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Chapter 11

Neuronal and Mixed Neuronal-Glial Tumors of the Central Nervous System

Mohammed M.A. Al Barbarawi,
Mohammed Z. Allouh and Suhair M.A. Qudsieh

Additional information is available at the end of the chapter

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1. Introduction

Objective: Neuronal and Mixed Neuronal-glial Tumors of the Central Nervous System are frequently encountered in the neurosurgical practice. *Differentiation of neuronal tumors from the more common glial tumors is crucial because neuronal tumors have favorable clinical outcomes and are generally curable with total surgical resection alone, whereas gliomas typically require further chemo-radiotherapy depending on their histologic grade and have poor prognosis. At histopathologic analysis, neuronal tumors are usually classified as pure neuronal cell tumors (gangliocytoma, Lhermitte-Duclos disease (dysplastic cerebellar gangliocytoma], central neurocytoma) and mixed neuronal-glial tumors (ganglioglioma, desmoplastic infantile ganglioglioma, dysembryoplastic neuroepithelial tumor, ganglioneuroma) In this chapter, we review the WHO classification of each type of neuroepithelial cell tumours and the incidence and distribution. The clinical presentation and neuroimaging will also be briefed, then we describe the specific histopathologic characteristics, immunohistochemestry and genetic suscipitability of the various neuronal tumors of the central nervous system and finally demonstrate the outcome of these lesions.*

2. Contents

2.1. Ganglioglioma and gangliocytoma

Ganglioglioma and gangliocytoma are well-differentiated, slowly growing benign neuroepithelial tumors. with World Health Organization (WHO) grade I. higher grade is based on the degree of malignancy in the glial-cell component. They represent around 1% of all central nervous system (CNS) tumors, However it is frequently oencountered in children and young adults between age 8 and 25 years. Gangliogliomas contain mature neoplastic neuronal cells, neoplastic glial cells, astrocytic cells, and ganglion cells, and may display mitotic activity. These lesions are curable by total removal.

2.2. Central neurocytoma and extraventricular neurocytoma

Central neurocytoma and extraventricular neurocytoma are WHO grade II tumors composed of regular rounded cells that have undergone neuronal differentiation. Central neurocytomas are typicaly located within the lateral ventricles just next to the foramen of Monro, whereas extraventricular neurocytomas are located within the brain parenchyma. Both characteristically occur in young adults. The outcome is favorable after complete resectioning.

2.3. Dysembryoplastic neuroepithelial tumor

Dysembryoplastic neuroepithelial tumor (DNT) is frequently a benign, supratentorial glial-neuronal WHO grade I tumor. DNT occur mainly in children or young adults, who usually present with intractable partial complex seizure. Characterized by a predominantly cortical location, DNT histopathologically exhibits a complex columnar and multinodular architecture, and is often associated with cortical dysplasia.

2.4. Desmoplastic infantile astrocytoma and desmoplastic infantile ganglioglioma

Desmoplastic infantile astrocytomas (DIAs) and desmoplastic infantile gangliogliomas (DIGs) are almost WHO grade I tumors that are often cystic and commonly occur in infants. Composed of a prominent desmoplastic stroma with neuroepithelial components, mainly neoplastic astrocytes in DIAs or astrocytes together with variable neuronal components in DIGs, they involve the cerebral cortex and leptomeninges, and are often adherent to the dura. The natural course is benign.

2.5. Rosette-forming glioneuronal tumor of the fourth ventricle

Rosette-forming glioneuronal tumor of the fourth ventricle (RGNT) is a usually rare and slowly growing WHO grade I tumor. It is commonly affecting young adults, RGNT is composed of two distinct histological cells types; uniform neurocytes which form rosettes and/or perivascular pseudorosettes and astrocytic cells similar to pilocytic astrocytomas. The prognosis is good upon surgical removal.

2.6. Cerebellar liponeurocytoma

This rare type of cerebellar tumors is WHO grade II tumor that typically occurs in adults. It is Composed of neuronal, astrocytic, and some lipomatous cells, they tend to recur after initial treatment.

2.7. Papillary glio-neuronal tumor

Papillary glio-neuronal tumors is a well defined and benign with WHO grade I. the natural course is insidius. It is composed of flat to cuboidal, GFAP-positive astrocytes lining

hyalinized vascular pseudo-papillae and synaptophysin-positive interpapillary sheets of neuronal cells. Upon microscopy, it exhibits different sizes of large and intermediate neuron "ganglioid" cells.

2.8. Spinal paraganglioma

Spinal paraganglioma is encapsulated, benign, neuro-endocrine WHO grade I tumor. Arising from neural crest cells and composed of segmental or collateral autonomic ganglia (paraganglia), It is primarily involving the cauda equine and filum terminale region. The uniform main cells exhibit neuronal differentiation and forming compact nests (Zellballen) surrounded by cells and a delicate capillary network within the CNS.

3. Gangliogliomas and gangliocytomas

3.1. Definition

Gangliogliomas and gangliocytomas are well-differentiated, slowly growing benign neuroepithelial neoplasms that consist of neoplastic, mature ganglion cells. Both gangliogliomas and gangliocytomas are a type of neuroepithelial tumor that is the most frequent pathology observed in patients with long-term epilepsy. A gangliocytoma in the absence of neoplastic glial-cell development and a ganglioglioma in the presence of neoplastic glial-cell development. (1)

3.2. WHO grading

Gangliocytomas and most gangliogliomas are categorized as WHO grade I tumors (1).

Some gangliogliomas with anaplastic features of the glial component are categorized as WHO grade III tumors (anaplastic gangliogliomas). Criteria for grade II types has also been suggested (2, 3).

3.3. Incidence and gender distribution

These uncommon neoplastic lesions represent only 0.4% of all CNS tumors and 1.3% of all brain tumors (3,4). The age of patients is variable, ranging from 2 months to 70 years. Data from 5 large series of a total of 626 patients indicate an average age at diagnosis ranging from 8.5 to 25 years and a male: female ratio ranging from 1.1:1 to 1.9:1 (5,6,7,8). In one study, the mean age in children at diagnosis is 9.5 years, with a slight female prevalence (9).

3.4. Localization

The vast majority of gangliogliomas (>70%) occur in the temporal lobe. However, Gangliocytomas and most gangliogliomas may occur throughout the CNS, including in the

cerebrum, brain stem, cerebellum, spinal cord, optic nerves, and pituitary and pineal glands. (2, 6, 7, 8, 10).

3.5. Clinical features

Variable clinical symptoms of gangliocytomas and most gangliogliomas are encountered and related to tumor size and site. Seizure is usually the initial presenting symptoms. Gangliocytomas and gangliogliomas are the most common tumors associated with chronic and intractable temporal lobe epilepsy and observed in 15% to 25% of patients undergoing epilepsy surgery (11,12).duration of symptoms ranging from 1 month to 50 years before diagnosis, with a median interval of 6 to 25 years (6,7,8). Tumors affecting the brain stem or spinal cord frequently present with crossed paresis or long-tract lesion and sphincteric disorder of a mean duration of 1.25 and 1.4 years, respectively (6).

3.6. Neuroimaging

Computed tomography (CT) of a ganglioglioma or gangliocytoma may indicate a well-circumscribed solid mass or cyst with a mural nodule and some calcification, and slight or absent contrast enhancement. Skull scalloping may be noted adjacent to superficial cerebral tumors. These lesions appear hypointense on T1-weighted and hyperintense on T2-weighted magnetic resonance imaging (MRI), with well-defined masses showing enhancement absorption that can range from none to vivid and may be solid or only on the rim or nodular (13,14) **. Figure 1**

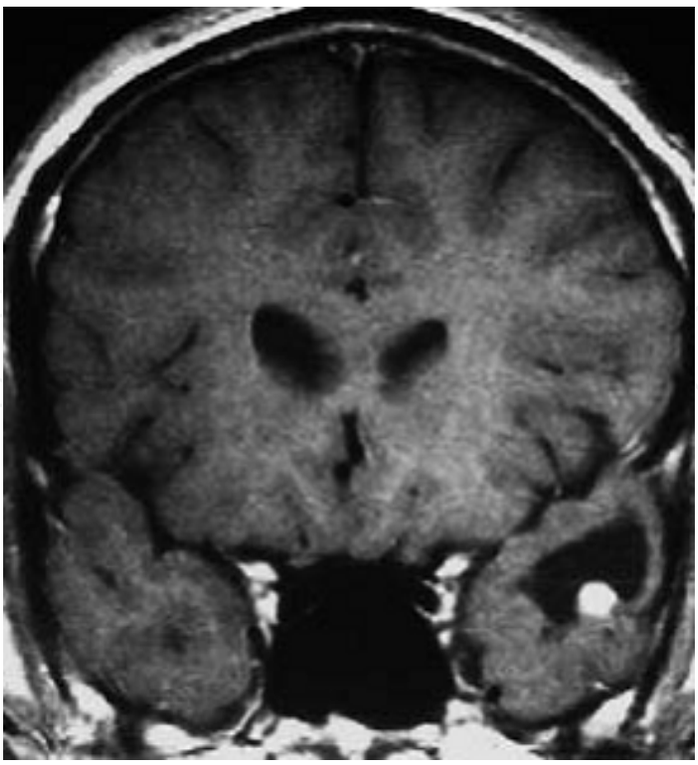

Figure 1. MRI

3.7. Macroscopical features

Gangliogliomas are solid or cystic lesions, characteristically with little mass effect. Calcification may be observed, whilst hemorrhage and necrosis are rare (8)

3.8. Histopathology

A primary characteristic of gangliogliomas is a mixture of neuronal and glial-cell elements that may display a striking heterogeneity. Gangliocytomas consist of clusters of large, multipolar neurons with immature features. The matrix contains non-neoplastic glial components and a network of reticulin fibers. Immature neurons are characterized by the loss of cyto-architectural arrangement of subcortical localization, a grouped appearance, enlargement of cells, and aggregation of Nissl bodies. Multinucleated neurons may present in 50% of cases. On the other hand, the glial element in gangliogliomas, which comprises the proliferation part of the tumor, shows considerable inconsistency, and may include any glial-cell type with Rosenthal fibers and eosinophilic granular bodies. Thestroma is typically fibrillary and may contain a microcystic component with mucous material. Occasional mitotic activity may be noted, and is typically compatible with the diagnosis of ganglioglioma, whereas necrosis is absent unless the glial component is undergoing malignant transformation. Other histopathological features that may be seen in gangliogliomas are calcifications, extensive lymphatic infiltrates with perivascular spaces or within the tumor substance or brain tissue, and a capillary network that forms an angiomatous constituent. In high-grade (anaplastic) gangliogliomas, malignant changes almost always involve the glial component and may be seen at the site of a previously removed ganglioglioma (2, 3, 5, 7, 8). **Figure 2A**

3.9. Immunohistochemistry

No specific marker is available to differentiate dysplastic and neoplastic neurons from normal and mature neurons. Neuronal protein markers, such as synaptophysin, neurofilaments, MAP2, and Neu N, are used to reveal the neuronal component in gangliogliomas.. However, use of the onco-fetal CD34 antigen can be positive, as CD34 is absent in neural cells of the adult brain but consistently expressed in 70% to 80% of gangliogliomas, especially those arising from the temporal lobe (15). Staining for GFAP reveals the astrocytic component the neoplastic glial element of gangliogliomas. Contrary to that seen in diffuse gliomas, MAP2 immunoreactivity is usually weak or absent in the astrocytic component of gangliogliomas (16). **Figure 2B**

3.10. Electron microscopy

The presence of neurons with dense core granules is a characteristic feature of gangliogliomas and gangliocytomas. Neuronal synaptic junctions may be few or completely absent (5,17). Observation of round protein bodies in gangliogliomas has also been mentioned (18).

