Clinical Application of Pathology

BRAIN TUMOURS II – Neuronal and Mixed Neuronal-glial

System: Nervous

Causes: Cancer

Quiz: IMED4121 – Brain I - infections and Tumours

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Introduction: This module is intended to continue where Brain Tumours I – Glial finished. The aim is to develop a framework to illustrate potential histogenic relationships between the various tumour types, a common histogenic starting point being primitive neuroepithelium. Primitive neuroepithelium develops into medullary epithelium, from which are derived the putative precursor glial cell (glioblast or spongioblast) and the putative precursor neuronal cell (neuroblast).

From the glioblast, differentiation may occur along astrocytic, oligodendrocytic and ependymal lines. Tumours can develop at any one point in the pathway.
CLASS – Neuronal and mixed neuronal-glial tumours

WHO grade I

Gangliocytoma – 9492/0

Definition: is rare tumour made up of mature neurons with no glial component. It is associated with a fibrillar neuropil-rich stroma.

Sites: commonest site is the temporal lobe but it can arise in the cerebellum, brainstem, floor of the third ventricle, and spinal cord.

Incidence: account for 0.1 – 0.5% of brain tumours.

Age: peak age is between 10 years and 30 years but can occur at any age.

Gender: no predilection.

Clinical presentation: commonest symptom is epilepsy but varies depending upon location. The patient can have increased intracranial pressure, endocrine disorders and focal symptoms. May give no symptoms but are an incidental finding when imaging is performed for another purpose.

Macroscopic: slow growing and usually do not become malignant.

Imaging: CT - the tumour typically appears hyperattenuating on non-contrast imaging. There is little associated mass effect and usually no surrounding vasogenic oedema. Calcification and cyst formation can be present. In the example below – a frontal lobe tumour -, courtesy of Assoc Prof Frank Gaillard. Radiopaedia.org, rID 4299, the arrow is pointing to the solid part of the tumour and it does enhance after contrast (PC). In this case there is some surrounding oedema – see low attenuation.

MRI - same patient as the CT. Left image is a T2 and the right image T1W post contrast

- T1: solid components typically hypointense
- T2: solid components are typically mildly hypointense; cystic areas are hyperintense; calcification if present can be hypointense. Post contrast the solid part enhances.
Microscopic: composed of abnormal mature ganglion cells. The neoplastic cells have large polygonal nuclei, prominent nucleoli and Nissl substance. Binucleate and trinucleate ganglion cells are demonstrated.

Molecular pathology: Lack immunoreactivity to glial fibrillary acidic protein (GFAP).
Show positive staining of the cytoplasm and the process of some ganglion cells with synaptophysin.
Treatment: surgical removal.

Prognosis: Complete resection of supratentorial gangliocytomas can be achieved in more than 75% of cases. Even after subtotal (partial) resection, clinically relevant re-growth of the tumour is rare. Therefore, although total resection is optimal, the outlook is reportedly good even after subtotal resection.

DYSPLASTIC GANGLIOCYTOMA OF CEREBELLUM – (Lhermitte-Duclos) – 9493/0

Definition: this condition is an abnormality of the cerebellar cortex, manifest principally by large neurons in the internal granular layer which becomes hypertrophied.

Site: cerebellar cortex.

Peak age: 3rd and 4th decades of life but can occur at any age.

Gender: no difference between the sexes.

Frequency: rare

Demographics: no geographical pattern.

Clinical presentation: headache, movement disorders, tremor, visual disturbances, diplopia and electroencephalogram (EEG) changes. The symptoms are of raised intracranial pressure and cerebellar dysfunction.

Associated conditions:

- Cowden disease – then called COLD syndrome (Lhermitte-Duclos-Cowden)
- disorders of cortical formation – megalencephaly, grey matter heterotopia, polymicrogyria.
- polydactyly, hydromyelia, macroglossia, localized gigantism, leontiasis ossea

Molecular pathology: often have mutations in enzymes involved in the Akt/PKB signaling pathway, which plays a role in cell growth. Mutation in PTEN gene on chromosome 10q leads to increased activity of AKT and mTOR pathways.
**Macroscopic:** slow growing mass like a hamartoma, usually found in the left cerebellar hemisphere and only rarely extends to the opposite cerebellar hemisphere. It may involve the vermis. The white matter is reduced. The sketch, courtesy of the Armed Forces Institute of Pathology, shows the arrows indicating the extent of the hypertrophied folia on the left.

![Sketch showing hypertrophied folia](image1.jpg)

**Imaging:** the hamartomatous mass is shown on the MRI T2 weighted image below – see arrows at the edge of the thickened outer layers of the cerebellum. Courtesy of A/Prof Frank Gaillard. Radiopaedia.org, rID: 6632.

![MRI T2 weighted image](image2.jpg)

There is rarely enhancement post gadolinium. Image below courtesy of Dr Alessandro Spano Mello, Radiopaedia.org, rID: 32289.
**MR spectroscopy:**

Shows elevated lactate, NAA reduced by 10%, myo-inositol reduced by 30-80%, choline reduced by 20-50% and a reduced cho/cr ratio.

**PET:** FDG-PET scan shows increased uptake by the tumour.

**Microscopic:** One sees enlarged circumscribed cerebellar folia, internal granular layer is focally indistinct due to infiltration and is occupied by large ganglion cells, loss of the middle Purkinje cell layer, myelinated tracks in outer molecular layer, underlying white matter is atrophic and gliotic ganglion cells replace the usual population of closely aggregated small uniform cells of the granular layer.

Note the loss of normal cerebellar cortical microarchitecture, large ganglion cells – bottom left – efface the internal granular layer.
This image is the same tissue showing large ganglion cells at higher magnification.

**Immunohistochemistry:** stains positive for synaptophysin.

**Treatment:** As the dysplastic mass grows very slowly, initial treatment may merely deal with any associated hydrocephalus.

**Prognosis:** surgical resection is often curative with only a few case reports of recurrence.

However, if there is an association with Cowden syndrome of multiple hamartomas, there is an increase in risk of other neoplasms, such as breast, endometrial, colon, kidney and thyroid cancers.

**GANGLIOGLIOMA – 9505/1**

**Definition:** a well-differentiated tumour composed of both neuronal cells and glial cells, the latter being usually astrocytes.

