistry;

These tumours express neuronal and neuroendocrine markers, including synaptophysin and neurofilament proteins. The image below shows immunopositivity for synaptophysin. Also neuron-specific enolase, MAP-2 and class-III beta tubulin will be at least focally immunoreactive in most medulloblastomas.

Various degrees of glial or neuroblastic differentiation are noted, suggesting that the primitive cell of origin possesses the capacity for bi-potential differentiation.

Reticulin-free nodules of the desmoplastic variant are typically reactive for markers of neuronal lineage. Vimentin is typically reactive although quite nonspecific. Variable expression for neurofilament proteins has been documented, and immunoreactivity is dependent on the neurofilament subtype and the antibody used.
Glial fibrillary acidic protein (GFAP) is most often reactive in cells with fibrillary processes that appear to represent reactive (intratumoral) astrocytes. Occasional examples of medulloblastoma (estimated at around 10% of these tumors) will show distinct GFAP-immunoreactivity of the perinuclear cytoplasm. Rare examples of medulloblastoma may contain spindle cells or occasionally "strap" cells with cross-striations consistent with myogenic differentiation and, accordingly, show strong reactivity for desmin (and other myogenic markers).

**MEDULLOBLASTOMA VARIANTS**

**Desmoplastic/nodular medulloblastoma – 9471/3** is a histologic variant, has a firm consistency, with abundant reticulin-rich stromal component, and reticulin-poor, nodular, pale islands with expression of markers of neuronal differentiation.

**Associated** with: nevoid basal cell carcinoma syndrome.

**Site:** Occurs predominantly in the lateral cerebellar areas of adolescents and adults.

**Mean age:** 18 years (compare with classic medulloblastoma where age is 3 – 5 years).

**Microscopic:**

Tumour within reticulin-rich areas is usually highly cellular and proliferatively active, whereas the reticulin-poor nodular foci show less mitotic activity and more neuronal differentiation.

Image, courtesy of Dr Adekunie Adesina. Medscape Jan 14, 2015, shows pale nodules of differentiating neuroblasts (neurocytes). There is abundant intervening less differentiated internodular regions. Infiltration of the meninges and subarachnoid space may be apparent, as well as frank invasion of adjacent structures. Fibrous reaction may be from leptomeningeal cells in the arachnoid space. It may have a better prognosis than classic medulloblastoma.
The internodular areas are more densely cellular and contain prominent reticulin.

**Extensive nodularity medulloblastoma – 9471/3** – is another variant arising in children younger than 3 years. Imaging courtesy of Adekunie Adesina. Medscape Jan 14, 2015, shows a left sided lateral cerebellar mass with “grapelike” nodular appearance which is characteristic of this condition. It arises in children less than 3 years. It may undergo neurocytic or gangliocytic maturation after chemotherapy/radiotherapy.

**Microscopy** shows the tumour with minimal or no internodular component, unlike nodular/desmoplastic.
Large cell/anaplastic medulloblastoma – 9470/3

A variant of cerebellar medulloblastoma composed of large neoplastic cells with vesicular nuclei and prominent nucleoli as well as a superficial resemblance to a large-cell lymphoma was first described by Giangaspero and colleagues (see the following image). This large-cell variant accounts for approximately 2-4% of all medulloblastomas and can be demonstrated to exhibit neuronal differentiation by immunohistochemical detection of neuronal lineage antigens such as synaptophysin. It may be distinguished from the atypical teratoid/rhabdoid tumor (AT/RT) by its strong expression of INI-1 (BAF47); AT/RT is typically negative for this antigen. The large-cell medulloblastoma is a more aggressive variant and is less responsive to standard therapies.

The image above, courtesy of Dr Adekunie Adesina and below courtesy of Dr Nat Pernick. PathologyOutlines.com, 27th Nov 2013, is of large cell medulloblastoma. There are large vesicular nuclei, distinct nucleoli and a vague resemblance to large cell lymphoma.

The image below is also a large cell/anaplastic variant.

Anaplastic medulloblastoma - - 9470/3- 15% of medulloblastomas, was previously separate from large cell medulloblastoma but in the 2016 WHO Classification has been included with it. There is
cytologic anaplasia, frequent cell wrapping (see arrows) and apoptotic bodies in this intraoperative cytopreparation. There is high mitotic activity with atypical forms. Biologically aggressive.

The image below shows again cell wrapping and – see arrow on apoptotic bodies.

Rarely medulloblastomas may show evidence of skeletal muscle (medullomyoblastoma) or melanocytic differentiation. Data on the natural history of these tumours suggest a similar biologic behaviour as more typical medulloblastoma types.