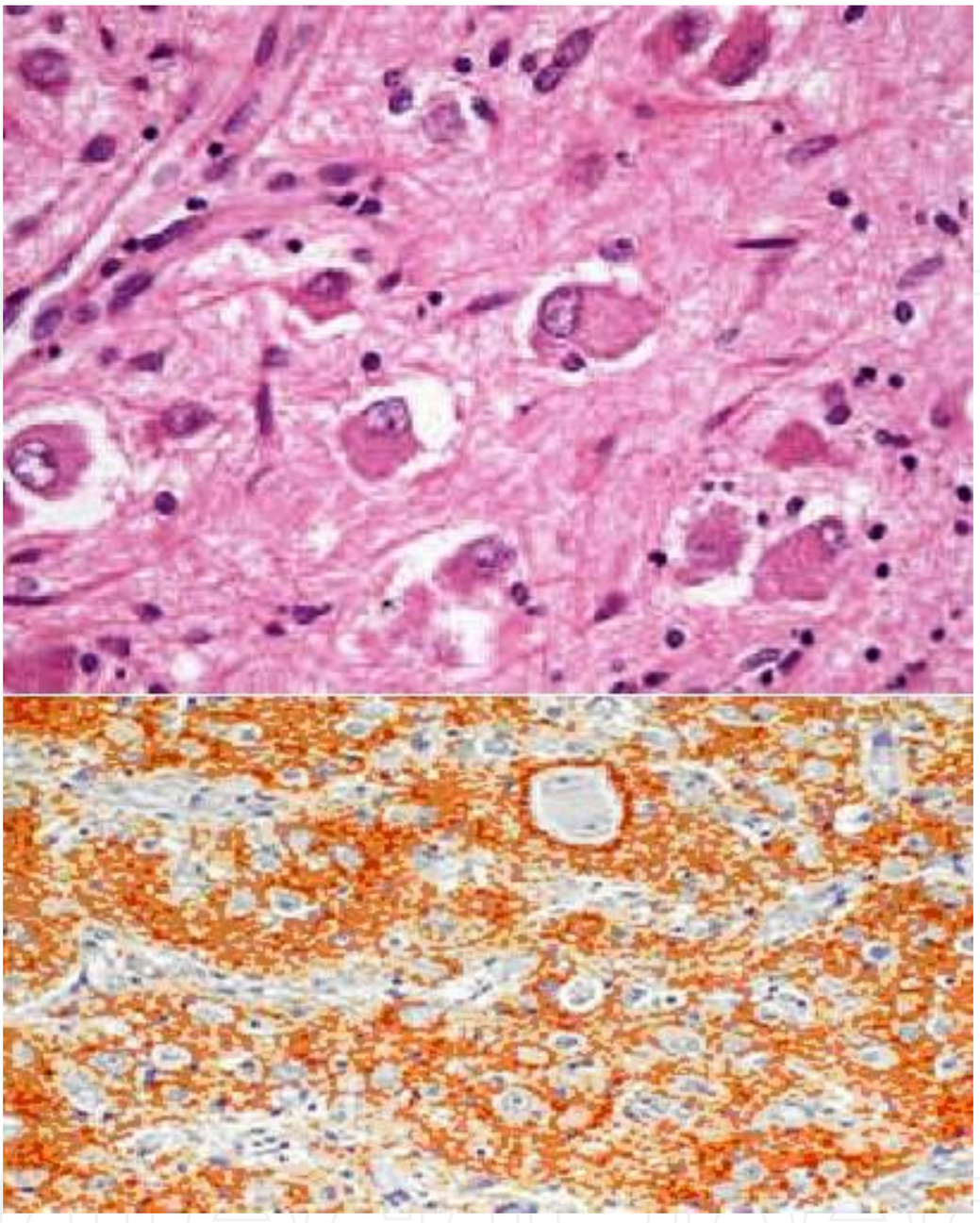

Figure 2. A and B

3.11. Proliferation index

Ki-67/MIB-1 labeling the glial component has shown values ranging from 1.1 to 2.7%. Mitotic activity is low (5,7).

3.12. Genetic susceptibility

Genetic vulnerability to the development of gangliogliomas and gangliocytomas has not been well established. Previous studies reported a ganglioglioma of the optic nerve in a patient with neurofibromatosis type 1 (19) and a ganglioglioma in a Peutz-Jeghers patient

(20).. Mutational analysis of the tuberous sclerosis 1 (TSC1) and TSC2 genes revealed significant sequence alterations in the TSC2 gene, including polymorphisms in intron 4 and exon 41, in patients with gangliogliomas. In a further study of ezrin and radixin genes, coding for the interaction partners of TSC1 and TSC2 was not observed (30,31,32).

Chromosomal abnormalities have been recorded in one-third of cases, in the approximately 30 cases of gangliogliomas that have been studied cytogenetically, a change in chromosome 7 was the most one observed. The karyotype was found to be abnormal in 3 cases with unfavorable outcomes. (21,22,23,24,25,26). Chromosomal imbalances have been detected in 5/5 gangliogliomas by comparative genomic hybridization. Although partial loss of chromosome 9p and gain of chromosome 7 has been observed in several patients, abnormal epidermal growth factor receptor (EGFR) expression was not observed in these cases (27). A study of 14 cases (11 WHO grade I and 3 WHO grade III) failed to show TP53 mutation, PTEN mutation, or CDK4 and EGFR amplification, whereas CDKN2A deletion was observed in two-thirds of cases of anaplastic ganglioglioma (28). However, TP53 mutation was only noted in the recurrence of a WHO grade I ganglioglioma (29).

3.13. Histogenesis

The histogenesis of gangliogliomas and gangliocytomas still not understood. However, evolution from a dysplastic, abnormal glio-neuronal precursor with subsequent neoplastic transformation of the glial element has been proposed (33).

3.14. Prognosic factors

Favorable prognosis is observed in patients with long-standing epilepsy with temporal localization and complete surgical resectioning. These lesions are typically benign tumors with a 7.5-year recurrence-free survival rate of 94%.. Anaplastic changes, such as mitotic activity and microvascular proliferation and necrosis, in the glial component similar to those observed in high-grade gliomas.

4. Central neurocytomas and extraventricular neurocytomas

4.1. Definition

Central neurocytomas and extraventricular neurocytomas are neoplasms composed of uniform round cells with neuronal differentiation. Central neurocytomas are typically located in the lateral ventricles in the region of the foramen of Monro and extraventricular neurocytomas in the brain parenchyma. These tumors are usually seen in young adults and have a favorable prognosis.

4.2. WHO grading

Central neurocytomas correspond histologically to WHO grade II tumors (1).

4.3. Historical background

"Central neurocytoma" expression was used by Hassoun et al. (34) to describe a neuronal tumor with pathological features to differentiate it from cerebral neuroblastomas that occurs in young adults, it is commonly located in the third ventricle, and histologically may resemble oligodendrogliomas. They were also reported in other locations. The term central neurocytoma should be restricted to neoplasms located within the intracerebral ventricles. Tumors similar to central neurocytomas but occurring within the cerebral hemispheres ("cerebral neurocytomas") or the spinal cord (35, 36,37) have subsequently been mentioned and described as "extraventricular neurocytoma" these tumours are now given to neoplasms that arise within the CNS parenchyma and have histological features with the more common central neurocytomas but exhibit a wider morphological spectrum. Neurocytic differentiation has been reported in an increasing number of tumors with specific morphological characteristics, some of these have been categorized as new entities, such as cerebellar liponeurocytomas, papillary glioneuronal tumors, or their variants (38, 39, 40).

4.4. Incidence and sex distribution

The incidence ranged from 0.25% to 0.5% of all intracranial tumors. In an analysis of 243 cases, age at clinical manifestation is almost variable ranging from 8 days to 67 years (mean age, 29 years), with 69% between the ages of 20 and 40 year. Both sexes are equally affected (40, 34).

4.5. Localization

Central neurocytomas are usually located supratentorially in the lateral or the third ventricle. With most common site is the anterior part of the lateral ventricles (50%), more frequently on the left, followed by combined extension into the lateral and third ventricles and a bilateral intraventricular location. Attachment to the septum pellucidum is common, but isolated third-ventricular occurrence is rare. (40, 41)

4.6. Clinical features

The majority of patients present with symptoms of increased intracranial pressure rather than with other neurological deficit. The clinical history is short (mean 3.2 months). Central neurocytomas may present as acute hemorrhage or as an incidental finding on imaging (41).

4.7. Neuroimaging

On CT scans, mass is typically isodense or slightly hyperdense. Enhancement is common . Calcifications and cystic changes may be observed. MRI scan shows heterogeneous hypointensity on T1-weighted images and fluid- attenuated inversion recovery (FLAIR) and hyperintensity on T2-weighted images and FLAIR, with a well-defined margin mild to strong enhancement after gadolinum injection (42). **Figure 3**

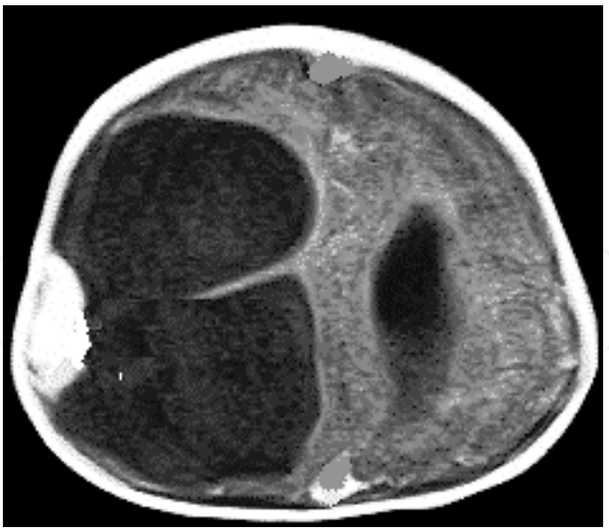

Figure 3.

4.8. Macroscopical appearance

Intraventricular tumors are typically grey in color and friable with varying calcifications, these tumours are vascular and with occasional hemorrhage. (43,44)

4.9. Histopathology

Central neurocytomas have a benign histological appearance and may display various architectural patterns, even within the same specimen, including an oligodendroglioma-like honeycomb appearance, large fibrillary areas mimicking the irregular “rosettes” in pineocytomas. These lesions are neuroepithelial tumors composed of uniform round cells that show immunohistochemical and ultrastructural features of neuronal differentiation, fibrillary areas mimicking neuropils, and a low proliferation rate. Cells are isomorphous, having a round or oval nucleus with a finely speckled chromatin and an occasional nucleolus, cells arranged in straight lines, or perivascular pseudorosettes similar to those noted in ependymoma tumours. Calcifications are usually seen in around 50% of cases, normally distributed throughout the tumor. Blood vessels, classically arranged in a linear architecture pattern, giving an endocrine appearance. Rarer findings may include Homer Wright rosettes and ganglioid cells (43,44).

