Glioneuronal Tumors

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J.-C. Tonn et al. (eds.), *Oncology of CNS Tumors,*
DOI: 10.1007/978-3-642-02874-8_11, © Springer-Verlag Berlin Heidelberg 2010

11.1 Neuronal and Mixed Neuronal–Glial Tumors

Neuronal and mixed neuronal–glial tumors are thought to arise from neuroepithelial cells. According to the 2007 WHO classification, this group of tumors comprises ganglioglioma and gangliocytoma, desmoplastic infantile astrocytoma (DIA) and ganglioglioma, dysplastic cerebellar gangliocytoma (Lhermitte–Duclos disease), dysembryoplastic neuroepithelial tumor (DNT), central neurocytoma, cerebellar liponeurocytoma (CLN), paraganglioma of the cauda equina (PCE), and the more recently recognized subtypes papillary glioneuronal tumor, rosette-forming glioneural tumor of the fourth ventricle and extraventricular neurocytoma [31]. These tumors are composed of cells with a neuronal differentiation, sometimes accompanied by a second cellular component with a glial phenotype. In general, the cells of both lineages are well differentiated. Some of these tumors may be associated with cortical dysplasias. Neuronal and mixed neuronal–glial tumors usually carry a favorable prognosis.

Neuronal and mixed neuronal–glial tumors are rare. In a series of 4,076 consecutive adult and pediatric patients with intracranial tumors undergoing surgery (including epilepsy surgery) at our institution, neuronal and mixed neuronal–glial tumors were diagnosed in only 254 (6.2%) patients (Table 11.1).

Table 11.1 Prevalence of neuronal and mixed neuronal–glial tumors in our series of adult and pediatric patients surgically treated for intracranial tumors from January 1992 to June 2004, including epilepsy surgery. Numbers kindly provided by Prof. Dr. T. Pietsch and Prof. A. Becker, Institute of Neuropathology, University of Bonn

	n	%
Neuronal and neuronal–glial tumors (6.2% of total)		
Gangliogliomas	181	71.0
Anaplastic gangliogliomas	4	1.6
Desmoplastic infantile gangliogliomas	1	0.4
Gangliocytomas	2	0.8
Dysplastic cerebellar gangliocytomas	1	0.4
Dysembryoplastic neuroepithelial tumors	51	20.1
Central neurocytomas	4	1.6
Cerebellar liponeurocytomas	0	0.0
Paragangliomas of the filum terminale	10	3.9
Total	254	100.0
Frequent intracranial tumors (93.8% of total)		
Gliomas	1,253	32.7
Meningiomas	1,111	29.0
Metastases	607	15.8
Pituitary adenomas	482	12.6
Neurinomas	266	6.9
Ependymomas/subependymomas	59	1.5
Lymphomas	44	1.1
Subtotal	3,822	100.0
Total	4,076	

11.2 Ganglioglioma and Gangliocytoma

11.2.1 Epidemiology

Ganglioglioma (GG) is the most frequent neoplasm within the group of neuronal and mixed neuronal–glial tumors. The incidence is 0.3–5.2% in large adult brain tumor series and up to 14% of intra-axial tumors in pediatric patient cohorts [8, 22, 33, 51]. In our series of 4,076 patients with intracranial tumors, GGs were diagnosed in 4.4% of cases. In pediatric series, the mean age at diagnosis is at the end of the first decade, while in adult patient series, it is in the third decade. Anaplastic GGs may occur more often in older patients when compared to their benign counterparts [8]. GGs are diagnosed slightly more often in males than in females.

Gangliocytoma (GC) is clinically, radiologically, and histologically closely related to GG. GCs are rare tumors. In the above-mentioned series of 4,076 consecutive patients with surgically treated intracranial tumors, we encountered only two GCs (but 181 GGs). GCs are usually diagnosed in children and young adults.

11.2.2 Symptoms and Clinical Signs

GGs may occur throughout the CNS. The vast majority are located in the supratentorial compartment, with a preference for the temporal (and frontal) lobe. Infratentorial and spinal GGs are rare. We have recently analyzed a series of 203 supratentorial GGs. The tumor was located in the temporal lobe in 76% and in the frontal lobe in 10% of cases. A non-temporal tumor location has been associated with histological atypia and anaplasia, and an adverse clinical course [34].