Histologic transformation of more typical types of medulloblastoma to an anaplastic type is recorded

*Anaplasia associated with MYCC oncogene amplification.*

Cytogenetic abnormalities that have been described in childhood medulloblastoma include loss of 17p, amplification of MYCC (c-myc), amplification of MYCN (N-myc), and isochromosome 17q. Data on these tumours indicate that the frequency of MYCC amplification is 5% to 10%. Fluorescence in situ hybridization is a tool for demonstrating these features. The finding is associated with a poorer prognosis. Image courtesy of Dr Nat Pernick. PathologyOutlines.com 27th Nov 2013.
MRI can be used to demonstrate Diffusion restriction as an ADC map which is consistent with high cellularity. **Diffusion weighted imaging (DWI)** is a form of MR imaging based upon measuring the random Brownian motion of water molecules within a voxel of tissue. Generally densely cellular tissues or those with cellular swelling exhibit lower diffusion coefficients, and thus diffusion is particularly useful in tumour characterisation and cerebral ischaemia.

**Mass spectroscopy** shows elevation of choline but little, if any, N-acetyl aspartate (NAA) peak. Elevation of the taurine peak may also be seen.

**Treatment:** reference for the text material that follows is Medscape Jan 14 2015, Dr Adesina.

**Aggressive surgery** followed by radiation of the entire cranio-spinal axis with boost to both the primary tumour site and focal CNS metastatic sites. Adjuvant chemotherapy may also be beneficial.

**Radiation Therapy:**

**Average-risk disease**

Reducing the amount of craniospinal radiation in an attempt to decrease morbidity without jeopardizing survival appears to be successful in this group.

The dose for average-risk medulloblastoma patients enrolled on Children’s Oncology Group (COG) last completed trial was 23.4 Gy to the craniospinal axis followed by 32.4 Gy boost directly to the primary tumour site. In both the poor-risk and average-risk groups, the total radiation dose to sites of known disease is 55.8 Gy.

The rate for 5-year progression-free survival was 62% for patients treated in the prone position and 76% for supine patients.
It was found that permanent alopecia correlated with irradiation dose with a threshold of about 21 Gy (relative biological effectiveness) with high-dose chemotherapy and 30 Gy with conventional chemotherapy.

**Poor-risk disease**: The current recommendation is 36 Gy to the craniospinal axis, followed by a boost of 19.8 Gy to the primary tumour site and an additional 19.8 Gy to focal metastatic sites. The amount of boost that can be given is limited by the presence of the optic nerves within the radiation field or if more than two thirds of the supratentorial compartment volume is within the radiation field.

**Spinal disease** that is visible after 30.6 Gy of the prescribed 36 Gy to the craniospinal axis receives an additional boost up to a total of 45 Gy if the tumour is located above the termination of the spinal cord and as much as 50.4 Gy if the tumour is located below the termination of the cord.

**Infants**

Radiotherapy for patients **younger than 3 years, the poorest risk group**, remains controversial. Because the effects of radiotherapy on intellectual development are most severe in this age group, attempts have been made to delay or omit radiation by using chemotherapy. However, in the most recent COG study, infants receiving chemotherapy alone had a 29% 3-year progression-free survival rate for those without dissemination and only 11% for those with metastasis. The Pediatric Oncology Group (POG) reported that, in infants with medulloblastoma treated initially with chemotherapy followed by delayed radiation, the 2-year progression-free survival rate was 34%.

Trials are currently underway to avoid or delay radiotherapy in this population by using cycles of high-dose chemotherapy followed by autologous stem cell rescue. Initial reports have indicated a good response rate to chemotherapy, and, although overall survival (30-40%) is comparable to prior studies, most patients who survived in the latest trials did not receive radiotherapy. Infants with desmoplastic tumour treated with chemotherapy fare better than those with classic tumours because 70% or more can be successfully treated without radiotherapy.

**Chemotherapy**

**Average-risk disease** The most encouraging results with adjuvant chemotherapy have been reported in children with non-disseminated medulloblastoma receiving 8 cycles of lomustine (CCNU), vincristine, and cisplatin chemotherapy for approximately 1 year following conventional dose radiotherapy and concomitant vincristine.

Latest trials indicate that children aged 3-10 years who received this regimen with reduced-dose craniospinal radiation have a superior survival rate compared to those who received standard radiation alone. The current 3-year progression-free survival rate for those receiving adjuvant chemotherapy is approximately 80%.

**Poor-risk disease**

Chemotherapeutic agents that have been found to be most effective for this disease are cisplatin, carboplatin, cyclophosphamide, and vincristine.

To improve survival rates in this group, current trials are investigating the use of high-dose chemotherapy (most commonly using carboplatin and thiotepa-containing regimens) and
autologous stem cell rescue after a course of conventional craniospinal radiotherapy and chemotherapy.