These tumour may mimic, and must be distinguished from, oligodendroglioma, ependymoma, pineocytoma, and dysembryoplastic neuroepithelial . In rare cases, anaplastic histological features, including high mitotic activity and microvascular proliferation, have been observed. In some conditions, necrosis was associated with anaplastic features. Necrosis may also be observed in rare cases that are otherwise without malignant features, may be s as a vascular effect (41, 44, 46, 47, 48,49). **Figure 4A**

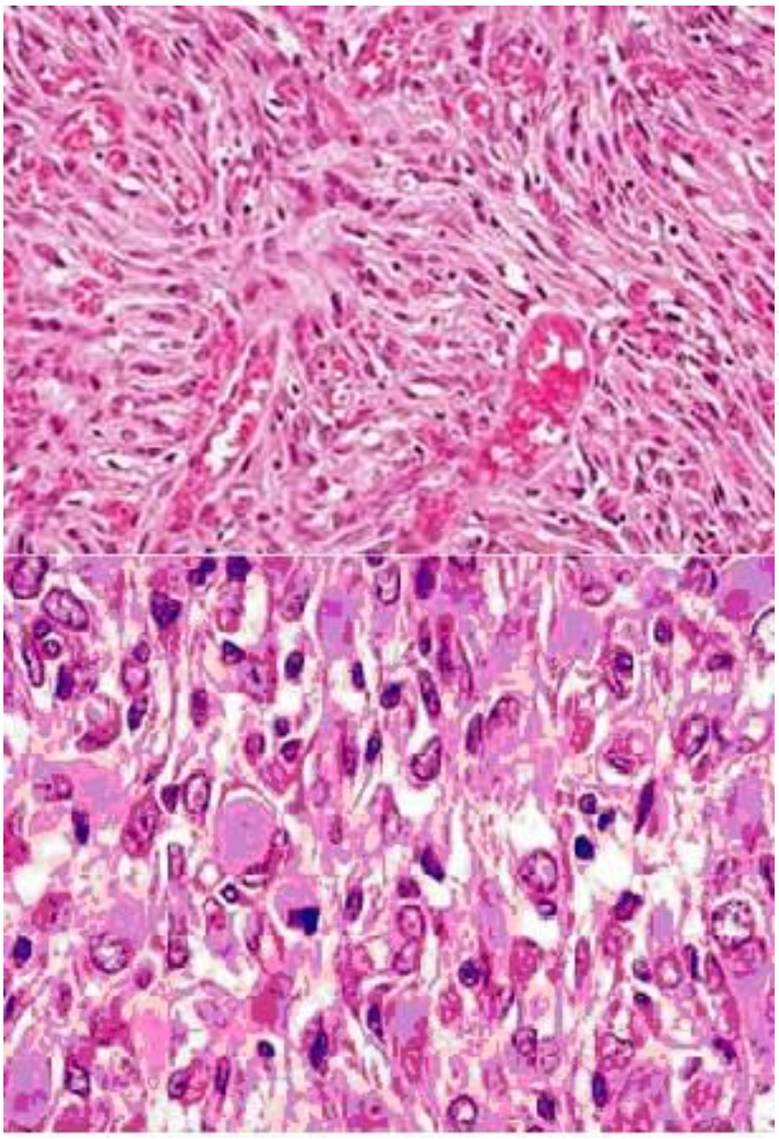

Figure 4. A and B

4.10. Immunohistochemistry

Synaptophysin is the most suitable and reliable diagnostic marker, with immunoreactivity diffusely present in neuropils, especially in fibrillary zones and perivascular nuclei-free cuffs (48). A significant number of nuclei are immunopositive for NeuN in almost all cases (50). The mean labeling index was 74% in one series of 11 cases, with a significantly lower Ki-67 staining rate for cells expressing NeuN (51). In extraventricular lesions, intracytoplasmic and para-nuclear immunolabeling must be cautiously inferred whenever other histological, immunohistochemical, or ultrastructural data of neuronal differentiation is lacking. Of particular interest is the anti-Hu antibody because it labels the nuclei of neurocytes (52). Chromogranin A and neurofilament staining are typically absent except when ganglion cells are present Although most studies found that GFAP was expressed only in trapped reactive astrocytes, the antigen has been detected by some studies in tumor cells (44, 45, 53 ,54). **Figure 4B**

4.11. Electron microscopy

Electron microscopy may be required when expression of specific neuronal markers (synaptophysin, NeuN) is questionable and in other extraventricular neoplasms mimicking central neurocytomas. The central neurocytoma cells show uniform round nuclei with a finely discreted chromatin and a small nucleolus in a few cells. The cytoplasm contains mitochondria, a prominent Golgi apparatus, and several rough endoplasmic reticulum cisternae, often arranged in concentric lamellae. copious thin and combined cell processes containing microtubules and dense core and clear vesicles are always observed (41,55).

4.12. Proliferation index

MIB-1 labeling indices are classically low, usually less than 2%. However, Tumors with indices greater than 2%, as in one series in which they were found to be 3% , are referred to as "atypical neurocytomas" and associated with a significantly shorter recurrence-free interval (53, 56, 57).

4.13. Genetic susceptibility

Unclear, but central neurocytoma was observedin patients with von Hippel-Lindau disease (58). The molecular pathogenesis of central neurocytomas remains unknown, the observation of several genetic alterations, mainly chromosomal gains, has been reported. In one study, gain on chromosome 7 was observed in 3 of 9 neurocytomas (59). However, another study found no EGFR amplification in central neurocytomas (60). In related studies, gains on chromosomes 2p, 10q, 18q, and 13q were found in over 20% of tumors in one study ; an isochromosome 17 and complex karyotype were observed in 2 studies (61, 62, 63); and TP53 mutations and MYCN amplification were reported to be rare or absent in several studies (45, 60, 63, 64, 65).there are two studies that reported loss of 1p and 19q, 1 study reported allelic loss on 1p as well as an inability to detect 19q (64), whereas the other study reported 6 of 9 tumors showed loss at 1 or more loci on 1p and that 5 tumors showed 19q loss. These data suggest that central neurocytomas are genetically distinct from oligodendrogliomas. Although the expression profiles of cerebellar liponeurocytomas appear to have a closer relationship to those of central neurocytomas, the lack of TP53 mutations in central neurocytomas suggests the involvement of different genetic pathways (60, 66,67).

4.14. Histogenesis

Central neurocytomas were previously thought to be derived from precurssor cells of the septum pellucidum (34). Still, the indication of both astrocytic and neuronal differentiation in some tumor cells by various approaches in vivo and in vitro has suggested that they are derived from neuroglial precursor cells with a potential to undergo dual differentiation. These precursor cells might arise from the subependymal layer of the lateral ventricle or from the ventricular region. (45,54, 68).

4.15. Prognostic factors

The natural course of central neurocytoma is classically benign. Total surgical resection is the most important prognostic factor. recurrence is frequent with incomplete removal, but the residual tumor growth can be treated with radiotherapy. CNS dissemination is rare. (57, 66, 69, 70). central neurocytomas is rarely aggressive (44,47). Patients with central neurocytomas and a MIB-1 labeling index (LI) >2% or >3% have significantly shorter recurrence-free intervals. Involvement of the periventricular parenchyma involvement may be associated with poor outcome (71, 72).

4.16. Extraventricular neurocytomas

Extraventricular neurocytomas are usually well-defined and contrast-enhancing lesions that often have a cyst–mural nodule complex which is usually useful in distinguishing them from histologically similar neoplasms, such as oligodendrogliomas. Histologically, extraventricular neurocytomas may be identical to central lesions, but are often more complex, less cellular, and more likely to contain ganglion cells or ganglioid cells with nuclei that are larger than those of neurocytes. Lower cellularity, in combination with the presence of perinuclear haloes, may give these lesions the appearance of oligodendrogliomas. Although GFAP-positive glial cells have been observed, it has been difficult to identify them as clearly neoplastic. Hyalinized vessels and dense calcification are common (73).

5. Dysembryoplastic neuroepithelial tumors

5.1. Definition

Dysembryoplastic neuroepithelial tumors (DNTs) are usually benign. They are supratentorial glio- neuronal neoplasms that seen in children or young adults. Characterized by a cortical location and intractable partial complex seizures, they ideally demonstrate a complex columnar and multinodular structural design and are often associated with cortical dysplasia (74).

5.2. WHO grading

DNTs correspond histologically to WHO grade I tumors. (1)

5.3. Historical background

DNTs were first recognized as lesions in patients who had undergone epilepsy surgery for the treatment of longstanding, drug-resistant partial seizure sand showed unusual morphological features, including cortical topography, multinodular architecture, a “specific glioneuronal component” with a columnar structure. No recurrence with long term follow up even in patients with incomplete partia resection. Several factors strongly suggested a dysembryoplastic origin, the term “dysembryoplastic neuroepithelial tumor” was proposed for these lesions (74).

In the 1993 WHO Classification of Tumors Affecting the Central Nervous System (36), DNTs were included in the category of “neuronal and mixed neuronal-glial tumors.” With

"complex form," and "simple type" (75). Later , "non-specific histological forms" were addedd. Furthermore, it has been indicated that DNTs may be seen in the infratentorial location (76, 77, 78,79).

5.4. Incidence

Incidence is variable. In a study of patients who were treated surgically for epilepsy, the incidence of "typical" DNTs was reported to be 12% in adults and 13.5% in children (80), whereas it was reported to be 19% to 22% in all patients in a series that included "non-specific" histological variants (78,81,82). Among all neuroepithelial tumors diagnosed in a single institution, DNTs were identified in about 0.2% among patients aged more than 20 years and in 1.2% of the patients under the age of 20 years (83).

5.5. Age and sex distribution

In about 90% of cases, the first seizure attack occurs before 20 years of age, but it may present from 3 weeks to 38 years (84,85). though patients are often diagnosed in the 2ed or 3rd decade of life, detection of DNTs by imaging in children or young adults with recent onset seizures has become more common, leading to more surgical intervention for treatment of DNTs in pediatric neurosurgery. It was observe that males are more slightly affected. (86, 87, 88, 89,90).

5.6. Localization

There is a predilection for the temporal lobe and for involvement with mesial structures although DNTs may be located in any part of the supratentorial cortex, (80, 81,82,83,84). In one series of patients treated in a general practice, temporal lobe involvement was found in 50% or fewer of cases (85,86). DNTs have also been found in the area of the caudate nucleus (76,77) or lateral ventricle, the septum pellucidum, the trigonoseptal region (88), the midbrain and tectum , and the cerebellum or cerebellum and brain stem (89,90,91,92). In total, 25 extracortical cases have been reported. In addition, 4 cases of multifocal DNTs have been reported, indicating that these tumors may arise in the region of the third ventricle, the basal ganglia, and the pons (93, 94,95).

5.7. Clinical presentation

Drug -resistant partial complex seizure is the typical presentation with or without secondary generalization, and no focal neurological deficit. The duration of seizures prior to surgical resection can vary from weeks to many years, leading to variability in patient age at pathologic diagnosis(79, 73,74, 97,98).

5.8. Neuroimaging

The cortical location of the lesion in the absence of both mass effect and peritumoral edema are important criteria in differentiating between DNTs and gliomas. DNTs typically encompass

the thickness of the normal cortex and, in a minority of the cases, have an area of signal abnormality that extends into the subcortical white matter. The cortical location of the lesion is easily identified on MRI than on CT. DNTs appear hyperintense on T2-weighted images and hypointense or iso-intense on T1-weighted images. They often have a pseudo-cystic or multi-cystic appearance although true cyst formations are rare and small (91). In tumors located at the convexity, scalloping of the overlying bone is often observed on scans , a finding supports the diagnosis of DNT(, 77, 99,100, 101,102). Calcifications are rare. Contrast enhancement on CT or MRI is not common, it is often appearing as rings rather than homogeneous enhancement. Such ring-shaped contrast enhancement may be observed on a previously non-enhancing tumor on scans (96, 102). Increased tumour size, without peritumoral edema, may also be observed on imaging follow-up. However, these changes are naturally not signs of malignant transformation but rather as a result of ischemic or hemorrhagic changes (103,104).

5.9. Macroscopy

DNTs vary in size from several millimeters to several centimeters. In their typical location, they are often easily identified superficially at the cortical, and may show exophytic development, but indicate no involvement of leptomeninges. The most typical feature is viscous consistency of the glioneuronal component, which may be associated with multiple or single firmer nodules, and spreading out of the affected cortex (68).

5.10. Histopathology

The histological hallmark of a classical DNT is the presence of a "specific glio-neuronal constituent." This element is characterized by columns formed by bundles of axons lined by small oligodendroglia-like cells that are oriented perpendicularly to the cortical surface between which neurons with normal cytology appear to float in a pale, eosinophilic medium. There are also elements of scattered GFAP-positive stellate astrocytes. Depending on the amount of fluid extravasation, subtle variation from a columnar to o a more packed in structure may be observed . Several histological forms of DNTs have been mentioned, but their subclassification has no clinical or therapeutic implications (76,77). **Figure 5A.B**

5.11. Complex and non specific forms

In the complex form of a DNT, glial nodules, which give the tumor a feature of multinodular pattern, are seen in association with a specific glio-neuronal element. The variable appearance of these tumors is due to the presence of multiple cells of astrocytic, oligodendrocytic, and neuronal components. The glial components seen in the complex forms of DNTs have a highly variable form due to many causes : 1- they may form typical nodules with diffuse pattern; 2- they may mimic usual categories of gliomas and may illustrate unusual features; 3- they usually resemble low-grade gliomas, but may demonstrate nuclear atypia, some mitotic activity, or microvascular-like proliferation and ischemic necrosis; 4- they display a microvascular network. Within the glial components, typically calcified vessels are frequent that may behave as vascular malformations and be responsible for bleeding (65,66,86, 99,101,103, 104,105).