**Sites:** commonest site is the temporal lobe but these can occur anywhere in the CNS.

**Incidence:** most frequent of the neuronal-glial group. Accounts for around 2% of all primary intracranial tumours, and up to 10% of primary cerebral tumours in children.

**Peak age:** children and young adults.

**Gender:** No gender preference.

**Clinical presentation:** epilepsy

**Molecular pathology:** it is the grade of the glial component that determines biological behaviour. Dedifferentiation into high grade tumours does occasionally occur, and it is usually the glial component progressing to a glioblastoma. Only rarely it is the neuronal component transforming into a neuroblastoma.
**Imaging:** variable appearance. Commonest is a well demarcated cystic lesion with a mural nodule. This configuration is shared with other low grade gliomas such as pilocytic astrocytoma and pleomorphic xanthoastrocytoma.

Calcification is common (35%) and contrast enhancement occurs in 50%. Peritumoral oedema is very uncommon. See the MRI image below, courtesy of Hani Al Salam, Radiopaedia.org, rID: 8667

![MRI Image](image_url)

**Microscopic appearance:** see a neoplastic population of neuronal and ganglion cells. There are rounded vesicular nuclei with prominent nucleoli and abundant cytoplasm containing Nissl substance in a polygonal cell body. The neoplastic ganglion cells are abnormally clustered, lack the orderly distribution and lamination of non-neoplastic cortical neurons and are sometimes very pleomorphic with multinucleation and occasional cytoplasmic vacuolation. Binucleate and multinucleate neurons are a useful diagnostic feature but are not always present.

The example below shows close and irregular clustering of the neoplastic ganglion cells, which have large polygonal nuclei, prominent nucleoli and Nissl substance. The gliomatous component may resemble a number of astrocytomas and rarely other glioma patterns.

![Microscopic Image](image_url)
Additional features suggestive of the diagnosis include a lobular architecture with a reticulin rich stroma, desmoplastic areas, perivascular lymphocytic infiltrates, dystrophic calcifications and eosinophilic granular bodies. The latter features are not unique to ganglioglioma as they can be seen in other low grade tumours, particularly pilocytic astrocytoma and pleomorphic xanthoastrocytoma but are very unusual in diffuse/infiltrative gliomas, especially those which are high grade.

Errors: when neuronal cells are not recognized either because the ganglionic component is not prominent or is less well differentiated than usual, a diagnosis can be difficult. Also solid tumours (45% cases) can expand the overlying gyrus. Lesions located in the spinal cord may present difficulties.

Lastly, ganglioglioma can be confused with various diffuse gliomas. This results from the entrapment of non-neoplastic neuronal cells in diffuse glioma, or the presence of large astroglial cells mimicking a ganglionic component in pleomorphic high grade gliomas. When diffuse gliomas involve cortex, the entrapped neuronal cells lack dysplastic features and binucleation and retain orderly polarity.

To assist in the separation, one can search for a mutation in BRAF V600E because these are present in 25% of paediatric and adult gangliogliomas but this mutation is extremely rare in diffuse gliomas.

Ganglion cell tumours form compact masses and lack the diffuse growth pattern of diffuse gliomas.

Immunohistochemistry: markers for synaptophysin, neurofilament, aid in the recognition of the ganglionic cells which may sometimes demonstrate chromogranin A positivity. GFAP, in combination with the neuronal markers, helps distinguish the astrocytic component, which is usually well-differentiated and resembles either pilocytic astrocytoma or low grade fibrillary astrocytoma.

Genotypic: IDH1/2 testing of tumours suspected of being ganglioglioma is recommended especially in the adult population. Gangliogliomas with aggressive behaviour may represent mis-diagnosed diffuse gliomas involving cortex and entrapping cortical neurons. A study found the presence of mutant IDH1 in tumours diagnosed as ganglioglioma correlated with a greater risk of recurrence and malignant transformation and/or death compared with tumours that were IDH1 wild type. Also the age of patients with IDH1-mutant gangliogliomas was higher than those without mutations.

Treatment: surgical excision is usually curative.

Prognosis: Local resection is the treatment of choice and determines prognosis. In the brain where a reasonable resection margin can be achieved, prognosis is good. In the spinal cord where this is not possible without devastating deficits local recurrence is very common.

If only incomplete resection is achievable, or tumour recurrence occurs, then radiotherapy may be of some benefit.

**DESMOPLASTIC INFANTILE ASTROCYTOMA AND GANGLIOGLIOMA – 9412/1**

(previously desmoplastic infantile ganglioglycoma (DIG) and desmoplastic infantile astrocytoma (DIA) were listed as separate entities but in the 2016 WHO classification have been drawn into one entity)

Definition: a rare tumour arising in the cerebral hemispheres during the first two years of life.
**Sites:** predilection for a frontoparietal localisation and may sometimes involve more than one lobe.

**Incidence:** rare tumour – less than 0.1% of cerebral tumours.

**Peak age:** majority occur in infants less than one year of age.

**Gender:** $M:F = 2:1$

**Clinical presentation:** infants show increasing head circumference and relatively acute development of focal neurological deficits/signs which can occur in as little as 5 days or may be over a period of 3 months. Seizure activity is uncommon.

**Imaging:** demonstrate a large solid and cystic mass, often with involvement of the leptomeninges and dural attachment. Solid areas, particularly those related to the leptomeningeal surface, often demonstrate marked contrast enhancement and a large unilocular or multiloculated cystic component is often prominent. Although macroscopically well demarcated, there is often microscopic evidence of an infiltrative growth pattern.

**MRI** – on T1W and T2W are isointense and post Gd show marked contrast enhancement.

The MRI T1W image is courtesy of Dr Sanjay Prabhu, Radiopaedia.org, rID : 23298.

**CT** - The solid portion of these large masses is typically slightly hyperattenuating and usually located along the cortical margin of the mass. Following administration of contrast, these masses usually enhance intensely, and may demonstrate a dural tail.

Calcification is not a feature of desmoplastic infantile ganglioglioma.

**Microscopic:** of desmoplastic infantile ganglioglioma varies considerably. Comprises mixed neuroepithelial populations (astrocytes, variable differentiated neuronal cells and poorly differentiated components) with a predominant component of desmoplasia (growth of fibrous or connective tissue).