**Infants**

In children younger than 3 years, evidence suggests that some do respond, at least partially, to chemotherapy. In patients with minimal residual postoperative disease, this response may be long-lasting.

Ongoing trials are investigating high-dose chemotherapy (carboplatin and thiotepa) and stem cell rescue, following induction with chemotherapeutic agents similar to those used in the treatment for older children with poor-risk disease.

Methotrexate, both intra-thecally and intravenously, is being added to more conventional chemotherapy in some studies; primarily for infants with partially resected and/or disseminated tumours.

**Relapsed disease**  Current studies investigating the use of biologic agents that specifically target the most common molecular alterations described in this disease, such as tyrosine kinase inhibitors that block the function of EBB2, are ongoing.

**Surgery - Suboccipital craniotomy**

Because the tumour is often friable, gentle suction is used. Microdissection is used to remove adherent portions. Modern neurosurgical techniques permit complete or near-complete resection with little or no significant increase in morbidity and mortality rates compared with more conservative surgery.

Because surgical estimates of the extent of resection may not be reliable, postoperative MRI evaluation for residual disease is required within several days of the procedure.

**Complications:** As many as 40% of patients have some degree of new neurologic dysfunction postoperatively. One ill-defined syndrome is posterior fossa syndrome, characterized by mutism, cerebellar dysfunction, supranuclear cranial nerve palsy, and hemiparesis that occurs 12-48 hours after surgery. As many as 50% of patients have residual deficits.

**Ventriculoperitoneal shunt**

Approximately 50% of patients require placement of a ventriculoperitoneal shunt at the time of operation (or shortly thereafter) because of unresolving obstructive hydrocephalus. Third ventriculostomy is increasingly used to avoid the placement of a permanent ventricular shunt.

**Medication summary**

Historically, the most active drugs have been DNA alkylators which cause DNA damage and disrupt DNA replication and so inhibit tumour growth and promote tumour cell death. The agents with the longest clinical history in the treatment of medulloblastoma are vincristine, lomustine (CCNU), and cisplatin.

e.g. Vincristine is a plant-derived vinca alkaloid used during radiotherapy and in combination with other chemotherapeutic agents which acts as a mitotic inhibitor binding tubulin. Lomustine is a DNA
alkylator used in combination with other chemotherapeutic agents which causes interstrand and intrastrand DNA-DNA crosslinks resulting in damage to the DNA template and inhibits DNA replication.

Cisplatin is a heavy metal coordination complex that exerts its cytotoxic effect by platination of DNA. A mechanism analogous to alkylation, leading to interstrand and intrastrand DNA crosslinks and inhibition of DNA replication. Used in combination with other chemotherapeutic agents.

Most regimens require the concomitant use of an antiemetic.

**Follow up outpatient care;** Radiotherapy is performed for approximately 6 weeks. Monitoring of response and treatment-associated side effects is done weekly during radiotherapy and every 2 weeks during chemotherapy. Reevaluation immediately before each cycle of chemotherapy is necessary to document resolution of previous treatment-related toxicities.

Following the completion of therapy, assessments are conducted every 3 months for the first 12-18 months, every 6 months for the next 2 years, and then annually, provided no complications have occurred. Imaging studies - MRI with contrast of the head is performed at the completion of radiotherapy, after every 2 cycles of chemotherapy, and at the end of therapy. Unless clinically indicated, follow-up MRI scans after the completion of therapy are performed in conjuncture with the physical and neurologic examination schedule.

MRI with contrast of the spine is performed only at the completion of therapy and annually thereafter unless metastatic spinal disease was observed, in which case more frequent evaluation may be necessary.

**Laboratory studies** – toxicity associated with therapy is carefully monitored.

Weekly CBC counts are necessary during radiotherapy and chemotherapy, as well as liver function studies, electrolytes, renal function, and a hearing test before each cycle of chemotherapy and again at the end of treatment. Baseline studies are performed before the initiation of any therapy. These tests may need to be performed annually for the first 3-5 years after therapy. Baseline endocrinologic and neuropsychologic evaluation is performed at the completion of therapy and annually thereafter. Additional tests for the purposes of monitoring specific investigational protocol treatment-related toxicity (eg, echocardiogram, pulmonary function) may be required.