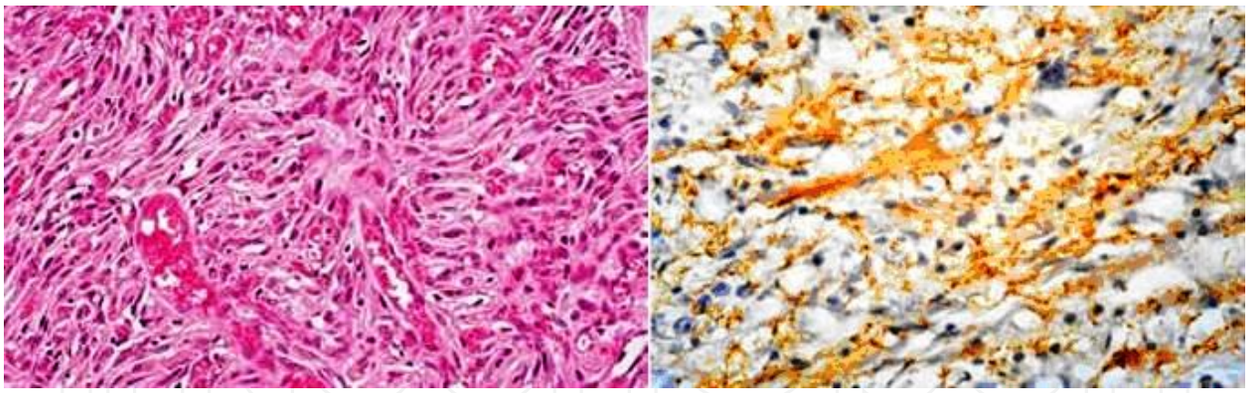

Figure 5. A and B

"Non-specific" histological variants of DNTs, identified according to clinical presentation as well as their cortical location, neuroimaging features, and steadiness on long-term preoperative imaging follow-up, have been described (77). Due to lackness the specific glioneuronal element and multinodular architecture, these variants are often histologically indistinguishable from low-grade gliomas. The diagnosis of these tumors thus requires that the clinical presentation and neuro-imaging appearance of the lesion be taken into consideration. Non-specific histological types account for 20% to 50% of DNTs in many studies (79,106,). Although gliomas identified in patients with long-term epilepsy during epilepsy surgery are typically associated with a distinctly benign course the diagnosis of "non-specific" histological variants of DNTs still debatable (107,108,110).

5.12. Simple form

Morphologically, the simple form of a DNT consists of a unique glioneuronal component it shows a patchy pattern owing to the proximity of foci of tumor and a well-defined cortex (76),.

5.13. Cortical dysplasia and Neuronal distribution of DNTs

Dysplastic disorganization of the cortex has been observed in up to 80% of DNT cases in studies with adequate sampling (111,112). Supratentorial cortical DNTs contain mature neurons that, both in the tumor itself and in the area of cortical dysplasia, may show different degrees of cytological anomaly. Thoug, DNTs do not have atypical or immature neurons that look like dysplastic ganglion cells as observed in gangliogliomas. Some tumor cells with an oligodendrocytic appearance have been found to occasionally express neuronal markers and display axo-somatic synapses suggesting that what is called "oligodendroglial-like cells" of DNTs and it may undergo early neuronal differentiation. However, using in-situ hybridization indicates that oligodendro-glial-like cells copy myelin genes and express myelin oligodendrocyte glycoprotein protein, indicating oligodendro-glial demarcation (113, 114,115, 116).

5.14. Cortical topography

The borders of the tumor often match with those of the cortex to a very large degree. it also appears to involve the adjoining white matter. However, as neurons are typically found in

even the deeper parts of the tumor and in the neighboring white matter, such association is high likely indicates disordered neuronal migration (117).

5.15. Diagnostic criteria

The diagnosis of DNT should be taken into consideration in every case in which all of the following criteria (76, 77, 80. 81) are present:

1. the presence of partial complex seizures with/ without secondary generalization beginning before age 20
2. the absence of progressive neurological deficit.
3. the presence of a supratentorial lesion with a predominantly cortical topography, best indicated on MRI
4. the absence of mass effect on CT or MRI, except if related to a cyst
5. the absence of peritumoral edema on the scans

5.16. Comparison between DNTs and gangliogliomas

Differential diagnosis of DNTs and gangliogliomas may be tricky on account of several factors: 1- the clinical presentation of gangliogliomas is often similar to that of DNTs. 2- the immature ganglion cells of gangliogliomas may not be present in a small or inadequate sample. 3- Gangliogliomas may show a multinodular arrangement, 4- small gangliogliomas may show a predominant cortical topography.

A ganglioglioma is suspected when a tumor shows perivascular lymphocytic infiltration, a network of reticulin fibers, and a large cystic component. as gangliogliomas may undergo malignant transformation, their distinction from DNTs is important from a prognostic point of view. (118, 119, 120,121).

5.17. Comparison between DNTs and low-grade gliomas

The above clinical and radiological criteria help in distinguishing benign DNTs from diffuse gliomas. In diagnosis, it is important to consider that 1- in diffuse gliomas, so-called "floating" neurons may be present, 2- in low-grade diffuse gliomas, infiltrative microcystic activity may cause to the formation of a construction that mimics a "specific glio-neuronal element"; 3- some oligodendrogliomas, a nodular pattern may be seen, 4- in diffuse gliomas, secondary architectural changes in the cortex caused by the expansion of gliomas into the cortex may be not easy to differentiate from the presence of dysplastic cortical disorganization (76,77,80.81)..

5.18. Genetic susceptibility

DNTs have reported in patients with neurofibromatosis type 1 (NF1) and with XYY syndrome (122,123,124).

5.19. Proliferation index

Variable MIB-1 labeling indices of DNTs have been reported from 0% to 8% focally (79, 81, 84).

5.20. Histogenesis

Many factors have suggested that DNTs are a malformative origin, including the presence of focal cortical dysplasia and migrated neurons in the adjacent white matter, young age of symptom onset, and bone deformity adjacent to the tumor. Some observations indicate that they may be derived from secondary germinal layers. the histogenesis of DNTs remains unknown (74,77,81, 125)

5.21. Prognostic factors

DNTs are benign lesions. Their stability was indicated in a study of 53 patients for whom successive pre-operative CT or MRI was available with a mean duration of follow-up of 4.5 years (102). Long-term clinical follow-up typically shows no evidence of recurrence, even in patients with incomplete surgical resection (76, 97,99, 102, 107, 126). Risk factors for post operative recurrent seizures at long-term follow-up include longer pre-operative history of seizures, cortical dysplasia next to DNT and residual tumour (85, 100, 127, 128). Malignant transformation is extremely rare, only 2 cases reported from 700 cases of DNTs (129).

6. Desmoplastic infantile astrocytomas and desmoplastic infantile gangliogliomas

Desmoplastic infantile astrocytomas **(**DIAs) and desmoplastic infantile gangliogliomas (DIGs) are usually large cystic tumors occurring in infantile period that typically affect the cerebral cortex and leptomeninges and are often attached to the dura. DIGs contain neoplastic astrocytes and neuronal components while DIAs contain only neoplastic astrocytes.

6.1. WHO grading

Histologically, DIAs and DIGs correspond to WHO grade I tumors.

6.2. Historical annotation

DIAs were originally described by Taratuto et al in 1982. (130) as meningocerebral astrocytomas attached to the dura displaying a desmoplastic reaction. Their subsequent description as superficial cerebral astrocytomas attached to the dura (131) led to the delineation of a previously unknown entity. In 1993, this entity was included in the WHO Classification of Tumors Affecting the Central Nervous System (132) under the term “desmoplastic cerebral astrocytoma of infancy.” In 1987, VandenBerg et al reported observation of desmoplastic supratentorial neuroepithelial tumors of infancy with diverse

differentiation ("desmoplastic infantile gangliogliomas") in the same clinical setting. They described the histopathology of DIGs as differing from that of DIAs due to the presence of a neuronal component with variable differentiation in the former. (133). Since both types of lesions have similar clinical and neuroimaging features they have been currently categorized together as DIAs or DIGs in the WHO Classification.

6.3. Incidence

DIAs and DIGs are rare tumours and only observed in childhood whose rate can only be estimated from their reported frequency in institutional series. One series of 6500 CNS tumors in patients of all ages reported only 22 cases of DIG at a rate of 0.3% (134). In a series of CNS intracranial tumors limited only to the pediatric age group reported 6 cases of DIA, accounting for 1.25% of all childhood brain neoplasm. While, reports limited to brain tumors of infancy have found that DIAs and DIGs account for 16% of intracranial tumors (131,135).

6.4. Age and sex allocation

In a study, the age range for 84 reported cases of DIA and DIG was found to be 1 to 24 months. Males ae more commonly affected, with Male:female ratio is 1.5:1. The large majority of infantile cases present within the first year of life. However, several non-infantile DIA, DIG between 5 to 25 years have been reported (136, 137).

6.5. Localization

DIAs and DIGs invariably arise in the supratentorial region and commonly involve more than one lobe, most frequently the frontal and parietal lobes, followed by the temporal and less commom the occipital lobe (137).

6.6. Clinical presentation

The clinical features of DIAs and DIGs are of short duration and include increasing head circumference, tense and bulging fontanelles, lethargy, and sun set sign. Patients may also present with seizuresor focal motor signs, calvarial bulging over the tumor may also be observed (136).

6.7. Neuroimaging

On CT, these lesions are seen as large, hypodense cystic masses with a solid isodense or slightly hyperdense superficial portion that extends into the overlying meninges and shows contrast enhancement. The cystic portion is typically located deep within the tumor, where the solid portion is peripheral. The MRI T1-weighted images are characterized by a hypointense cystic component with an isointense peripheral solid component that takes contrast. On T2-weighted images, the cystic component is hyperintense and the solid portion is heterogeneous. Edema is usually absent or light (138). **Figure 6**

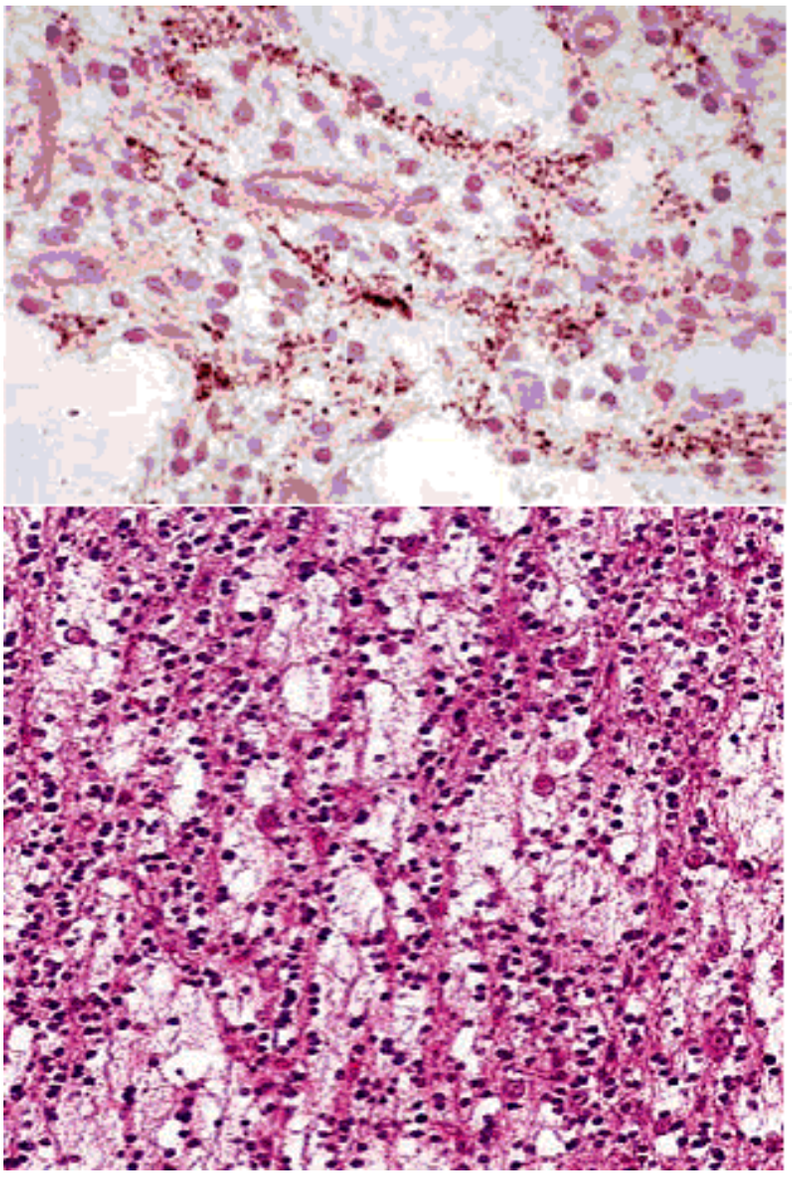

Figure 6. A and B

6.8. Macroscopy

DIAs and DIGs are typically large tumors, measuring up to 13 cm in diameter, with deep multiloculated cysts filled with clear or xanthochromic fluid. The solid superficial portion is primarily extracerebral, attached to leptomeninges and the superficial cortex, it is firm or rubbery in consistency, and grey or white in color.