GGs present with epileptic seizures in 85–97% of the cases. Long-standing pharmacoresistant epilepsy is frequent [20, 33]. Eighty-five percent of cases in the series from our institution reported by Luyken et al. presented with long-term (≥2 years) epilepsy (median 12, range 2–45 years) [33]. Drug-resistant epilepsy is less frequent in patients with histologically atypical and anaplastic tumors [34]. Focal neurological deficits are rare in supratentorial GGs. Due to their location, infratentorial and spinal GGs will manifest more often with focal neurological deficits and increased intracranial pressure. The duration of preoperative symptoms is usually shorter (months to a few years) than in supratentorial GGs [29, 40]. This is also true for cases with histologically atypical and anaplastic GG.

GCs most commonly occur in the cerebral hemispheres, especially the temporal lobes. They often present with long-standing epilepsy [11, 26, 52]. GCs of the spinal cord, hypothalamus, and pineal gland have been described. Pituitary GCs may deserve some special mention. They grow more often in the anterior than in the posterior lobe and are quite frequently associated with pituitary adenomas. The clinical presentation is that of a pituitary adenoma. In some cases of coexisting intrasellar GC and pituitary adenomas, the "GC" may simply consist of a collection of adenoma cells with a neuronal differentiation. In others, the association between a GH/PRL-producing adenoma and a GC may be a causal one. Some data suggest that chronic overstimulation of the pituitary by a GH-releasing hormone producing GC may result in adenoma formation [16, 28, 42, 52].

11.2.3 Diagnostics

The majority of GGs are hypo- to isointense on T1-weighted MRI (90%) and hyperintense on T2-weighted images (70%). Tumor cyst formation occurs in 30–50% of the cases. The classic MRI pattern of GG, i.e., a cystic mass with a solid mural nodule, is found in about 40% of cases. Contrast enhancement of the solid portion is variable and occurs in 35–50% of tumors. The non-enhancing tumor component involves the cerebral cortex as well as white matter and is delineated best on FLAIR images. Usually there is little mass effect and no peritumoral edema (Fig. 11.1). MRI does not allow for a reliable differentiation between benign and non-benign GG. An uncharacteristic MRI appearance and perifocal edema may be more frequent in histologically atypical and anaplastic GG [34]. CT discloses tumor calcifications in 30–50% of the cases. Pressure erosions of the overlying calvaria may be present [52].

GC and GG are usually indistinguishable on MRI and CT. Some GCs may present with a dural tail mimicking a meningioma [52].