**Morbidity:** Despite successful treatment, a significant number of patients have neurocognitive and endocrinologic deficits. Although most long-term survivors have normal intelligence, many subsequently develop learning difficulties that require individualized educational programs. Biochemical growth deficiency is observed in 70-80% of patients, and some degree of growth impairment is present in well over half of patients after treatment. Thyroid and gonadotropin hormonal deficiency may also occur. **Craniospinal radiation, a mainstay of treatment, has been implicated as a major cause of these deficits.**

Because of the immunosuppressive effects of chemotherapy, trimethoprim sulfamethoxazole and nystatin are commonly prescribed for prophylaxis against *Pneumocystis carinii* pneumonia and mucocutaneous candidiasis, respectively, for the duration of treatment. Granulocyte colony stimulating factor (GCSF) following chemotherapy may be used in treatment regimens expected to cause marked neutropenia.
Complications include the following:

- Obstructive hydrocephalus
- Neurologic impairment including academic difficulties.
- Pain secondary to metastasis
- Chemotherapy-induced effects
  - Anaemia
  - Thrombocytopenia and increased risk for bleeding
  - Neutropenia and increased risk for life-threatening bacterial, viral, and fungal opportunistic infections
  - Nephrotoxicity, ototoxicity, hepatotoxicity, and neurotoxicity
- Radiation-induced effects
  - Neurocognitive and endocrinologic dysfunction
  - Mineralizing microangiopathy with ischemia or infarct
  - Secondary CNS and thyroid malignancies

Prognosis: tumour spread and staging are utilised to assess prognosis.

Intra axial tumour spread along CSF pathways is characteristic of medulloblastoma and is identified in about 30% of patients at presentation. Subpial and parenchymal infiltration of tumour cells is not uncommon. Distant metastases are exceptional. Occasionally, tumours have metastasized outside of the nervous system via ventriculo-peritoneal shunts or other iatrogenic means.

Risk group stratification is currently based on 3 principal features; age, extent of postoperative residual disease, and the metastasis stage (M stage) derived from the Chang classification staging system. The M stage classification is as follows:

- M0 - No gross subarachnoid or haematogenous metastasis
- M1 - Microscopic tumour cells found in CSF
- M2 - Gross nodular seeding in cerebellum, cerebral subarachnoid space, or in the third or fourth ventricles
- M3 - Gross nodular seeding in spinal subarachnoid space
- M4 – Extra-neuro-axial metastasis.

The specific risk groups based on this classification scheme are defined:--.

- **Average-risk disease**: defined as patients older than 3 years who are at stage M0 with less than 1.5 cm$^2$ of residual tumour postoperatively. The 5-year survival rate for this group is currently more than 80%
- **Poor-risk disease**: defined as patients older than 3 years who are at stage M1-M4 and/or with more than 1.5 cm$^2$ of residual tumour postoperatively. The 5-year survival rate for this group is currently 30-60%
- **Infants**: This group is defined as patients younger than 3 years. This group has the worst prognosis, regardless of M stage and extent of postoperative residual disease. The 5-year survival rate is approximately 30%; however, patients with metastatic disease do considerably worse. Those infants with desmoplastic tumors are more likely to survive.

**Biologic parameters have been related to outcome.** In retrospective studies, children with tumours that have increased expression of TRKC and WNT are more likely to survive, whereas those with increased amplification of MYCC oncogene or increased ERBB2 expression have a poorer prognosis.
Real-time biologic tumour analysis will likely supplement clinical parameters used for stratification in the future. Histologic features of severe anaplasia have been associated with poorer survival.

Patients who do survive often experience significant neurologic impairment due to unavoidable side effects of radiotherapy, and current research is focused on identifying biomarkers of disease that will allow for better risk assessment and more refined treatments that are directed to individual tumour types.

**GENETICALLY DEFINED MEDULLOBLASTOMA subgroups**

Medulloblastoma is now recognized as comprising distinct molecular disease subgroups. Its primary, consistently identified subgroups are characterized by mutational activation of the Sonic Hedgehog (SHH subgroup; approximately 25% of cases) or Wnt/Wingless (WNT subgroup; 10% to 15% of cases) developmental signaling pathways, signature transcripational and genomic profiles, and associations with specific clinical disease features and outcomes.

**WNT-activated – 9475/3 (new in 2016 classification)** – this tends to have a good prognosis. It is found exclusively in the cerebellar peduncle. It is not seen in infancy. M : F = 1 : 1.

**SHH-activated & TP53 mutant – 9476/3** – found in infants and adults but not children. Prognosis is good in infants but other age groups only intermediate prognosis. M : F = 1 : 1.

**Medulloblastoma SHH-activated & TP53 – wildtype – 9471/3** good prognosis

**Group 3 – 9477/3** found in infants and children but not adults. Poor prognosis. Slight male preponderance.

**Group 4 – 9477/3** – found in children, rare in infants, slightly better prognosis than group 3.


Assessing which group/type the tumour belongs to can assist with therapy. For example, poor survival of patients with TP53 mutant medulloblastoma may be related to radiation resistance. Since constitutive activation of the WNT pathway by administering lithium to the patient sensitizes TP53 mutant medulloblastoma cells (and protects normal neural stem cells from radiation), this oral drug may represent an attractive novel therapy for high-risk medulloblastomas.