6.9. Histopathology

The DIA or DIG composed of neuroepithelial tumor with 3 characteristic components: a main desmoplastic leptomeningeal component, a poorly differentiated neuroepithelial component, and a cortical component. The desmoplastic leptomeningeal component consists of a mixture of fibroblast-like spindle-shaped cells and pleomorphic, neoplastic, and neuroepithelial cells with

eosinophilic cytoplasm, both of which are arranged in fascicles or in a whorled pattern. Reticulin impregnations show a prominent reticulin-positive network surrounding almost every cell and mimicking that of a mesenchymal tumor. Astrocytes are the main tumor-cell feature in DIAs or the predominant neoplastic population associated with immature neurons in DIGs. The type of neoplastic neuron may range from atypical ganglionic cell to a small polygonal cell (133,139).

In addition to this desmoplastic leptomeningeal component, both DIAs and DIGs contain a group of poorly differentiated neuroepithelial cells with small, round, deeply basophilic nuclei and minimal surrounding perikarya. Such an immature component lacking desmoplasia may predominate in some areas. A cortical component devoid of desmoplasia may also be seen that is often multinodular, with some nodules being microcystic (139).There is a sharp delineation between the cortical surface and the desmoplastic neoplasm, Virchow-Robin spaces in the underlying cortex are often occupied with tumor cells. Calcifications are frequent. Mitotic activity and necrosis are rare. Some tumors may be slightly vascular (137, 140, 141, 142). **Figure 7A.B**

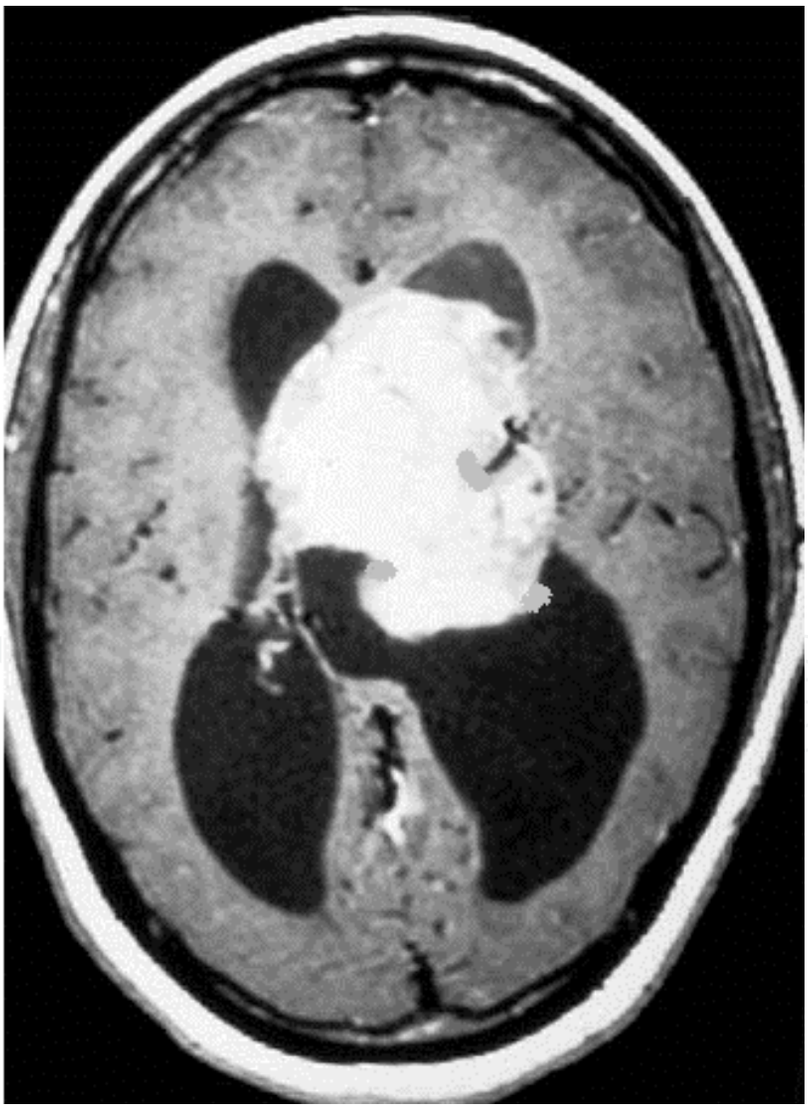

Figure 7.

6.10. Immunohistochemistry

In the desmoplastic leptomeningeal component, fibroblast-like cells express vimentin. As most other neuroepithelial tumor cells react with GFAP, astrocytes predominate in this component. Antibodies to collagen typr VI react in a reticulin-like pattern around tumor cells (143,144). Expression of neuronal markers (synaptophysin, NF-H, and class III ß-tubulin) has been observed in both the neoplastic neuronal cells as well as cells lacking apparent neuronal differentiation (145). In the poorly differentiated neuroepithelial component, cells react with not only GFAP and vimentin but also with neuronal markers and MAP2 Desmin expression may be present (134,145, 146, 148); but epithelial markers (CAM 5.2, AE1/AE3, and EMA) are usually absent (145). **Figure 8A.B**

6.11. Electron microscopy

Astrocytic tumor cells are characterized by intermediate filaments typically arranged in bundles as well as scattered cisternae of rough endoplasmic reticulum and mitochondria with extensive basal lamina. Fibroblasts containing granular endoplasmic reticulum and well-developed Golgi complexes (141, 142). The neuronal cells of DIGs contain dense core secretory granules and neurofilaments. Immunoelectron microscopy has shown filamentous reactivity to NF-H in these neuronal cell bodies as well as processes lacking involvement of the basal lamina. (149).

6.12. Proliferation index

Mitotic activity is rare and, when present, is mostly restricted to the undifferentiated, small-cells in DIGs (134,139). Ki-67 labeling indices reported in the literature range from less than 0.5% to 5%, with the majority of studies reporting them as less than 2% (150). Proliferation does not appear to be related to clinical behavior in completely resected tumors but may expect more aggressive nature in subtotally resected cases. In 3 cases analyzed by flow cytometry, the S-phase fraction ranged from 3.7% to 12%, with a mean of 6.6% (151, 152, 153).

6.13. Histogenesis

The cellular origins of DIAs and DIGs is yet to be known. The presence of primitive small-cell populations that express both glial and neuronal proteins suggest that these cells are progenitor cells to the more differentiated neuroepithelial components and supports the contention that DIAs and DIGs are embryonal neoplasms programmed to progressive maturation (42,155). Origination from the specialized subpial astrocytes that form a continuous, limiting basal lamina providing their terminal processes could account for a comparable phenomenon occurring in desmoplastic infantile tumors and for their superficial localization. The lack of genetic alterationsas observed in most diffuse astrocytomas suggests they are not related to these neoplasms (142,143).

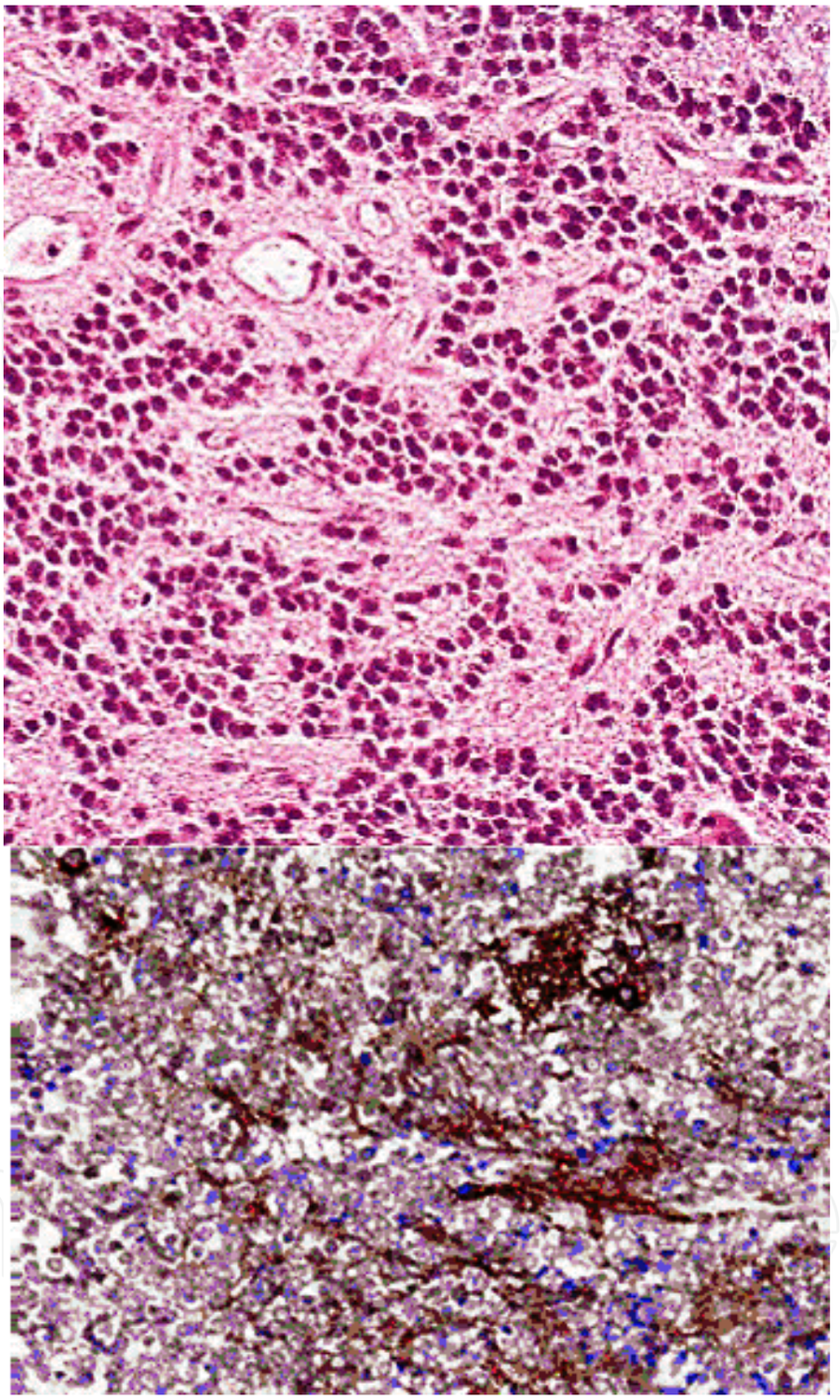

Figure 8. A and B

6.14. Genetics susceptibility

A comparative genomic hybridization study of 3 cases of DIA and DIG revealed no consistent chromosomal gains or losses (150). Molecular studies of DIAs revealed no loss of heterozygosity on chromosomes 10 and 17 and the absence of TP53 mutations (142,152). One

case of DIG showed a loss on 8p22-pter, whereas one case of DIA showed a gain on 13q21. (154).