The desmoplastic areas consist of spindle cells and variably conspicuous neuroepithelial populations in abundant collagenous stroma. The former comprise a mixture of astrocytic, neuronal and small
primitive cells – which may be why DIG and DIA are now one group together. The neuronal component is extremely heterogeneous in character, ranging from large ganglionic cells through to smaller neuroblastic forms lacking desmoplasia. Densely cellular areas populated by small anaplastic cells with high rates of mitotic activity and sometimes proliferation and necrosis. The small cell populations appear to represent primitive neuroepithelial populations, capable of divergent differentiation along astrocytic or neuronal lines.

Differential diagnosis is from the classical ganglioglioma: differences include - it manifests in infancy, has a fronto-parietal location and has the unique presence of desmoplasia and small primitive neuroepithelial cells.

The example below illustrates the stromal desmosplasia characteristic of these lesions. The stromal desmoplasia and spindle and storiform (cartwheel pattern) cell arrangements are evident and large ganglion-like cells are recognisable centrally – see arrow.

The Desmoplastic infantile astrocytoma (DAI) itself lacks a neoplastic neuronal component.

**Immunohistochemistry:**

- **Desmoplastic component**: vimentin+, GFAP+, type IV collagen+, reticulin (pericellular pattern), trichrome (stoma)
- **Astrocytic cells**: GFAP+, S-100+
- **Neuronal cells**: synaptophysin+, NeuN+, neuron specific enolase+
- **Poorly differentiated small cells**: vimentin+, GFAP+, synaptophysin+
- **Proliferation index**: <2% (higher in the poorly differentiated small cell component)

**Treatment**: Surgical resection is the treatment of choice. The large size of these lesions and the firm attachment to the dura makes complete resection difficult.

In cases of partial resection, adjunctive chemotherapy may be considered and has been reported to produce some reduction in tumour volume.

**Prognosis**: following complete or near complete resection, the prognosis is good.
Rarely cranio-spinal seeding and metastases can occur.

Residual disease may not grow and has occasionally spontaneously regressed.

**DYSEMBRYOPLASTIC NEUROEPITHELIAL TUMOUR (DNET) – 9413/0**

**Definition:** this is a multinodular, intracortical lesion often associated with temporal lobe epilepsy in young adults.

**Sites:** medial and lateral temporal lobes most common sites – 60% cases. Frontal lobe in 30%. Also found in the caudate nucleus, septum pellucidum, floor of the third ventricle, pons and cerebellum.

**Associated conditions:** rarely DNET and ganglioglioma may coexist. Cortical dysplasia is seen in 80% of cases.

**Incidence:** found in 1.2% of people under the age of 20 years and in 0.2% of people over the age of 20 years.

**Peak age:** 8 – 19 years.

**Gender:** slight male preponderance.

**Clinical presentation:** presents in young adults with a long history of treatment-resistant complex partial seizures. If the tumour is in the cerebellum the presentation is more commonly ataxia, rather than seizures.

**Macroscopic:** very slow growing lesions arising from cortical or deep grey matter.

**Imaging:** CT – low density and no enhancement. Calcification in 30%.

**MRI** – well-demarcated, multilobular cortical lesion which is hypointense on T1 weighted images and hyperintense on T2WI. Bone remodeling of the adjacent calvarium is observed in 60%. There is very little vasogenic oedema around the mass. Enhancement may occur in 30% and this may be heterogeneous or a mural nodule. These features are shown in the case below, courtesy of Assoc. Professor Frank Gaillard, Radiopaedia.org, r ID : 41022.
**Microscopic:** the histological patterns observed may be complex and diverse. The example below illustrates the pattern of an isolated ganglion cell, - see arrow -which appears to ‘float’ within myxoid matrix, in a background of small uniform neurocyte-like /oligodendrocyte-like cells.

![Microscopic Image](image)

Another example shows patterned well circumscribed nodules within the cortex.

![Another Example Image](image)

The next image shows ‘floating’ neurons, lying in myxoid matrix, and scattered amongst small OLC (oligodendrocyte-like cells).

![Next Image](image)
Classical forms of DNET comprise two components; distinct cortical nodules and a diffuse internodular component. The cortical nodules have a somewhat ‘patterned’ architecture, are rich in Alcian blue positive mucinous material, and contain a population of small uniform cells, which often have prominent perinuclear halos and are cytologically indistinguishable from oligodendroglioma. These ‘oligodendrocyte-like cells’ OLC) are believed capable of divergent glial and neuronal differentiation, but only a small proportion show evidence of early neuronal differentiation with advanced neuronal differentiation being unusual. OLC can be distributed in a variety of patternless patterns within the nodules but demonstrate a tendency to cluster around vascular spaces often forming targetoid, ribbon-like or alveolar patterns. OLC also extend between the nodules and involve the cortex, which may also demonstrate features of cortical dysplasia.

Neurones ‘floating’ in mucin are a common feature of DNET and are found in spaces formed by the OLCs. Such floating neurons are found in both the nodular and internodular components but are not specific to DNET.

Whether they represent an intrinsic component of DNET, or are simply cortical neurons entrapped in mucoid material is unclear. The pathognomonic ‘specific glioneuronal component’ of DNET may occasionally be identified in the internodular zone. It has a characteristic columnar appearance, with the columns oriented perpendicular to the cortical surface. The columns comprise neurons and their neuritic processes which extend and are surrounded by the OLC, in association with extracellular mucin and vessels.

**Types:** both simple and complex forms of DNET are recognized. In addition to the specific glioneuronal element and/or areas of cortical dysplasia, complex forms of DNET contain glial nodules. The glial nodules vary in appearance and may morphologically resemble pilocytic astrocytoma, diffuse astrocytoma or oligodendroglioma.
**Immunohistochemistry:** Some granular perivascular synaptophysin positivity may be seen in tumour neuropil in DNET but this is a non-specific finding. Occasional examples of OLC demonstrate synaptophysin positivity and there is inconsistent GFAP positivity.

**Molecular pathology:** DNET lacks IDH mutations and up to 30% have BRAF V600E mutations, features which may aid in diagnosis. The presence of BRAF mutation in DNETs supports a relationship between DNETs and gangliogliomas, pointing to the pathogenic role of BRAF in different entities within the large spectrum of glio-neuronal tumours together with other lower grade tumours, such as pilocytic astrocytomas and pleomorhach xanthoastrocytomas.

**Treatment:** surgery. Do not require postoperative adjuvant therapy as a rule, although rarely malignant transformation has been described.