**Summary of Treatment and Prognosis of Medulloblastoma:**

Treatment typically consists of surgical resection, radiation therapy, and chemotherapy. In general the tumours are quite radiosensitive.

Prognosis depends on complete surgical resection, and presence of CSF metastases at the time of diagnosis, which are generally common in infants and children (~25%) and uncommon in adults (~2%) ¹.

Expression of the c-erbB-2 (HER2/neu) oncogene is useful in staging of medulloblastomas. Increased c-erbB-2 expression (shown by immunohistochemistry staining) reflects an increase in the proliferative activity of a tumour (widely used in breast cancer staging) so if positive, the prognosis is
poor but if negative is better. Note that ERBB2 is a proto-oncogene and is on the long arm of chromosome 17 (17q12). It opposes apoptosis so if present, the prognosis is poor.

- no CSF metastases, complete surgical resection and negative c-erbB-2 expression: 5-year-survival 100%
- no CSF metastases, complete surgical resection and positive c-erbB-2 expression: 5-year-survival 54%
- CSF metastases and/or incomplete surgical resection: 5-year-survival 20%

**OTHER CNS EMBRYONAL TUMOURS**

**Overview:** Currently medulloblastoma, embryonal tumour with multilayered rosettes characterized by C19 MC alteration and the atypical teratoid/rhabdoid tumour characterized by INI1 or BRG1 alterations represent genetically defined embryonal tumours of the CNS.

Many paediatric embryonal CNS tumours previously classified as embryonal tumour with abundant neuropil and true rosettes, ependymoblastoma and medulloe epithelioma, are now included in the group of embryonal tumour with multilayered rosettes characterized by the C19MC alteration. It should be noted that any CNS embryonal tumour with 19MC amplification or fusion qualify for this designation, including those lacking distinctive histopathological features.

There are, however, a number of CNS embryonal tumours for which a molecular classification are not yet possible. Histologically one resembles embryonal tumour with multilayered rosettes and is included alongside that tumour as embryonal tumour with multilayered rosettes NOS; another resembles atypical teratoid/rhabdoid tumour and is included alongside that tumour as atypical teratoid/rhabdoid tumour, NOS.

Others, which are not genetically defined, include medulloe epithelioma, neuroblastoma, ganglioneuroblastoma, and CNS embryonal tumour, NOS.

The introduction of embryonal tumour with multilayered rosettes characterized by C19 MC alteration has complicated the classification as it is unclear whether their epidemiological and clinical data differ greatly from that of the ‘umbrella’ group of medulloe epithelioma, neuroblastoma, ganglioneuroblastoma, and CNS embryonal tumour, NOS. For simplicity, each of these entities is discussed individually below.

**CNS NEUROBLASTOMA – 9500/3**

This tumour shares essentially identical microscopic appearances to the cerebellar medulloblastoma.

CNS neuroblastoma (previously CNS S-PNET) accounts for 5% of all CNS primitive neuroepithelial tumours and for 1% of paediatric brain tumours.

***S-PNET ‘SUPRATENTORIAL PRIMITIVE NEUROEPITHELIAL TUMOUR’ TERMINOLOGY IS NO LONGER USED.***

**Definition:** Primary cerebral neuroblastoma is a rare type of primitive ectodermal tumour, typically described in children as a large intra-parenchymal supra-tentorial mass frequently containing cysts,
calcification and spontaneous haemorrhage with little associated oedema. Sub-arachnoid tumour seeding is common. This tumour is generally considered to be a specific subset of primitive neuroectodermal tumours although neuropathologic controversy exists. 2016 WHO classification places it under a heading of Embryonal Tumours as an entity. Detailed electron microscopy to identify neurosecretory granules may be required for the exact diagnosis. These tumours are malignant lesions with a high rate of recurrence after therapy and frequent subarachnoid metastases.

**Incidence:** only 2% of all neuroblastomas occur in the brain.

**Age:** The commonest age is less than 5 years but these tumours have been reported in adults in their 30’s.

**Clinical presentation:** Supratentorial CNS neuroblastomas and ganglioneuroblastomas, will result in focal neurologic deficits, such as hemiparesis and visual field loss, depending on which portion of the cerebral cortex is involved. They may also result in seizures and obtundation. Medulloepitheliomas and ependymoblastomas may occur anywhere in the CNS, and presentation is variable. Usually there is significant neurologic dysfunction associated with lethargy and vomiting.