6.15. Prognostic factors and outcome

Follow-up studies indicate that gross total removal is the treatment of choice. In a study 14 of patients with DIGs (median follow-up, 8.7 years), no mortality or evidence of tumor recurrence was observed (134).. In cases of subtotal resectioning or biopsy, most tumors are stable or recurre slowly. In 1 study, 2 tumors showed radiologic evidence of tumor regression following incomplete resectioning . Dissemination of these tumors through the CSF has been reported but rare,(151,156) Long-term tumor control in cases of DIA and DIG can be achieved by total surgical resectioning despite the presence of primitive-appearing cellular aggregates with mitotic activity or foci of necrosis.. However, tumor evolution has been reported in cases of DIG that underwent subtotal removal , including those with high proliferative indices and anaplastic features (149,157,158)

7. Rosette-forming glioneuronal tumor of the fourth ventricle

7.1. Definition

This type of posterior fossa tumours is a rare and slowly growing neoplasm in the fourth ventricular region, predominantly affecting young adults, and composed of uniform neurocytes forming rosettes or perivascular pseudorosettes and astrocytes mimic pilocytic astrocytoma.

7.2. Grading

The rosette-forming glioneuronal tumor (RGNT) corresponds to WHO grade I (1).

7.3. Synonyms

A neoplasm displaying features of RGNT was early reported as a “dysembryoplastic neuroepithelial tumor (DNT) of the cerebellum” . However, Komori et al. described RGNT as a distinct entity as a variant of mixed glio-neuronal tumor (159,160). Wheares, Preusser et al. confirmed RGNT as a tumor entity (161).

7.4. Age and sex distribution

The age range at disease presentation is 12–59 years (mean, 33 years). With a slight female preference.

7.5. Incidence and localization

RGNT is a rare brain tumor. In five different studies, only 17 cases were reported. These lesions arise in the midline and occupy the fourth ventricle and may be the aqueduct, it may

extend to involve the adjacent brain stem, cerebellar vermis, pineal gland, or thalamus(160,161, 163, 164,165).

7.6. Neuroimaging

MR imaging reveals a relatively circumscribed, solid tumor in the fourth ventricular region, showing low intensity on T1-weighted images and high intensity on T2-weighted images, , and focal or heterogenous gadolinium enhancement. Secondary hydrocephalus is common (164,165) .

7.7. Clinical features

The clinical presentation of RGNT is most often with headache due to of obstructive hydrocephalus, and unsteadiness. Cervical pain is occasionally experienced. Rarely discovered incidentally. **Figure 9**.

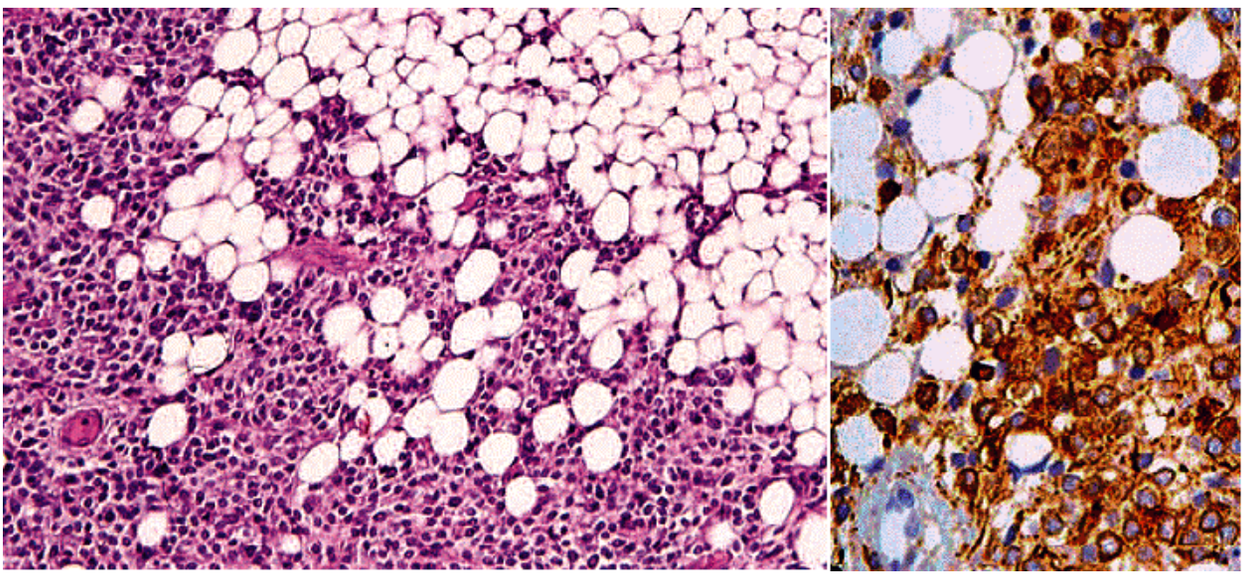

Figure 9.

7.8. Histopathology

RGNTs are well demarcated, but some infiltration into the brain stem and cerebellar parenchyma may be observed. They are characterized by a biphasic neurocytic and glial architecture. The neurocytic component consists of a uniform group of neurocytes. these cells have spherical nuclei with finely granular chromatin, inconspicuous nucleoli, scant cytoplasm, and delicate cytoplasmic processes forming neurocytic rosettes and/or perivascular pseudorosettes. Neurocytic rosettes feature ring-like arrays of neurocytic nuclei surrounding delicate eosinophilic neuropil cores. While the perivascular pseudorosettes feature delicate cell processes radiating toward vessels. The neurocytic rosettes and perivascular pseudorosettes when viewed longitudinally, may show a columnar arrangement.. These neurocytic structures may lie in a partly microcystic, mucinous matrix.

The glial component of RGNT typically dominates, and in some areas may resemble pilocytic astrocytoma. Astrocytic tumor cells are spindle to stellate in shape, with elongated to oval nuclei and moderately dense chromatin. Cytoplasmic processes often form a compact to loosely textured fibrillary background. Rosenthal fibers, eosinophilic granular bodies, microcalcifications, and hemosiderin deposits may be observed. In some areas, the glial component may be microcystic, containing round, oligodendroglia-like cells with some perinuclear halos. Vessels may be thin-walled and dilated or hyalinized. Thrombosed vessels and glomeruloid vasculature may also be noted. The adjacent cerebellar cortex has no features of dysplasia (160,162, 164, 165). **Figure 10A**

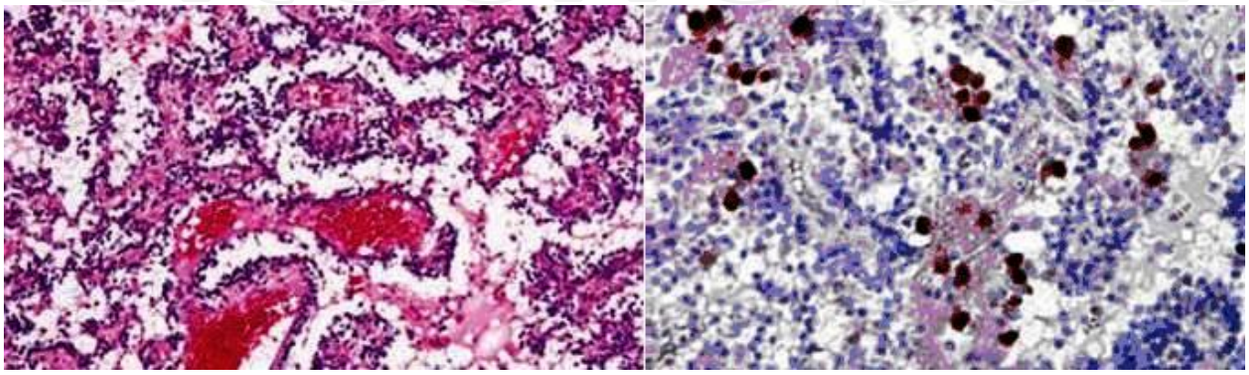

Figure 10. A and B

7.9. Immunohistochemistry

Immunoreactivity for synaptophysin is present at the centers of neurocytic rosettes and in the neuropil of perivascular pseudorosettes.furthermore, the cytoplasm and processes of neurocytic tumor cells may express MAP-2 and neuron-specific enolase. GFAP and S-100 immunoreactivity is shown in the glial part, but absent in the rosettes and pseudorosettes. (160, 162, 164). **Figure 10 B**.

7.10. Proliferation index

Ki-67 labeling indices are low, being less than 3% in reported cases, Mitosis is absent (165).

7.11. Genetic susceptibility

One reported patient with RGNT had a Chiari type I malformation (160). No other evidence of an underlying neurological disorder or association with a familial tumor syndrome has been reported.

7.12. Histogenesis

The histological investigations indicate that RGNTs arise from the brain tissue surrounding the infratentorial ventricular system. An origin of RGNT from the subependymal plate; the remnants of the periventricular germinal matrix has been suggested (160).

7.13. Outcome

The clinical outcome of these primary benign neoplasm is favorable in terms of survival, but disabling cerebellar features postoperatively have been reported in approximately half the cases (160).

8. Papillary glio-neuronal tumor

8.1. Definition

A well circumscribed, clinically insidius and histologically biphasic cerebral neoplasm composed of flat to cuboidal, GFAP-positive astrocytes lining hyalinized vascular pseudopapillae and synaptophysin-positive interpapillary collections of sheets of neurocytes, large neurons, and ganglioid cells.

8.2. Grading

Papillary glioneuronal tumors is corresponding to WHO grade I. late aggressive behavior has been reported (1,165).

8.3. Historical annotation

The papillary glioneuronal tumor, was first established as a distinct clinicopathological entity by Komori et al. in 1998 and listed in the 2000 WHO classification as a variant of ganglioglioma, (166). Some tumors were previously described under a variety of names, including pseudopapillary ganglioglioneurocytoma and pseudopapillary neurocytoma with glial differentiation (167,168).

8.4. Incidence, age and sex distribution

They are very rare neoplasms; and only a few cases have been reported (169.170). These tumors may occur at any age. There is no gender preference. The mean age at presentation is 27 years; the oldest and youngest patient reported was 75 and 4 years, respectively (171,172)..

8.5. Localization

These tumors are generally seen in the cerebral hemispheres, with a predilection for the temporal lobe.

8.6. Neuroimaging

On MRI and CT imaging, the tumors appear as well defined, solid and/ or cystic, with some contrast-enhancement there is usually little mass effect. A cyst-mural nodule architecture may be observed (166, 169.173).

8.7. Clinical features

Mainly headache and seizures. Focal deficits, cognition, and emotional disorder may also be encountered. (174).

8.8. Histopathology and immunohistochemistry

Papillary glioneuronal neoplasms is characterized by a prominent pseudopapillary manner in which a single or pseudostratified layer of small, cuboidal glial cells with rounded nuclei and scant cytoplasm covers hyalinized blood vessels, as well as interpapillary sheets or focal collections of neurocytes, and occasionally ganglion cells or medium-sized ganglioid cells with accompanying neuropil.

At the immunohistochemical level, vessels with mural hyalinization are ensheathed by a layer of small, uniform, GFAP-positive cells with rounded nuclei and scant cytoplasm. In some cases, OLIG2-positive, GFAP-negative glial cells surround this layer. These glial elements lack both nuclear atypia and mitotic activity. Interpapillary neuronal elements show considerable variation in size and shape. all get stained with antisera to synaptophysin, NSE, and class III-tubulin. The majority of neuronal cells are positive for NeuN, but NFP expression is mostly confined to larger ganglioid and ganglion cells. Membranous immunoreactivity for NCAM is also found (166, 172, 175), but chromogranin-A expression is lacking. Minigemistocytes which show intense GFAP immunoreactivity, are occasionally noted in the interpapillary spaces. Microvascular proliferation or necrosis is rare. Even in cases with increased proliferative activity. At the periphery of the lesion, scattered tumor cells are mixed with gliotic brain tissue containing Rosenthal fibers, eosinophilic granular bodies, hemosiderin, and microcalcifications are encountered; this results in a a blurred tumor edge (165, 175). **Figure 11 A.B**

8.9. Electron microscopy

The ultrastructure of few papillary glioneuronal tumors has been studied. Three cell types have been reported: astrocytic; neuronal; and poorly differentiated neurons. Neurons vary in size: large forms with abundant organelles lie between the papillae; their neuronal processes filled with parallel microtubules showed terminations containing clear vesicles and occasional synapses. The poorly differentiated cells contain mitochondria, ribosomes, occasional dense bodies, intermediate filaments and microtubules, but no well-formed dense core granules. Astrocytes contain bundles of intermediate filaments, and are separated from vessels by a basal lamina. Minigemistocytes and OLIG-2-expressing oligodendrocyte-like cells may also be present (165, 166, 171).