**Prognosis:** patients usually undergo resection and even in cases of incomplete resection, seizures frequently cease.

**PAPILLARY GLIONEURONAL TUMOUR – 9509/1**

**Sites:** supratentorial in location, with a predilection for temporal and periventricular locations.

**Incidence:** rare

**Peak age:** occurs in all age groups

**Gender:** no gender predilection

**Clinical presentation:** headaches or seizures

**Imaging:** well circumscribed solid but partially cystic lesions with variable enhancement of the nodule. Calcification is a frequent finding.

**Microscopic appearance:** pseudopapillary pattern.

PGNT has a unique morphology, with distinct glial and neuronal components evident in most cases. The glial component demonstrates a pseudopapillary architecture.
A single or focally stratified layer of GFAP positive astrocytic cells lines stromal cores containing thick hyalinised vessels. See arrows in example below.

The intervening neuronal component demonstrates a spectrum of differentiation and is found between the pseudopapillary regions. It is formed by synaptophysin positive neuronal cells, including neurocytes, ganglion cells and hybrid ganglioid forms, contained within neuropil.

Pilocytic gliosis with eosinophilic granularbodies and Rosenthal fibres, haemosiderin, and areas of calcification are often evident in the surrounding tissues. Differential diagnostic considerations include pilocytic astrocytoma and ganglioglioma. In the majority of cases anaplastic features have not been described. Immunohistochemistry determines proliferation index is low. However, atypical forms with necrosis, endothelial proliferation, increased mitotic activity and high proliferation indices have been described.

In the example on the next screen see features.

Immunohistochemistry: shows evidence of mixed glial and neuronal differentiation. Glial elements:

- GFAP+
- Neuronal elements: synaptophysin+
- Low proliferation index (Ki67 is 1-2%)

Electron microscopy: Three cell types: astrocytic, neuronal, glioneuronal progenitor cells.

Molecular pathology: A recently identified t(9;17)(q31;q24) translocation with the resultant novel fusion oncogene SLC44A1-PRKCA is a molecular aberration which may prove to be a defining feature of PGNT and useful in its distinction from other mixed neuronal-glial tumours.
Treatment: surgery is the usual management.

Prognosis: disease-free survivals of up to 7 years with no local recurrences except in the more aggressive forms.

**ROSETTE FORMING GLIONEURONAL TUMOUR OF THE FOURTH VENTRICLE – 9509/D**

**Definition:** slow growing, glialneuronal tumour, first described in 1998 by Komori et al.

**Sites:** midline tumour involves the 4th ventricle in 60% or aqueduct of Sylvius and cerebellar vermis and hemispheres. However, rarely has been reported in the spinal cord, the optic chiasm and pineal region, cerebello-pontine angle, tectum, thalamus, third ventricle and spinal cord.

**Incidence:** very rare tumour, 43 cases reported by 2011.

**Peak age:** mean age is 30 years.

**Gender:** slight female preponderance.

**Clinical presentation:** clinically extremely indolent. Symptoms mainly depend on the location of the tumour; commonly presenting with ataxia and headache. If the patient is symptomatic, the clinical findings may be secondary to obstructive hydrocephalus, ataxia being the most common kind. Other clinical findings of nausea, vomiting, headaches, vertigo, visual disturbances, neck pain, and rigidity have been described.

**Associated conditions:** An association with type 1 neurofibromatosis (NF-1) has been demonstrated in some cases.

**Molecular pathology:** site of origin hypothesized to involve the periventricular germinal matrix.

**Macroscopic:** well circumscribed but may invade surrounding tissues, thus involving the cerebellum, pons and the pineal region. RGNT may be solid or multicystic and occasionally multifocal. Range in size from 1 – 5 cms.

**Imaging:** MRI shows a well circumscribed lesion which often has cystic components. Post contrast show a heterogenous enhancement which can be nodular, linear, ring or spot-like in character.

- variable solid-cystic components
  - RGNTs appear as solid lesions in 40%
  - mixed solid and cystic changes are seen in 35% cases
  - cystic only features in 25%
- the majority of RGNT (70%) show variable gadolinium enhancement
  - focal enhancement pattern was most commonly observed (50%)
  - heterogeneous pattern (19%)
  - minimal enhancement (13%)
  - ring and nodular enhancement pattern (9%).
- calcification (25%)
A T2W image – axial and coronal of another patient shows the midline posterior fossa tumour which is heterogeneous and hyperintense. Courtesy of Kumar M, Samant R, Ramakrishnaiah R, Fitzgerald RT, Burgin K, Van Hemert R and Angtuaco E. Radiol Case Rep 2013, 8(1) : 740.

**Microscopic:** Histologically, RGNT are well circumscribed and demonstrate a distinctive, biphasic histological pattern, with patterned neurocytic and astroglial components.

The neurocytic component consists of small cells with round hyperchromatic nuclei in a background of mucinous matrix, forming rosettes around central aggregates of fibrillary material, with positive synaptophysin staining. The glial component consists of astrocytes with eosinophilic fibrillary processes, resembling pilocytic astrocytoma, with positive immunostaining for glial fibrillary acid protein (GFAP) and S-100 protein. The nuclei of tumour cells are round and small, with no mitosis or atypia.
Marked atypia, mitotic activity or significant MIB-1 labelling is not observed in either component.

The neurocytic component consists of a cytologically uniform population of neurocytic cells, forming small neurocytic and/or perivascular pseudorosettes, in a fibrillary and partly microcystic matrix. The small rosettes have eosinophilic and synaptophysin positive cores and may form cribriform-like aggregates, which sometimes lie within microscopic cavities adjacent to the glial component.

Perivascular columnar arrays of neurocytic cells may resemble the specific glioneuronal element of DNET. Occasional dysmorphic ganglion cells may be observed in RGNT, but the ‘floating’ neurons of DNET are absent.

**Immunohistochemistry:** granular synaptophysin positivity is observed in the matrix of both the rosettes and perivascular pseudorosettes. Variable NeuN reactivity has been reported in the neurocytic cells.

**Ultrastructurally:** the neurocytic cells elaborate processes containing microtubules and occasional dense core granules. Mature synaptic contacts may also be formed. The second component of RGNT, which is astrocytic in character, often predominates. This often resembles a pilocytic astrocytoma, with fibrillary spindle cells seen in a background containing occasional Rosenthal fibres, granular bodies, glomeruloid vessels and calcifications.