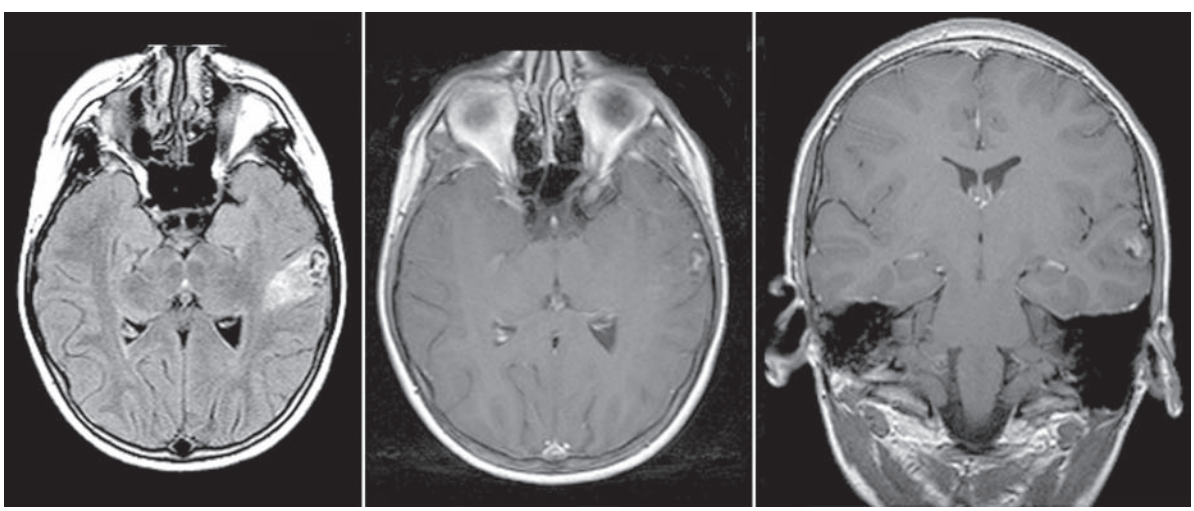

Fig. 11.1 Ganglioglioma of the left temporal lobe. The tumor is hyperintense and partially cystic on proton-weighted images (*left*). On T1-weighted images the mural module within the cyst is contrast enhancing (*middle* and *right*). There is little mass effect and no peritumoral edema

11.2.4 Staging and Classification

GGs are composed of dysplastic ganglion and glial (usually astrocytic, rarely oligodendrocytic) tumor cells. The histopathological differential diagnosis can pose significant challenges and includes both high- and low-grade neoplasms, such as diffuse astrocytomas, oligodendrogliomas, dysembryoplastic neuroepithelial tumors (DNT), pilocytic astrocytomas (PA), and pleomorphic xanthoastrocytomas (PXA). Tumors misdiagnosed, e.g., as low-grade gliomas by a less experienced pathologist, are not infrequently encountered. GCs are composed of large and often dysplastic ganglion cells located in a stroma consisting of non-neoplastic glial cells [6].

The recently revised WHO classification distinguishes only between GG WHO grade I and the rare anaplastic variants corresponding to WHO grade III. Data from our institution are more in line with the 2000 WHO classification and support a three-tiered grading system, i.e., the inclusion of an intermediate diagnostic category (atypical GG WHO grade II). In a series of 203 patients, GG WHO grade I accounted for 87%, histologically atypical GG for 10%, and WHO grade III tumors for 3% of the cases [34]. GGs may evolve into secondary glioblastomas. Histologically confirmed progression into a glioblastoma was seen in 5/203 (2.5%) cases at our institution (but 5/11 = 45% of patients undergoing surgery for recurrent tumors) [34]. GGs are not infrequently associated with cortical dysplasias [6, 20, 33]

GCs are assigned to the WHO grade I.

11.2.5 Treatment

Surgery. Complete resections of supratentorial GGs/GCs can be achieved in >75% of cases [33, 34]. Tumor growth in the insula and basal ganglia may preclude a complete resection. Clinically relevant regrowth after a subtotal resection is rare. In the large series reported by Luyken et al. [33], a subtotal resection was performed in 21% of the tumors. After a median follow-up of 8 years, a repeat operation was deemed necessary in only 8%, including two patients with WHO grade III recurrences. These data support a conservative surgical approach to GGs in eloquent areas, including an attempt at preserving the optic radiation in temporal tumors. In contrast, recurrence rates of 33% and 60% after surgery for histologically atypical GG and GG WHO grade III justify aggressive cytoreduction in such cases [34]. The degree of resection proved a powerful predictor of recurrence in the GG series reported by Im et al. [20] and in the cohort of atypical and anaplastic GGs described by Majores et al. [34].

Surgical morbidity and perioperative mortality are low in patients with supratentorial intraaxial GG/GC. Surgical morbidity mainly reflects tumor location. Visual field cuts are often inevitable in temporal lobe surgery. Surgery for insular tumors carries a significant risk for hemiparesis and aphasia. Radical surgery is rarely if ever possible for brain stem GG. Gross total tumor removal for spinal GG is reported in up to 80% of the cases [29, 40]. Risks and complications of transsphenoidal surgery for sellar GC parallel those seen in pituitary adenoma surgery.

Radiotherapy. There is probably no indication for radiotherapy after surgery for a GC or GG WHO grade I, and after complete resections of histologically atypical GGs. Radiotherapy has been linked to malignant transformation and will not routinely cure GG [48, 51]. Postoperative radiotherapy should be prescribed for patients with anaplastic GG WHO grade III.

Chemotherapy. A role for postoperative chemotherapy of GG/GC has not been established yet. Anectodal experience suggests its use in selected cases of anaplastic and recurrent GG [22, 34].