8.10. Proliferation index

MIB-1 labeling indices are usually low, in the range of 1–2%. Only 1 tumor featuring minigemistocytes showed an increased (10%) labeling index in that unusual element (165).

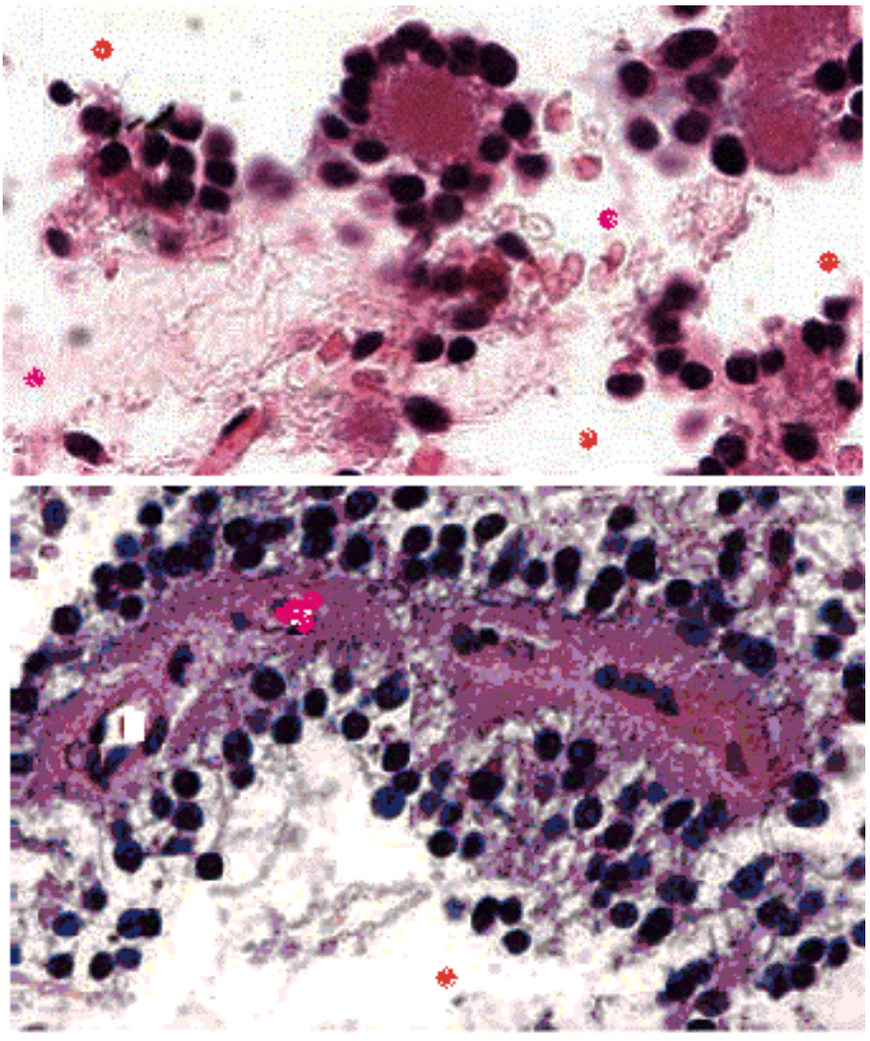

Figure 11. A and B

8.11. Genetic susceptibility

Papillary glioneuronal tumors reported to date have been sporadic in occurrence. (175).

8.12. Histogenesis

The histogenesis of papillary glioneuronal tumors is uncertain, but an origin from multipotent precursors capable of divergent glioneuronal differentiation is supposed. (166).

8.13. Prognosis

The cystic formation, indolent course and low proliferative activity are given a favorable clinical outcome. In most cases, gross total resection without adjuvant therapy is curable with long-term survival. (165).

9. Cerebellar liponeurocytoma

9.1. Definition

A very rare cerebellar neoplasm with variable neuronal, astrocytic, and focal lipomatous differentiation, and low proliferative potential; the tumor usually has a favorable clinical course.

9.2. Grading

Data available advocate that this tumor typically corresponded to WHO grade I (1). However, recurrences have been reported in almost 50% cases, typically without the histological features of malignant transformation. (176).

9.3. Synonyms and historical annotation

Bechtel et al. Reported a case of lipomatous medulloblastoma in a 44-year-old man. in 1978 (177). Subsequently 28 more cases were reported. The terms neurolipocytoma (178), medullocytoma (179), lipomatous glioneurocytoma (180), and lipidized mature neuroectodermal tumor of the cerebellum (181). The WHO Classification in 2000 (1) included the term "cerebellar liponeurocytoma". However, This term is now widely accepted, and is supported by genetic analyses indicating that this lesion is not a variant of medulloblastoma (170). Clinical, histopathological, immunohistochemical, and genetic data strongly suggest that the cerebellar liponeurocytoma comprise a rare but distinct clinico-pathological entity. Some tumors with features of liponeurocytoma have also been observed in supratentorial locations. (182, 183, 184)..

9.4. Age and sex distribution

In the 29 patients with cerebellar liponeurocytoma reported (182, 185, 186, 187,188,189), the mean age was around 50 years (range, 24–77 years), with a peak in the third to sixth decade of life. This is in contrast with the age distribution of cerebellar medulloblastomas, more than 70% of which occur in children (178). There is no significant gender predilection (13 men and 16 women) in patients with cerebellar Liponeurocytoma (186, 187,188,189).

9.5. Clinical features

Non specific symptoms such as Headache and signs of raised intracranial pressure may be the initial presentation, resulting from either the lesion itself or obstructive hydrocephalus. Cerebellar signs are also frequent (188).

9.6. Neuroimaging

MRI appearance is variable, and may be related to the distribution and proportion of lipidized tissue. On T1-weighted MRI, the mass is generally hyperintense but

heterogeneous. Hyperintense streaks on T2-weighted images have been associated with the macroscopic appearance of adipose tissue at surgery. Enhancement with gadolinium is usually irregular. Peritumoral edema is usually absent (,190, 191).

9.7. Localization

These neoplasms are predominantly located in the cerebellar hemispheres, followed by in the vermis. And rarely in the cerebellopontine angle. Raely, liponeurocytomas have been diagnosed in the supratentorial ventricular system at a rate to approximately 3% of central neurocytomas. There are 2 cases of cerebellar neurocytomas without adipose tissue have been reported (182, 185, 192, 193). In 1 case, it was shown that the lipid vacuoles progressively accumulate and coalesce within cells, maintaining neurocytic features, and indicating tumoral lipidization rather than true adipose metaplasia. These observations justify the description of central liponeurocytoma as a separate entity, and these lesions contribute to histogenetic and biological characteristics with cerebellar liponeurocytoma (194, 195,196).

9.8. Histopathology

Biphasic in appearance, the tumor consists of small neuronal cells with the cytology of neurocytes and focal lipomatous differentiation, characterized by lipidized cells resembling mature adipose tissue. Tumor cells have round or oval nuclei, and often show a clear cytoplasm resembling neoplastic oligodendrocytes, but also have many morphological similarities to medulloblastoma and clear cell ependymoma. Despite the cellularity of the lesion, tumor cells have a uniform cytological appearance, with absent or very few mitotic figures and aggressive features. No malignant transformation noted (194, 195,196). **Figure 12A**

9.9. Immunohistochemistry

Neuronal differentiation is observed by a reliable, diffuse expression of NSE, synaptophysin, and MAP-2. Accordingly, several reported cases were diagnosed as neurocytoma or neuroblastoma, rather than medulloblastoma. Focal GFAP expression by tumor is also seen, indicating astrocytic differentiation (184). Immunoreactivity for neuronal markers and GFAP is also seen in the adipose cells, indicating an abnormal differentiation of tumor cells rather than an entrapped adipocytes. It is crucial to note that xanthomatous histiocytes, as are occasionally observed in ordinary medulloblastomas, are not considered evidence of lipomatous differentiation. Two reports mention additional immunoreactivity to desmin, and morphological features of incipient myogenic differentiation (177,181). **Figure 12 B**

9.10. Differential diagnosis

The most important differential diagnosis is medulloblastoma with lipidized cells. The distinction between these 2 lesions is crucial, since medulloblastomas with lipidized cells

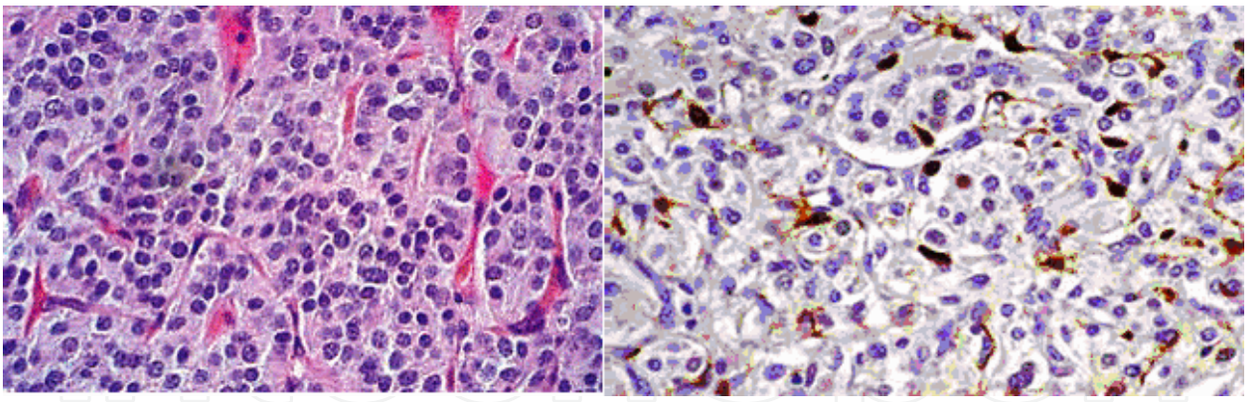

Figure 12.

require adjuvant radio/chemotherapy. Most importantly, the growth fraction is in the range of 15–40%, which is incompatible with a diagnosis of liponeurocytoma. Cerebellar liponeurocytoma is a neoplasm of adults, while lipidized medulloblastomas also occur in children (186, 188, 197, 198, 199). The liponeurocytomas may also mimic neoplastic oligodendrocytes and clear cell ependymoma (199).

9.11. Proliferation index

The Ki-67/ MIB-1 labeling index, is usually in the range of 1–3%, but may be as high as 6%, with a mean value of 2.5% . In the adipose component, the MIB-1 labeling index is even lower (184, 200).

9.12. Histogenesis

An origin from the external granular layer of the cerebellum cannot be ruled out, Immunoreactivity to neuronal antigens and GFAP includes cell bodies embracing fat globules. This suggests that the fat-containing cells result from lipomatous differentiation of tumor cells. The cell of origin is most likely a precursor cell with a preferential commitment to neuronal differentiation. (184,185,200).

9.13. Genetics susceptibility

Genetic analysis of 20 cerebellar liponeurocytomas revealed TP53 missense mutations in 4 cases (20%), a frequency significantly higher than that in medulloblastomas (6%). There was no case with a PTCH, APC, or ß-catenin mutation, each of which can be present in subsets of medulloblastomas. FISH analysis showed that isochromosome 17q, a genetic hallmark present in 40% of cerebellar medulloblastomas, was not enountered in any of the cases investigated. This finding supports the view that the cerebellar liponeurocytoma is a distinct entity and not a variant of medulloblastoma. cDNA expression profiles showed a relationship to central neurocytoma, but the presence of TP53 mutations, which are absent in central neurocytomas, suggests that they develop through different genetic pathways (182).

9.14. Prognostis

A review of published cases indicates that this lesion generally carries a favorable prognosis. Because of the rarity of this tumor and the lack of systematic follow-up data, survival and recurrence rates must be interpreted with some caution (182, 185).