In other instances this astrocytic element may have a nondescript and patternless character, including foci which may be relatively hypocellular and resemble a gliotic process. Vascular hyalinization and thrombosis, sclerosis, dystrophic calcification, and haemosiderin deposition complete the resemblance to a chronic degenerative process.

**Differential diagnosis:** it must be distinguished from pilocytic astrocytoma, other gliomas with a piloid glial component, and other glioneuronal tumours.

Key diagnostic features are, in addition to the presence of neurocytic and perivascular pseudorosette formation, its frequent posterior fossa localization and the presence of a distinct pilocytic astrocytoma-like component.
Treatment: attempted surgical excision can result in considerable morbidity. Neurological complications like nerve palsies, diplopia, and cerebellar ataxia have been reported.

Prognosis: good prognosis after complete resection but one case reported to recur after 10 years.

PARAGANGLIOMA of the FILUM TERMINALE – 8680/1 (Spinal paraganglioma)

Definition: rare extramedullary, intradural tumour arising in the cauda equina. Are rare neuroendocrine tumours of the extra-adrenal paraganglionic system.

Sites: cauda equina. Intracranial involvement by paraganglioma is rare and most commonly represents local extension from jugulotympanic tumours. Recently paragangliomas arising in the pituitary gland/ sellar region and pineal have been described.

Incidence: 33 cases reported by 2009

Age: occur 13 – 70 years, peak age 47 years.

Gender: slightly more frequent in males.

Clinical presentation: present with the cauda equina syndrome of low back pain, leg weakness and incontinence. Cauda equina paragangliomas frequently actively secrete neuropeptides, particularly 5-hydroxytryptamine and somatostatin, although symptoms related to this chemical production are usually absent. Additionally these lesions may be a rare source of superficial siderosis, and thus present with sensory neural impairment, cranial nerve dysfunction and myelopathy.

Macroscopic appearance: tumour is an extramedullary, intradural mass that may or may not demonstrate an attachment to the cauda equina.

All paragangliomas consist of nests (zellballen) of chief cells. They are highly vascular. 75% of paragangliomas are encapsulated.

Imaging: Neuroimaging demonstrates a well circumscribed, elongated and occasionally partially cystic mass which is hypo- to isodense and avidly enhancing on T1W and hyperintense on T2W.

CT scan Spinal paragangliomas appear as soft tissue masses inferior to the conus and they enhance vividly (as do paragangliomas elsewhere).

Large lesions may rarely demonstrate osseous erosion or remodelling of the adjacent vertebrae. Rarely lesions calcify.

MRI - these masses usually appear as well-circumscribed masses, inferior to the conus.

The “salt-and-pepper” appearance of neck and skull base paragangliomas may also be seen. Associated syringohydromyelia has been reported in some cases.

Signal characteristics include:

- **T1**: isointense
- **T2**
  - hyperintense
• **flow voids** are typically seen along the surface of and within the tumour nodule
  • haemorrhage is common, leading to a ‘cap sign’

**T1 C+ (Gd):** Intense enhancement is nearly always seen. The example below, courtesy of Associate Professor Frank Gaillard, Radiopaedia.org, rID: 19546.

**Angiography** demonstrates an intense early blush that persists into the late arterial and early venous phases.

**Differential diagnosis:**

Other intradural extramedullary tumours, particularly those located in the lumbar region; myxopapillary ependymoma, spinal schwannoma and spinal neurofibroma, spinal meningioma, dermoid, lipoma, drop metastasis. The last is rare in the lumbar region.

**Microscopic appearance:** shares many morphological, immunohistochemical, and ultrastructural features in common with paragangliomas of other anatomical sites, but they demonstrate frequent ganglionic differentiation (a feature seen in up to 50% of cases) and also express cytokeratin more frequently. Do not secrete catecholamines. Comprised of nests and broad anastamosing trabaculae of round to polygonal cells. Tumour cells separated by delicate fibrovascular septa (zellballen pattern – means balls of cells). Have moderately abundant eosinophilic cytoplasm, central round to oval nucleus with finely stippled chromatin, occasional nucleolus and intranuclear inclusions.

**Note below** zellballen pattern (left panel) and ganglionic differentiation (right panel)
**Immunohistochemistry:** show positivity for Neurofilament protein, Neuron specific enolase, chromogranin, synaptophysin. Some cases also show positivity for serotonin, somatostatin and occasional positivity for keratin.

**Ultrastructurally,** the tumour cells show intracytoplasmic dense core neurosecretory granules, lamellar stacks of rough EPR, well developed Golgi apparatus, fenestrated endothelial cells, cilia and fibrous bodies in the cytoplasm. The last two features occur only in paragangliomas of this site.

**Biochemistry:** CSF protein may be markedly elevated.

**Treatment:** Surgical resection is the treatment of choice, sometimes with preoperative embolization to reduce intra-operative blood loss.

**Prognosis:** although the majority is benign, local recurrence occurs in 10% of cases, probably a manifestation of the difficulty in achieving complete local resection in this anatomical site.

However, intracranial and intraspinal metastasis has been reported.

**NEURONAL and MIXED NEURONAL-GLIAL TUMOURS**

**WHO grade II**

**CENTRAL NEUROCYTOMA ~ 9506/1**

**Definition:** a neuroepithelial intraventricular tumour consisting of heterogeneous masses within the lateral ventricle.

**Sites:** lateral ventricles around foramen of Monro: 50%, both lateral and 3rd ventricles: 15% bilateral: 15%, 3rd ventricle in isolation: 5%

**Incidence:** account for less than 1% of intracranial tumours.

**Peak age:** 20 – 40 years

**Gender:** no predilection

**Clinical presentation:** symptoms of raised intracranial pressure, especially headache. If the tumour extends beyond the ventricle, the patient may present with seizures. A clinical course, often only a few months, is most common. Rarely central neurocytomas may be associated with sudden death secondary to acute ventricular obstruction or have a sudden presentation due to intraventricular haemorrhage.