**Microscopic:** Histopathological confirmation is required for definitive diagnosis.

These tumours are cellular and often lobulated neoplasms, formed by a population of neuroblastic cells, which may demonstrate Homer Wright rosette formation.

The tumour involves the cerebrum or suprasellar region. One sees undifferentiated or poorly differentiated small neuroepithelial cells which may demonstrate the capacity of differentiation along divergent lines.

**Histologic variation occurs within and among cerebral neuroblastomas.** The very poorly differentiated embryonal character of these tumours is displayed in cells that are larger than those in the classic medulloblastoma and have spheroidal, polygonal or pyramidal cytoplasmic outlines, vesiculated nuclei and small nucleoli. Rarely show Homer Wright rosette formation.

The image below is composed of small and generally undifferentiated cells. Neuroblastic differentiation, in the form of Homer-Wright rosettes – see the arrow – is evident.
Molecular pathology:

**CNS neuroblastoma with FOXR2 activation (CNS NB-FOXR2):** Representing 14% of embryonal cases, this subtype is characterized by genomic alterations that lead to increased expression of the transcription factor FOXR2. CNS NB-FOXR2 is primarily observed in children younger than 10 years, and the histology of these tumours is typically that of CNS neuroblastoma or CNS ganglioneuroblastoma (as described in the 2007 WHO classification). There is no single genomic alteration among CNS NB-FOXR2 tumours leading to FOXR2 overexpression, with gene fusions involving multiple FOXR2 partners identified.

[Cerebellar neuroblastoma is very rare. Ref: Pedram M, Vafaie M, Fekri K, Haghi S, Rashidi I, Pirooti Ch. Cerebellar Neuroblastoma in 2.5 Years Old Child. Iran J Cancer Prev. 2013; 6(3):174-6. When mature cells are present at the site of the cerebellum, the tumour may be classified as cerebellar ganglioneuroblastoma. When they form a lobulated pattern with cells streaming in a fine fibrillated background, they are designated cerebellar neuroblastoma. Have a better prognosis than the classic or desmoplastic medulloblastoma.

Light microscopic assay shows a small cell neoplasm with lobules of densely packed cells (lobulated pattern) and better differentiated cells. Neuron-Specific Enolase is positive.]

**Imaging of CNS Neuroblastoma:** There is calcification in 70% and minimal oedema. They are isointense to hypointense and have heterogeneous enhancement.

The **post contrast CT scan** below shows a very large, extensive hemispheric mass present in the left parieto-occipital region in a 12 year old girl. The white block arrow indicates the third ventricle displaced to the right of the midline. The cluster of thin black arrows indicate the perimeter of the very large mass. There is very little associated oedema.

**MR imaging** with contrast is helpful primarily for localization of peri and intraventricular lesions and is essential for revealing tumour recurrence around cysts and at surgical sites and for leptomeningeal seeding.
Primary CNS neuroblastoma has no pathognomonic appearance on CT or MR; thus it should be considered in the differential diagnosis of intraparenchymal or juxtaventricular masses.

**Treatment:** surgical removal followed by chemotherapy. Sometimes give radiotherapy.

**Prognosis:**
Primary cerebral neuroblastoma is an aggressive tumour with a relatively poor prognosis owing to local tumour recurrence and leptomeningeal seeding.

Patients who have disseminated disease at the time of diagnosis have a poor overall survival, with reported survival rates at 5 years ranging from 10% to 30%.

Extent of resection was found to be prognostic for those with localized disease at the time of diagnosis.

**CNS GANGLIONEUROBLASTOMA – 9490/3**

**Definition:** A rare embryonal tumour characterized by the presence of poorly differentiated neuroepithelial cells and groups of neurocytic and ganglionic cells.

**Incidence:** 5 per million annually

**Age:** usually in children under the age of 5 years but may occur in young adults.

**Site:** temporal lobe of the brain. Rarely found in the cerebellum.

**Racial:** no predilection.

**Clinical:** Signs and symptoms of cerebral neuroblastic tumours are related to the site of origin, and include seizures, disturbances of consciousness, increased intracranial pressure, and motor deficit.

**Microscopic:** shows highly cellular areas, composed of embryonal neuroblastic (immature) cells, intermingled with less cellular areas and clusters of mature ganglion cells.
Treatment: For cerebral ganglioneuroblastoma, the preferred regimen would seem to be neurosurgical removal, followed by chemoradiotherapy including temozolomide and radiotherapy.

If the tumour is mostly made up of benign type cells, surgery may be the only treatment required.

EMBRYONAL TUMOURS WITH MULTILAYERED ROSETTES (ETMR)– 9478/3 – new in 2016 WHO Classification.