Of 21 patients with follow-up data, 6 (29%) died within 6 months to 2 years, 5 (24%) died after 2–4 years and 10 (48%) survived 5–16 years after surgical intervention. The 5-year survival rate was 48% and the mean overall survival was 5.8 years. However, 62% of patients developed a recurrence from 1 to 12 years, and in 3 patients there was a second relapse 1 to 5 years later. Despite its aggressive course there is no malignant transformation observed. (176).

10. Filum terminale and spinal paraganglioma

10.1. Definition

A distinctive neuroendocrine neoplasm, usually encapsulated, slowgrowing, and benign, arising from specialized neural crest cells associated with segmental autonomic ganglia (paraganglia); it is composed of uniform chief cells displaying neuronal differentiation and forming compact nests (Zellballen), surrounded by sustentacular cells and a delicate capillary network. This type of neoplasm is mostly affecting the cauda equine and filum terminale

10.2. Grading

Paragangliomas of the cauda equine/filum terminale correspond histologically to WHO grade I (1).

10.3. Synonyms and historical annotation

The early terminology of paragangliomas is not well known. Early authors divided them into chromaffin and nonchromaffin on the basis of their reaction with chromic acid. However, since this reaction does not reliably reflect their functional activity, current terminology is based upon anatomical location as seen in carotid body paraganglioma (chemodectoma), jugulotympanic paraganglioma (glomus jugulare tumor).

10.4. Incidence and location

Paragangliomas of the CNS are infrequent, the vast majority present as lumber spinal intradural tumors in the cauda equina region. Since the first description of cauda equina region paraganglioma in 1970 (201), more than 210 cases have been reported. And 174 cases reported prior to 2003 (202). Paragangliomas of the cauda equine region comprise 3.4% to 3.8% of all tumors affecting this region (203, 204). Other spinal levels are involved far less often; 14 paragangliomas were reported in the thoracic region, most being extradural with

an intravertebral and paraspinal component (205, 206), and 2 tumors involved the cervical region (207, 208).

Intracranial paragangliomas are usually located in the posterior fossa; jugulotympanic paragangliomas (209). However, intracranial tumors have also been described. These locations include sellar region, the cerebellopontine angle, cerebellar parenchyma, and the fronto-temporal lobes (210, 211, 212, 213).

10.5. Age and sex distribution

Cauda equina paragangliomas generally affect adults. Patient age ranges from 9 to 74 years (mean, 46 years), with a slight predominance in males with Male:Female ratio at 1.4:1. Jugulotympanic paragangliomas are more common in Caucasians, with a strong female preference, and occur mainly in the fifth and sixth decades (209).

10.6. Clinical features

The most common presenting symptoms include a long standing history of low-back pain and sciatica. Sensory deficit, paraparesis, and sphincter disturbances are common in the later stage, while complete cauda equina syndrome is rare. An intracranial hypertension symptoms and signs was reported in 8 cases. Only 3 endocrinologically functional paragangliomas of the cauda equine region have been reported (214, 215, 216). The few reported paragangliomas of the thoracic spine presented with short term of signs of spinal cord compression (217). About 36% of glomus jugulare paragangliomas extend into the cranial cavity and produce headache, pulsatile tinnitus and lower cranial nerve involvement; rarely, signs of catecholamine secretion may be seen (209).

10.7. Neuroimaging

Cauda equina paragangliomas has no specific features. Most appear as isodense, homogeneously enhancing masses on CT. However, since CT without contrast may miss the lesion, MRI is the investigation of choice. MRI images typically show a well marked, may be with cystic component mass that is hypo- or isointense to spinal cord on T1-weighted images, with a vivd contrast enhancemnet. It appears as hyperintense on T2-weighted images. The presence of ecstatic and dilated vessels and a low signal intensity rim (“cap sign”) on T2-weighted images are considered diagnostically important feature. Plain radiographs are usually helpful, and show some scalloping of the vertebral bod y due to chronic bone compression (204, 218). **Figure 13**

10.8. Histopathology

Tumors are well differentiated, mimicking normal paraganglia, nearly half of cauda equina paragangliomas contain mature ganglion cells, as well as cells transitional between chief and ganglion cells. These lesions are composed of chief (type I) cells disposed in nests or lobules

(Zellballen pattern), and surrounded by a single layer of sustentacular (type II) cells. The Zellballen are surrounded by a delicate capillary network that may undergo sclerosis. The uniform round or polygonal chief cells possess central, round-to-oval nuclei, with finely stippled chromatin and inconspicuous nucleoli. Cytoplasm varies somewhat in quantity and is usually eosinophilic and finely granular. In some conditions, it is amphophilic or clear. Sustentacular cells are spindle-shaped. Encompassing the lobules, their long processes are often so attenuated that they are undetectable by routine light microscopy, and visible only on immunostains for S-100 protein. (219). Such "gangliocytic paragangliomas" are also found in other sites such as the duodenum and are analogous to phaeochromocytoma with neuronal differentiation. Some paragangliomas of the cauda equina region show architectural features similar to carcinoid tumors, including angiomatous, adenomatous, and pseudorosette patterns. Tumors composed predominantly of spindle and melanin-containing cells (melanotic paragangliomas) have also been described at this site, as has oncocytic paraganglioma (220, 221, 222). hemorrhagic necrosis may also occur, and scattered mitotic figures can be seen. these features are not of prognostic implication (223). **Figure 14A**

10.9. Immunohistochemistry

Chief and sustentacular cells can be identified by biomarkers. Chief cells are marked with Neuron-specific enolase (NSE), synaptophysin and chromogranin (228, 229). Chromogranin A reactivity parallels the Grimelius (argyrophil) reaction (219, 223,224). Neurofilament proteins are also useful markers of chief cells. Expression of serotonin (5H-T) and of various neuropeptides (somatostatin, leu, and metenkephalin) has been demonstrated in paraganglioma of the cauda equina region. Paranuclear cytkeokeratin immunoreactivity is particularly prominent in cauda equina examples. Sustentacular cells are uniformly reactive for S-100 protein, and usually show staining for glial fibrillary acidic protein (GFAP). Chief cells may also show variable S-100 immunoreactivity (220, 223, 225). **Figure 14B**

10.10. Electron microscopy

The characteristic ultrastructural features of chief cells is the presence of dense core (neurosecretory) granules measuring 100 to 400 nm (mean, 140 nm). Depending on their cytoplasmic electron density, "light" and "dark" chief cells are recognized. A layer of basal lamina is present at the interface of Zellballen and surrounding stroma. In addition to well-developed Golgi, extensive smooth endoplasmic reticulum, and lysosomes, chief cells may contain numerous atypical mitochondria, as well as paranuclear whorls of intermediate filaments (223, 226). Sustentacular cells are characterized by an elongated nucleus with marginal chromatin, increased cytoplasmic electron density, relative profusion of intermediate filaments, and low core granules (225, 226, 227).

10.11. Genetics susceptibility

It is not clear, there is no reported association of spinal paragangliomas with genetic abnormalit. However, Systemic paragangliomas may be multifocal, The association of spinal

paraganglioma with brain tumors, spinal epidural haemangioma, syringomyelia, and intramedullary cysts are encountered (228, 229, 230, 231), but these associations may be coincidental. Several autosomal dominant inherited syndromes predispose to paraganglioma or phaeochromocytomaas noted in von Hippel- Lindau disease (VHL); multiple endocrine neoplasia type 2 (RET mutations); neurofibromatosis type 1 (NF1). Multiple, benign, head and neck paragangliomas are often caused by SDHD mutations, while SDHB mutations are associated with phaeochromocytoma. There are only 4 families with the SDHC mutation have been identified. Spinal paragangliomas are considered non-familial, but a study of 22 spinal paragangliomas showed an SDHD germline mutation in 1 patient with recurrent spinal paraganglioma and a cerebellar metastasis (232).

10.12. Histogenesis

The histogenesis is unknow. Some authors favor an origin from paraganglion cells associated with regional autonomic nerves and blood vessels (233). Others have suggested that peripheral neuroblasts usually present in the adult filum terminale may undergo paraganglionic differentiation (229). Jugulotympanic paragangliomas presumably arise from microscopic paraganglia within the temporal bone. Some interesting cases have reported the coexistence of a paraganglioma and myxopapillary ependymoma in the cauda equina region (234, 235).

10.13. Prognostic factors

Tumor location is the most important predictive prognostic factor rather than histology of paragangliomas. For instance, the metastasis rate of para-aortic paraganglioma is high (28 to 42%), whereas that of carotid body tumors is only 2 to 9% (236). About 50% of the glomus jugulare tumors recur locally, but only 5% with distant metastastases (234, 237). The tumor vascularity has no significant value. The vast majority of cauda equina paragangliomas are slowly growing and curable by total excision. Based on long-term follow-up, it is estimated that 4% will recur following gross total removal (238, 239). Metastasis outside the CNS is rare (220). CSF seeding of spinal paragangliomas has been reported (240).

11. Conclusion

CNS neuroepithelial and neuronal tumours are usually benign and slow growing neoplasms with WHO grade I-II. They comprise a low percentage of the whole CNS neoplasms and may affect any part of the CNS. These lesions present with non specific symptoms and signs; but tend to cause intractable epilepsy when affecting the cerebral cortex. Along with clinical presentation and neuroimaging; the histopathology and immunochemistry confirm the diagnosis. Surgical resctioning is the treatment of choice with favorable prognosis and long term cure; adjuvant treatment is preserved to recurrent tumours or to high grade lesions

12. Table of summary

	Location	WHO	Type of cells	Specific features	prognosis
Ganglioglioma and Gangliocytoma	Throughout the CNS more common in Supratentorial. Temporal lobe predilection	Grade I Garde III	Immature ganglion cells and/ or astrocyte	Large neoplastic ganglion cells with/without glial components	Low grade favorable Higher grade : variable
Central Neurocytoma and extraventricular Neurocytoma	Supratentorial. Paraventricular	Grade I-II	Uniform ferentiated neurocyte	Oligodendroglioma-like honeycomb appearance, irregular "rosettes" perivascular pseudorosettes	Favorable
Dysembryoplastic Neuroepithelial tumour	Temporal lobe and mesial region	Grade I	glio-neuronal constituent	columns formed by bundles of axons lined by small oligodendroglia-like cells	Favorable
DIA , DIG	Supratentorial with frontal and parietal lobes predilection	Grade I	desmoplastic leptomeningeal, poorly differentiated neuroepithelial cells	Astrocytes are the main tumor-cell in DIAs. immature neurons in DIGs	Favorable
RGNT	4th ventricle and aqueduct cerebellar and brain stem	Grade I	a biphasic neurocytic and glial architecture.	The neurocytic rosettes ,perivascular pseudorosettes.	Favorable
Papillary Glio-neuronal tumour	Temporal lobe	Grade I	small, cuboidal glial cells,collections of neurocytes,and occasionally ganglion cells	pseudopapillary manner and pseudostratified layer of small, cuboidal glial cells, interpapillary sheets collections of neurocytes, ganglion cells.	Favorable
Cerebellar Liponeurocytoma	Cerebellar hemisphere , vermis CP angle, rarely supratentorial	Grade I	small neuronal cells with focal lipomatous differentiation,	small neuronal cells with the cytology of neurocytes and focal lipomatous cella, resembling mature adipose tissue	Favorable
Filum terminale and spinal paraganglioma	Cauda equine region. Jugulotympaniirial arely supratento	Grade I	mature ganglion cells, transitional cells between chief and ganglion cells	mature ganglion cells, cells transitional cells. Chief (type I) cells disposed in nests or lobules (Zellballen pattern) surrounded a delicate capillary network, and sustentacular (type II) cells.	Favorable

Table 1. Summary

Author details

Mohammed M.A. Al Barbarawi
Section of Neurosurgery, Department of Neuroscience, Faculty of Medicine, Jordan University of Science & Technology, Jordan

Mohammed Z. Allouh
Department of Anatomy, Faculty of Medicine, Jordan University of Science & Technology, Jordan

Suhair M.A. Qudsieh
Clinical department, Faculty of medicine, Hashemite University, Jordan

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