**Macroscopic:** intraventricular mass which is frequently attached to the septum pellucidum.

**Imaging:** CT - Central neurocytomas are usually hyperattenuating compared to white matter. Calcification seen in over half of cases, usually punctate in nature. In the non-contrast CT image below, the arrow points to dense calcification within a tumour blocking the right foramen of Monro. Cystic regions are frequently present, especially in larger tumours. Contrast enhancement is usually mild to moderate. Accompanying ventricular dilatation is often present.
MRI

- **T1**
  - isointense to grey matter
  - heterogeneous
- **T1 C+**
  - mild-moderate heterogeneous enhancement
- **T2/FLAIR**
  - typically iso to somewhat hyperintense compared to brain
  - numerous cystic areas (bubbly appearance), many of which completely attenuate on FLAIR
  - prominent flow voids may be seen
- **GE/SWI**
  - calcification is common, typically punctate
  - haemorrhage (especially in larger tumours) is common
  - uncommonly results in ventricular haemorrhage

**MR spectroscopy**

- may have a strong choline peak
- glycine peak (3.55ppm) has also been reported

MRI T2W image, shows tumour in the left lateral ventricle and is provided by courtesy of RMH Neuropathology, Radiopaedia.org, rID : 37664
Angiography

A tumour blush is frequently identified, with the mass supplied by choroidal vessels but no large feeding arteries are usually seen.

**Microscopic:** First described in 1982 - formed by a relatively monomorphic population of neurocytic cells, with uniform round nuclei, ‘salt and pepper’ granular chromatin patterns and a tendency to cytoplasmic clearing. Compact sheets of such cells, often with a delicate capillary vasculature and occasional collections of fibrillary neuropil-like material are typical findings.

Can be confused with oligodendroglioma on histology due to having a ‘fried egg’ appearance (central round nucleus and cytoplasmic retraction) appearance like that tumour but it does not have a co-deletion of 1p19q.

**Immunohistochemistry:** as proof that it is of purely neuronal origin, one finds positivity to neuronal markers like synaptophysin and neuronal specific enolase.
Molecular pathology

Several genes are part of the Wnt/b-catenin and sonic hedgehog signaling pathways or mainly linked to calcium function or maintenance of neural progenitors. Moreover, several genes are overexpressed in both CNs and PCs and/or PBs such as INSM1 and NEUROD4, involved in neural or neuroendocrine differentiation. The overexpression of eight genes in CNs (CHRD12, IGF2, Kiss-1, CAL2, NTS, NHLH1, RGS16 and SCGN) is confirmed by real-time RT-PCR. Of the genes overexpressed in the recurrent CNs compared to the primary CNs, AQP5, Kiss-1, FZD7, AURKB, UBE2C and PTTG1 are genes which may be involved in tumour progression. This shows the potential involvement of various genes in the pathogenesis of CNs. These genes could be potential candidate markers for improving the characterization of CNs and some could be involved in CN tumorigenesis.

A subset of neurocytoma contain readily identifiable mitotic activity and elevated MIB-1 labelling indices, findings which have been associated in some studies with an increased risk of local recurrence. Such lesions have been referred to as ‘atypical’ neurocytoma. Aggressive behaviour in the absence of histological evidence of anaplasia and in tumours having a low proliferation index has also been observed on occasion, and the precise relationship between the presence of atypical histological features and clinical outcome in central neurocytoma remains unclear.

**Differential diagnosis**: ependymoma, intraventricular meningioma, subependymoma, subependymal giant cell astrocytoma, choroid plexus papilloma, intraventricular metastasis, oligodendroglioma.

**Treatment**: Complete surgical resection is usually curative. When only incomplete resection is possible or extraventricular extension is present then adjuvant radiotherapy (and sometimes chemotherapy) may be added.

Cases of CSF dissemination have been reported, but are rare

**Prognosis**: 5 years survival is 81%.

**Variants**: **Ganglion neurocytoma**: shows differentiation towards ganglion cells.

The diagnosis of ganglioneurocytoma should be applied to tumours displaying the following characteristics: (i) clinical aspects such as location, demarcation and growth rate consistent with neurocytoma; (ii) transition between neurocytoma cells and ganglion cells; and (iii) ganglioid cells distributed throughout the tumour.

**EXTRAVENTRICULAR NEUROCYTOMA ~ 9506/1 (previously called cerebral neurocytomas)**

**Definition**: rare primary CNS tumour derived from neural cells.

**Sites**: predilection for the frontal lobe in nearly 50%

**Peak age**: 5 – 76 years, mean peak 34 years

**Gender**: no predilection

**Clinical presentation**: seizures, diplopia, headache and vomiting.

**Macroscopic**: well-circumscribed lesion which can be complex with solid and cystic components.
**Imaging:** variable contrast enhancing, often with a cyst-mural nodule. Often partly or mainly cystic and calcification is found in 10%. There may be peritumoral oedema. Calcification is frequent but haemorrhage is uncommon.

**MRI:**

In most instances the tumour is well-defined, cystic and heterogeneously solid, and involves the deep white matter or cortical gray matter of the cerebral hemispheres. Contrast enhancement occurs in the solid portions. The MRI images below show in A – a T1W axial view, a heterogenous left parietal mass with a fluid level medially. In B, T2W axial there is low signal in the mass. In C, T1W post contrast, there is extensive heterogeneous enhancement in the solid part of the mass. Images courtesy of Yang GF, Wu SY, Zhang LJ, Lu W, Tian W and Shah K. AJNR 2009. 30: 581-585.

![MRI Images](image)

**Differential diagnosis:** ganglioglioma, gangliocytoma, dysembryoplastic neuroepithelial tumour (DNET).

**Microscopic appearance:** Unlike the classical neurocytoma, there is a greater incidence of ganglion cell differentiation and immunohistochemical evidence of glial differentiation.

![Microscopic Image](image)

Uniform neurocytic cells together with neoplastic cells demonstrating astrocytic features (spindle nuclei and eosinophilic cytoplasmic processes).
Some extraventricular neurocytomas are well differentiated, while others show one or more histological features typically associated with aggressive behavior in other form of gliomas, such as vascular proliferation, necrosis and increased mitotic activity.

**Immunohistochemistry:** Focal glial fibrillary acidic protein (GFAP) immunopositivity is present in cells with neurocytic features in almost 50% of cases and more than one half exhibit either focal or diffuse ganglion cell differentiation. Neither feature appears to correlate with tumour behaviour.

**Molecular pathology:**

While 1p/19q deletion has been used as a molecular signature of oligodendrogial tumours, it has also been variably reported to occur in neurocytomas, especially those in extraventricular locations.