11.2.6 Prognosis/Quality of Life

In the series of 184 supratentorial GGs reported by Luyken et al., the 7.5-year recurrence-free survival was 97%. Lower recurrence rates were associated with WHO grade I, complete tumor removal, temporal location, and a long-standing history of seizures [33]. These data could be confirmed in a more recent analysis of our institutional experience focusing on higher grade GG. Five-year overall survival was 79% and 70%, and recurrence-free survival was 53% and 30% for histologically atypical GG and GG WHO grade III [34]. Variable recurrence rates (0–40%) have been reported in smaller series [20, 51]. Malignant transformation may occur in a significant number of patients as pointed out above [20, 33, 34]. Subarachnoid seeding has been reported in a few cases. Malignant progression accounted for all tumor-related deaths in the series by Majores et al. [34]. Overall, death due to progressive GG has been reported in 2–9% of patients [22, 33].

Quality of life after surgery for supratentorial GG/GC is good in the majority of cases. Symptomatic epilepsy will be cured by a tumor resection (and additional resection of perilesional tissue if required) in >80% of patients [33]. In patients with pharmacoresistant epilepsy, a presurgical epileptological evaluation is mandatory. Persistent and recurrent epilepsy may be due to incomplete tumor resections and the presence of additional cortical dysplasia [20, 33].

The prognosis for brain stem GG is good despite the fact that surgery is rarely if ever radical. Survival for up to 10 years without disease progression has been reported [29]. Recurrence rates of spinal GG are thought to be much higher (up to 27%) than those of cerebral GG. Malignant transformation of spinal GG has been described [40].

Prognosis after surgery for sellar GC is generally good and usually reflects the prognosis of the associated pituitary pathology [16, 28, 42, 52].

11.3 Papillary Glioneuronal Tumor

11.3.1 Epidemiology

The papillary glioneuronal tumor has been listed as a variant of ganglioglioma in the 2000 WHO classification. The 2007 WHO classification lists this tumor subtype as a distinct entity. A recent review identified only 37 cases reported in the literature to date. Tumors generally grow in the cerebral hemispheres with a predilection for the temporal lobe. Age at presentation varies, but most cases have been diagnosed in young adults. Both sexes seem equally affected [24, 60].

11.3.2 Symptoms and Clinical Signs

Typical clinical manifestations include seizures and headache. Unspecific (headaches) and asymptomatic presentations may be more frequent than in GG [24, 60].

11.3.3 Diagnostics

Neuroimaging features resemble those of GG. Periventricular (lateral ventricle) growth and lack of cortical involvement may be common [3, 24, 60].

11.3.4 Staging and Classification

Most tumors are benign and have been assigned to the WHO grade I. Cases with high proliferative activity and atypical histological findings have been reported [36, 47, 59, 60].

11.3.5 Treatment

Surgery. Gross total resections will usually result in long-term recurrence-free survival [36, 60].

Radiotherapy and Chemotherapy. Postoperative radiotherapy has been administered in a few cases (and chemotherapy in even fewer patients) with atypical histological findings and/or recurrence [47, 59].

11.3.6 Prognosis/Quality of Life

The prognosis and the postoperative quality of life of patients with papillary glioneuronal tumors is probably very similar to that of patients with ganglioglioma [36, 60].

11.4 Desmoplastic Infantile Ganglioglioma/Astrocytoma

11.4.1 Epidemiology

Desmoplastic infantile ganglioglioma (DIG) and astrocytoma (DIA) are rare supratentorial (most often frontoparietal) tumors. The majority of DIAs/DIGs occur within the first year of life. Tumors are diagnosed slightly more often in males [10, 57]. We observed one patient with a DIG in a series of 4,076 intracranial tumors in adult and pediatric patients.

11.4.2 Symptoms and Clinical Signs

DIAs/DIGs tend to be diagnosed following a short history of signs and symptoms of increased intracranial pressure, including an abnormal increase of head

circumference, tense fontanelles, drowsiness, poor feeding, and setting-sun sign. Focal neurological deficits and seizures may occur [10, 57].