Definition: are rare small round blue cell tumours of the central nervous system, and one of the most aggressive brain tumours.

Previously ETMR were known as embryonal tumour with abundant neuropil and true rosettes (ETANTR). 2016 update to WHO classification of CNS tumours has removed the earlier term in favour of embryonal tumours with multilayered rosettes (ETMR) which incorporates not only ETANTR but also CNS PNET (which has also been removed from the classification). This is due to the presence of amplification of the C19MC region on chromosome 19 (19q13.42) - in both CNS PNET and ETANTR, suggesting that these are the one entity with variable growth patterns. Also in the new classification under ETMR is C19MC-altered (or ETMR-NOS if C19MC amplification is absent)

Age: usually found in children less than 4 years, especially those under 2 years.

Gender: more common in girls, whereas the other embryonal tumours are more commonly equal in both sexes or more common in boys.

Sites: most are located supratentorially, being less commonly seen in the infratentorial region and very rarely in the spinal cord.

Clinical presentation: The clinical features are determined by the location and extent of the tumour. Increased intracranial pressure, seizures, hemiparesis, cerebellar signs, cranial nerve palsies, and other neurologic deficits have all been reported.

Imaging:

MRI

The tumour appears as a large, demarcated, solid mass featuring patchy or no contrast enhancement, with surrounding oedema, often with significant mass effect. A minority of the reported cases have shown cystic components and microcalcifications.

- **T1**: decreased intensity
- **T2**: increased intensity
- **T1 C+ (Gd)**: patchy or no contrast enhancement
Images below are courtesy of Neelima R, Easwer HV, Kapilamoorthy TR, Hingwala DR, Radhakrishnan. Neurology India 2012, 60 (1) : 96-99. Case 1-(a) T2W sagittal image showing a heterogeneous mass lesion in the left fronto-parietal region with solid and cystic components. (b) Post-contrast axial image shows minimal heterogeneous enhancement of the lesion. Case 2- (c) T2W axial image showing a heterogeneous mass lesion in the right parieto-occipital region with solid and cystic components (d) Post-contrast axial image shows heterogeneous irregular enhancement of the lesion.

**MR spectroscopy** shows choline peak and a high ratio of choline/aspartate suggesting hypercellularity of the tumour.
**Microscopic:** Embryonal tumors with multilayered rosettes (ETMS) are characterized by undifferentiated neuroepithelial cells resembling those of classic CNS PNET, abundant well-differentiated neuropil, and ependymoblastic rosettes scattered throughout paucicellular regions of neoplastic neuropil. Unlike medulloblastoma, ETMR has no epithelial-like formation. Instead, it has very characteristic ependymoblastic rosettes in both highly cellular as well as acellular areas.


(a) Photomicrograph of hypercellular zone with undifferentiated small cells in sheets. (b) Ependymoblastic rosettes in a paucicellular neuropil stroma. (c) Multilayered ependymoblastic rosettes with a mitotic figure and central round lumen. (d) Multilayered perivascular rosettes with undifferentiated cells and surrounding neurocytoma-like cells with clear cytoplasm in a neuropil stroma. (e) Undifferentiated cells and clear cells in a neuropil background. (f) Neoplastic large ganglion cells surrounded by small hyperchromatic cells (H and E).

**Immunohistochemistry:** LIN28A expression is positive in most.

**Molecular pathology:** amplification of the C19MC region on chromosome 19 (19q13.42) is characteristic.

**Treatment:**

Current treatment options for ETMR include surgical resection, systemic chemotherapy and craniospinal radiation where indicated.

**Prognosis:** is very poor with centres reporting that 75% of patients have died with a median survival of 9 months.
**MEDULLOEPITHELIOMA - 9501/3**

**Definition:** Medulloepithelioma is a rare, primitive, fast-growing brain tumour thought to stem from cells of the embryonic medullary cavity. Tumours originating in the ciliary body of the eye are referred to as embryonal medulloepitheliomas or diktyomas.

A highly malignant undifferentiated primitive neuroepithelial tumour of children, medulloepithelioma may contain bone, cartilage, skeletal muscle, and tends to metastasize extracranially.

**Age:** between 6 months and 5 years

**Imaging:** On non-contrast CT scan the lesion is either isodense or hypodense with variable heterogeneity and calcification. The tumour enhances with contrast. The CT images below – NC and PC are courtesy of Sundaram C, Vydehi BV, Reddy JJ, Reddy AK. Neurology India 2003, 51 (4) : 546-47. Child was 3 years old with a rapidly enlarging mass on the posterior aspect of the skull.

The non contrast CT shows a heterogeneous mass with destruction of bone and extension of tumour into the subcutaneous planes. There are areas of calcification, necrosis and oedema. Post contrast there was heterogeneous enhancement of the mass which involved both occipital lobes and had cystic change.