**Treatment:** surgery and sometimes followed by radiotherapy.

**Prognosis:** Local recurrence has been reported in 30% of cases. Subtotal resection, high proliferation rates, atypical histological features (mitotic activity > 3/10 HPF, geographic necrosis and/or vascular proliferation, older patient age group are associated with an increased risk of local recurrence.

**CEREBELLAR LIPONEUROCYTOMA – 9506/1 –**

*(previously called lipomatous glioneurocytoma)*

**Definition:** WHO definition: rare, well differentiated neurocytic tumour of the cerebellum that arises in adults and typically shows focal or regional lipomatous differentiation. It has a low proliferative potential and a more favorable prognosis especially when compared to medulloblastoma (MDB), from which it needs to be distinguished.

First described as an entity by WHO in 2000 and reclassified as a grade II neoplasm to reflect a higher recurrence rate than was previously appreciated.

**Sites:** Almost always in cerebellum (usually hemispheric, less commonly vermian or cerebellopontine angle or 4th ventricle). Rare supratentorial ‘central’ examples have also been reported.

**Incidence:** rare

**Peak age:** range 24 – 77 years (median 50 years)

**Gender:** no predilection

**Clinical presentation:** headache, cerebellar signs

**Macroscopic:** typically well circumscribed but mass effects may be evident in adjacent structures.

**Imaging:** tumour is intraaxial with the propensity for exophytic growth into the adjacent subarachnoid spaces and show heterogeneous hyperintense foci (due to their lipid content) on T1W images with variable contrast enhancement and are variably hyperintense on T2 images.
The MRI image above is T1W post contrast, courtesy of Oudrhiri MY, Raouzi N, El Kacemi I, El Fatemi N, Gana R, Maaqili MR, Bellakhdar F. Case Reports in Neurological Medicine.2014;2014, Article ID 186826. There is a heterogeneous, enhancing lesion of the right cerebellum extending to the CPA (cerebellopontine angle), causing mass effect and mild hydrocephalus. There was no associated oedema.

**Microscopic:** See small round cells mixed with lipomatous cells. Characterized by neurocytic differentiation with foci containing lipid laden cells imparting a lipoma-like appearance. Monomorphic small neurocytic cells, associated with adipose tissue accumulation. Mitotic activity is typically scanty, and endothelial proliferation and tumour necrosis tend only to be seen in unusually aggressive or recurrent examples.

**Immunohistochemistry:** reveals a tumour with astrocytic and neuronal differentiation (GFAP-NSE-synaptophysin positive) in which some focal areas of lipomatous differentiation are identified. The MIB-1 index may be <1%; There is no cellular immaturity or necrosis.

**Electron microscopy:**
- **Neurocytes:** microtubules and neurosecretory granules
- **Lipidized cells:** contain non-membrane bound lipid
**Molecular pathology:** recent molecular studies have suggested that central neurocytoma and cerebellar liponeurocytoma may be closely related lesions, and it has been suggested that the term ‘liponeurocytoma’ might be more appropriate to encompass these morphologically similar lesions which show neuronal differentiation and lipid accumulation, and occur in both cerebellar and cerebral locations.

**Treatment:** The patient shown in the MRI above underwent surgery. A soft grey tumour, with yellowish areas, was discovered and was well circumscribed. The anterior part of the tumour was encasing cranial nerves and was infiltrative toward the brainstem, which only allowed for sub-total removal. No cerebrospinal fluid shunt was inserted.

**Prognosis:**

- Overall favorable clinical outcome with no features of malignant progression, but frequent recurrences (50%)
- Prognosis may be less favorable if mitotic figures are present and >10% proliferative index

**NEURONAL and MIXED NEURONAL-GLIAL TUMOURS**

**WHO grade III**

**ANAPLASTIC GANGLIOGLIOMA – 9505/3**

**Definition:** there is a low grade neuronal plus an anaplastic glial component.

**Sites:** are most commonly unifocal, supratentorial in location, and found in the temporal lobes but cases have also been reported within the spinal cord, as well as in intraventricular locations.

**Incidence:** represents 1 – 5% of all gangliogliomas

**Peak age:** children and young adults

**Gender:** slight male preponderance

**Clinical presentation:** epilepsy, and results in diffuse local and distant failure within the craniospinal axis.

**Macroscopic:** can be solid or cystic and do not have haemorrhage or necrosis.

**Imaging:** radiologic diagnosis is difficult due to the wide variation in its degree of solid and cystic components, and contrast uptake. Tumours are typically isointense or hypointense on T1 imaging, hyperintense on T2 imaging, and contrast enhancement is generally irregular.

In the MRI series below image A is pre-operative and shows an irregular enhancing mass in the left frontal lobe extending to the cingulate gyrus. Image B is postoperative on day 12, showing multiple irregularly shaped enhancing lesions along the resection margin of the left frontal lobe and cingulate gyrus. Image C is 5 months post op and shows the irregular enhancing lesions in the resected margin of the left frontal lobe and cingulate gyrus had disappeared. Images D and E at 35 months postop, there is no evidence of recurrence. Images courtesy of Kang DH, Lee CH, Hwang SH, Park IS, Han JW, Jung SM. Korean Med Sc 2007 Sept 22 (Suppl) S139-S144.
**MR Spectroscopy:** Some studies have noted that MR spectroscopy of gangliogliomas may reveal distinct but non-specific choline peaks which may differentiate these from benign conditions, but not necessarily from other primary brain tumors.

**Microscopic:** graded by the degree of malignancy in the glial portion.
The histopathology above, courtesy of Lucas JT, Huang AJ, Mott RT, Lesser GJ, Tatter SB, Chan MD. Journal Neurooncol. 2015 May; 123(1):171-177. Shows in (A) the tumour composed of clusters of neoplastic ganglion cells with large nuclei, prominent nucleoli and abundant vacuolated cytoplasm (arrow). In image (B), some areas of the tumour display oligodendrogial features and admixed ganglion cells (arrow). In (C) the tumour has regions of necrosis (arrow) consistent with WHO grade III.

The immunohistochemistry (D) shows the neoplastic ganglion cells immunoreactive for neurofilament protein and image (E) shows the neoplastic glial cells are immunoreactive for glial fibrillary acidic protein (GFAP).