11.4.3 Diagnostics

DIAs/DIGs are usually very large tumors involving the cerebral cortex and overlying dura. They typically consist of a cystic, often septated component oriented towards the brain and a solid part attached to the cortex and dura. The cysts are hypointense on T1-weighted images and hyperintense on T2-weighted scans. The solid part of the tumor is usually heterogenous (mostly isointense) on T1- and T2-weighted images. Contrast enhancement of the solid part is intense and extends to the adjacent meninges. The cyst walls do not enhance. Peritumoral edema is not present. Entirely solid tumors with variable enhancement have been reported [52, 56]. CT does not provide additional information, and calcifications have not been described.

11.4.4 Staging and Classification

DIGs are composed of neoplastic astrocytic and ganglion cells embedded in a prominent desmoplastic stroma. Poorly differentiated neuroepithelial cells that may show foci of mitosis and necrosis are also present. The presence of this latter cell population does not alter the generally favorable prognosis of this tumor. Tumors without a neoplastic ganglion cell population are termed desmoplastic infantile astrocytoma (DIA). DIG and DIA both correspond to WHO grade I [10].

11.4.5 Treatment

Surgery. Surgery of these tumors is often challenging. The patients may be very young, and the tumors are usually large, often involve eloquent brain areas, and may adhere to venous sinus walls. Thus, complete tumor removal is not always possible, and surgical morbidity may be high [54].

Radiotherapy and Chemotherapy. Chemotherapy may be indicated in recurrent and progressive residual tumors if they are not amenable to repeat surgery. Radiotherapy has been advocated in children who failed chemotherapy and who are over 5–6 years of age [5, 54].

11.4.6 Prognosis/Quality of Life

Gross total tumor removal results in long-term survival documented for up to 2 decades. Patients with incomplete tumor resection have also been followed for years without progression of residual tumor [10]. Notably, in some patients spontaneous regression of residual DIA/DIG after incomplete tumor removal has been observed [54]. Isolated cases of DIA/DIG with a malignant clinical course have been reported [5, 19].

11.5 Dysplastic Cerebellar Gangliocytoma (Lhermitte–Duclos)

11.5.1 Epidemiology

Dysplastic cerebellar gangliocytoma (Lhermitte–Duclos) (DCGC) is a very rare cerebellar mass lesion, representing the major CNS manifestation of the phakomatosis termed Cowden disease. Cowden disease is caused by mutations of the PTEN gene. In our series of 4,076 patients with surgically treated intracranial tumors, including 254 neuronal and glioneural tumors, a DCGC was diagnosed in only 1 patient.

Adult-onset DCGC is considered pathognomonic for Cowden disease. In one series, 3 of 20 patients with Cowden disease were diagnosed with a DCGC by MRI [30]. Importantly, further manifestations of Cowden disease include multiple hamartomas of tissues derived from all three germ cell layers (in particular trichilemmomas, cutaneous keratoses, oral papillomas, and gastrointestinal polyps), but also an increased risk to develop breast (25–50% of all female patients!), thyroid (10%), endometrial, and other cancers [14, 38, 46].

Autosomal dominant transmission is seen in some cases, but most DCGCs probably arise de novo [14]. DCGCs may occur at any age, but are most common in the third to fifth decades of life. There is no gender predilection [14]. The failure to detect PTEN mutations in a number of pediatric patients may suggest a different biology (and possibly different clinical course) in such cases [14, 46].

11.5.2 Symptoms and Clinical Signs

At the time of diagnosis of DCGC, Cowden disease is present in 50–90% of the patients. The diagnosis of DCGC may precede the diagnosis of Cowden disease by years [14, 58]. Patients usually present with long-standing (mean 3–4 years) symptoms. Signs and symptoms of increased intracranial pressure are seen in 60–70%, cerebellar dysfunction in 50%, and cranial nerve deficits in 30% of the patients [14, 30, 38, 46].

11.5.3 Diagnostics

MR imaging shows a cerebellar hemispheric mass with a characteristic hypointense or isointense striated ("tiger-striped") pattern on T1- and isointense or hyperintense striated pattern on T2-weighted images corresponding to enlarged cerebellar folia (see below). The mass itself does not enhance (albeit patchy enhancement has been reported in a few cases). Some cases may show superficial linear enhancement of cerebellar veins. Lesions are hyperintense on diffusion-weighted images and isointense on diffusion-coefficient maps. This pattern is diagnostic and may obviate the need for a biopsy in asymptomatic patients. There is no perifocal edema [30, 38, 46].