**Microscopic:** image courtesy of Wikipedia and shows the characteristic neural tube like strands.
Treatment: gross total resection followed by radiotherapy

Prognosis
Median survival is only 5 months. However, medulloepitheliomas occurring in the eye or orbit do benefit from total resection and may have a good prognosis.

ATYPICAL TERATOID/RHABDOID TUMOUR (AT/RT) – 9508/3

Definition: it is a very rare, fast-growing tumour of the brain and spinal cord

Age: It usually occurs in children aged three years and younger, although it can occur in older children and adults.

Sites: About half of these tumours form in the cerebellum or brain stem. AT/RT may also be found in other parts of the central nervous system (brain and spinal cord).

Clinical presentation: because atypical teratoid/rhabdoid tumour is fast growing, signs and symptoms may develop quickly and get worse over a period of days or weeks.

- Morning headache or headache that goes away after vomiting
- Unusual sleepiness or change in activity level.
- Loss of balance, lack of coordination, or trouble walking.
- Increase in head size (in infants).

Risk factors: Atypical teratoid/rhabdoid tumor may be linked to a change in a tumour suppressor gene called SMARCB1. This type of gene makes a protein that helps control cell growth. Changes in the DNA of tumour suppressor genes like SMARCB1 may lead to cancer.

Changes in the SMARCB1 gene may be inherited and then tumours may form in two parts of the body at the same time (for example, in the brain and the kidney).


MRI showed a huge, lobulated intra-axial tumour occupying almost the whole of the left temporal lobe. It was mainly hypointense to grey matter on T1- and T2-weighted sequences. There were cystic components, as evidenced by areas of hyperintensity on T2-weighted images. It was large enough to cause effacement of the ipsilateral basal cisterns and a mild line shift of about 5 mm.
**Microscopic:** this example demonstrates the cellular heterogeneity which may be evident in these lesions. There is a background of small round primitive cells together with larger “rhabdoid cells”. The latter are also illustrated in the lower image and are characterized by large nuclei with prominent nucleoli and perinuclear inclusion bodies.

![Image of microscopic view](image1)

**Immunohistochemistry:** was positive for vimentin, glial fibrillary acidic protein (GFAP), and epithelial membrane antigen (EMA).

**Fluorescence in situ hybridization (FISH)** for INI1/hNSF5 gene showing a test (green) to reference (red) probe ratio of less than 0.8, consistent with loss of heterozygosity for the INI1 gene. The retained allele is usually mutated, with resulting loss of protein expression. Total loss of both alleles may also occur. See below. Image courtesy of Dr Adekunie Adesina. Medscape Oct 22, 2013.
Molecular pathology: AT/RT is defined by a specific gene mutation and loss of heterozygosity for the INI1/hSNF5 gene. Loss of heterozygosity and mutation of the retained allele of a putative tumour suppressor gene INI1(hSNF5/SMARCB1) located on chromosome 22q11.2 is the defining molecular characteristic of AT/RT. INI1 protein normally functions in chromatin remodelling, and its loss is associated with several other paediatric renal and soft-tissue tumours as well as with CNS AT/RT. It also very rarely has alterations in BRG1.

These alterations can be evaluated using immunohistochemistry for the corresponding proteins, with loss of nuclear expression correlating with genetic alteration (in the setting of adequate control expression).

CNS EMBRYONAL TUMOUR WITH RHABDOID FEATURES – 8508/3 is diagnosed when a tumour has the histological features of AT/RT but does not have either of the diagnostic genetic alterations. That is, a diagnosis of AT/RT requires confirmation of the characteristic molecular defect.

Treatment: The prognosis and treatment options depend on the following:

- Whether there are certain inherited gene changes.
- The age of the child.
- The amount of tumour remaining after surgery.
- Whether the tumour has spread to other parts of the central nervous system (brain and spinal cord) or to the kidney at the time of diagnosis.

CNS EMBRYONAL TUMOUR, NOS – 9470/3 includes tumours previously designated as CNS PNET.

NOTE; a diagnostic designation of NOS (not otherwise specified) is permitted where there is no access to molecular diagnostic testing. Hence there is insufficient information to assign a more specific code. A NOS designation represents those cases about which not enough is known pathologically, genetically and clinically so additional refinements in classification cannot yet be made.

ACKNOWLEDGEMENTS:

Pathology images: those not individually acknowledged in the text have as their source PathWest Laboratory Medicine WA.

Radiology images: those not individually acknowledged in the text have as their source Sir Charles Gairdner Hospital, The Queen Elizabeth II Medical Centre.

END