**Treatment:** following surgical resection, the patient may have chemotherapy and/or radiation.

**Prognosis:** 5-year survival is 65%.

**GLIONEURONAL TUMOUR WITH NEUROPIL-LIKE ISLANDS (GTNI) can be WHO grade II or III**

An apparently distinctive pattern of neuronal differentiation, the presence of neuropil-like islands, has been recognized in infiltrative astroglial neoplasms termed ‘glioneuronal tumour with neuropil-like islands’ (GTNI) which may be WHO grade II or grade III.

**Imaging:** In all cases the neuroimaging reflects the features of the underlying glioma component.


Shown in panels (A-C) are the MRI features in T1-weighted, T2-weighted and post-gadolinium T1-weighted studies, respectively. These demonstrate a solid lesion that was low intensity on a T1-weighted image (A) and high intensity on a T2-weighted image (B) between C1 and C6, and an enhanced lesion with gadolinium between C1 and C6 level (C)
Microscopy:

Characterized by focal, sharply outlined, round to oval islands composed of delicate, neuropil-like and synaptophysin+ matrix. Image below is courtesy of Dr E Abdelzaher. PathologyOutlines.com. 30th June 2014. On the left see neuropil islands floating in a sea of glial cells. The image on the right is the synaptophysis immune stain.

The neuropil islands comprise sharply circumscribed islands of intensely synaptophysin positive neuropil, which contain, and are rimmed by, small neurocytic elements and neuronal cells of variable size. These foci are scattered amongst predominant fibrillary, gemistocytic or protoplasmic astroglial elements.

The large islands of neuropil-like material in GTNI contrast with the small perivascular and Homer-Wright like rosettes of neuropil material that may form in both central neurocytomas and extraventricular neurocytoma.

The proliferative capacity of these tumours lies in their glioma component, which dominates the histological picture, and they seem to behave in a manner comparable with astrocytomas of equivalent grade. Although GTNI shares some morphological features with oligodendrogliomas with neurocytic differentiation, the two tumours appear different at the molecular genetic level. It is unclear whether these lesions represent gliomas with divergent neuronal differentiation, distinctive forms of glioneuronal neoplasm, or a reflection of the potential for glioneuronal histogenesis in gliomas in general.

Prognosis: similar to infiltrating astrocytoma of corresponding grade which may be WHO grade II or WHO grade III.

Although only a small number of cases have been reported to date, GTNI have the capacity to pursue an unfavourable clinical course, with reported instances of local recurrence, progressive parenchymal infiltration leading to death, and in spinal examples, CSF dissemination.

As such, they must be distinguished from other forms of glioneuronal tumour which are well differentiated, low grade, and generally associated with a favourable clinical course.
NEURONAL and MIXED NEURONAL-GLIAL TUMOURS

WHO grade unknown

DIFFUSE LEptomeningeAl GliONEURONAL TUMOUR (DLNT) – no IDC-0 code. (a new entity 2016)

Definition:  DLNT is a rare recently described entity (2010) that may represent a unique class of low-grade neuroepithelial tumour demonstrating variable neuronal/neurocytic and glial differentiation.

Sites: spine and cranium

Incidence: rare – unknown so far.

Peak age: range 2 – 7 years, mean 4 years

Gender: no predilection

Clinical Presentation: signs of increased intracranial pressure due to tumour occluding the subarachnoid space.

Imaging:  MRI will show meningeal involvement, manifest as diffuse thickening and contrast enhancement in cranial and spinal leptomeninges. In the spinal cord lesions these are discrete, often cystic and of variable morphology.

The MRI below, a 14 year old girl, courtesy of Lyle MR, Dolia JN, Fratkin J, Nichols TA, Herrington BL. Child Neurology 2015; 2(1) shows in the left image multiple spherical cystic lesions in both cerebral hemispheres. The right image is a post contrast T1W image where the long arrows are pointing to dural enhancement and the short arrow indicates a small nodule at C7/T1 level.

Additionally, as the cysts appear to be noncomplex in nature (i.e., without components of protein or blood), these cystic changes are likely perivascular spaces enlarging with collections of extracellular fluid developing secondary to progression of the leptomeningeal disease altering normal drainage pathways.
**Microscopic:** Mixed glioneuronal tumours are characteristically biphasic. However, diffuse leptomeningeal glioneuronal tumour is comprised of one cell population that variably stains for both glial and neuronal components.

Leptomeningeal biopsies show a thickened and fibrotic arachnoid infiltrated by monotonous cells with round nuclei and prominent perinuclear clearing.

In the example below, courtesy of Gardiman MP, Fassan M, Nozza P, Giangaspero F. Pathologica. 2012, 104(6): 428-31. Tumour samples were composed of a monotonous population of round cells (image A) arranged in pseudopapillary structures (image B). Diffuse immunoreactivity for synaptophysin is seen in image C and for GFAP in image D.

**Immunohistochemistry:** S100 is positive

**Molecular pathology:** Many demonstrate 1p loss and few 19q co-deletion. IDH is negative.

Chromosomal analysis for 1p19q co-deletion, or even a singular deletion of either 1p or 19q, can be useful in determining tumour aggressiveness and likely response to chemotherapy, especially to temozolomide. This co-deletion has been seen in both neurocytomas and adult oligodendrogliomas;
and it being seen in both tumour types can also support the idea of a common progenitor cell being the neoplastic culprit in diffuse leptomeningeal glioneuronal tumours. This co-deletion has demonstrated correlation with more aggressive disease in extraventricular neurocytomas and can be useful in assessment of potentially aggressive behavior of other tumour types, including diffuse leptomeningeal glioneuronal tumors. On the other hand, it has also been highly correlative with increased responsiveness to systemic chemotherapy, especially with temozolomide, with and without adjunctive radiotherapy, as well as disease prognosis.

**Diagnosis**: CSF cytology is usually negative and small meningeal biopsies may be non-diagnostic. The generally uniform histopathology, presence of 1p/19q deletions and variable neuronal and glial differentiation suggest that they may be within the oligodendroglioma-neurocytoma spectrum of tumours.

**Differential diagnosis**: must be distinguished from infective meningitis and disseminated high grade/metastatic meningeal disease because they respond to treatment and follow an indolent course.

**Treatment**: temozolomide and craniospinal irradiation

**Prognosis**: the response to temozolomide is very good but sometimes craniospinal irradiation is needed as well.

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**END**