CT shows a hypodense or mixed hypo-/isodense mass. The characteristic striated pattern of the lesion observed on MRI is not obvious on CT. Scattered calcifications may be present [52]. Concomitant CNS manifestations include megalencephaly, grey matter heterotopias, hydrocephalus, syringomyelia, cavernomas, and venous angiomas [14, 30, 38, 46].

11.5.4 Staging and Classification

DCGCs consist of an outer layer of abnormally myelinated axons originating in an inner layer of dysplastic and disorganized neurons. The proliferative activity is very low. Due to these changes, the folia of the cerebellum are dysmorphic and thickened. It is not entirely clear whether the DCGC is of hamartomatous or true neoplastic nature. MR spectroscopy and PET imaging have produced conflicting data consistent with a hamartoma on the one hand, but also pointing to a neoplastic nature of the lesion [14, 30, 38, 46]. DCGCs have been assigned to the WHO grade I. DCGCs usually involve only one cerebellar hemisphere, but bilateral and multifocal growth has been described.

It seems mandatory to evaluate and follow patients with DCGC for other manifestations of Cowden disease, in particular for breast, thyroid, and other cancers.

11.5.5 Treatment

Surgery. Due to their superficial cerebellar location, DCGCs are easily accessible. Poorly defined borders constitute the major technical issue during surgery. Incomplete resection of the lesion is thus not unusual [38]. Additional surgery for hydrocephalus control may be required.

Radiotherapy and Chemotherapy. Radiotherapy has been performed in a few patients with contradictory results. The low proliferative potential of DCGC and the underlying generalized tumor predisposition rather argue against the use of radiotherapy in patients with DCGC [14, 38, 46].

11.5.6 Prognosis/Quality of Life

The prognosis of DCGC is good. Even following incomplete resections, recurrence-free survival for up to 4 years has been described. Tumor recurrence requiring repeat surgery may be seen [38]. Malignant transformation has been described [53]. The patients' prognosis will be limited much more often by other neoplastic manifestations of Cowden disease (i.e., thyroid, breast, endometrial, and other malignancies) [14, 38, 58].

11.6 Dysembryoplastic Neuroepithelial Tumor

11.6.1 Epidemiology

Dysembryoplastic neuroepithelial tumor (DNT) is the second most common neuronal and neuroglial tumor. In our series of 254 neuronal and neuroglial tumors, DNTs were diagnosed in 20.1% of the cases. Since DNTs are

linked to chronic epilepsy, their incidence in epilepsy surgery series is 0.8–5% of all resective cases and up to 14% in tumor-related resective epilepsy surgery [13, 32]. However, in non-selected patient cohorts, DNTs are rare. In our mixed series of 4,076 patients surgically treated for intracranial tumors, DNTs were diagnosed in 1.25% of the cases. The majority of patients diagnosed with DNTs are in their second or third decade of life. The tumor has no obvious gender predilection.

11.6.2 Symptoms and Clinical Signs

The vast majority of DNTs are supratentorial tumors (most often of the temporal lobe) involving primarily the cortex. DNTs of the basal ganglia, cerebellum, and brain stem are rare. Supratentorial cortical DNTs are invariably linked to long-standing, usually partial epilepsy. We recently evaluated our institutional series of 61 patients. The mean duration of epilepsy was 8 years (range 1–42 years). Patients with the complex form of DNT were of significantly younger age at onset of epilepsy, as compared to patients with the simple form of DNT. DNTs do not cause new neurological deficits, but patients may present with stable congenital neurological deficits [13].

11.6.3 Diagnostics

DNTs are hypointense on T1- and hyperintense on T2-weighted MR images. On both sequences, they give the impression of being multimicrocystic/nodular, while true cysts are observed in less than 10% of the cases. Tumor tissue lacking pseudocysts was identified in 85% of our cases. Contrast enhancement is not common (20% of the cases). DNTs are usually confined to the cerebral cortex, but they may involve the adjacent white matter. Mass effect and perifocal edema are absent. The tumor may have been detected on MRI years prior to surgery without any evident growth (Fig. 11.2). New contrast enhancement or growth is rarely observed and does not indicate malignant

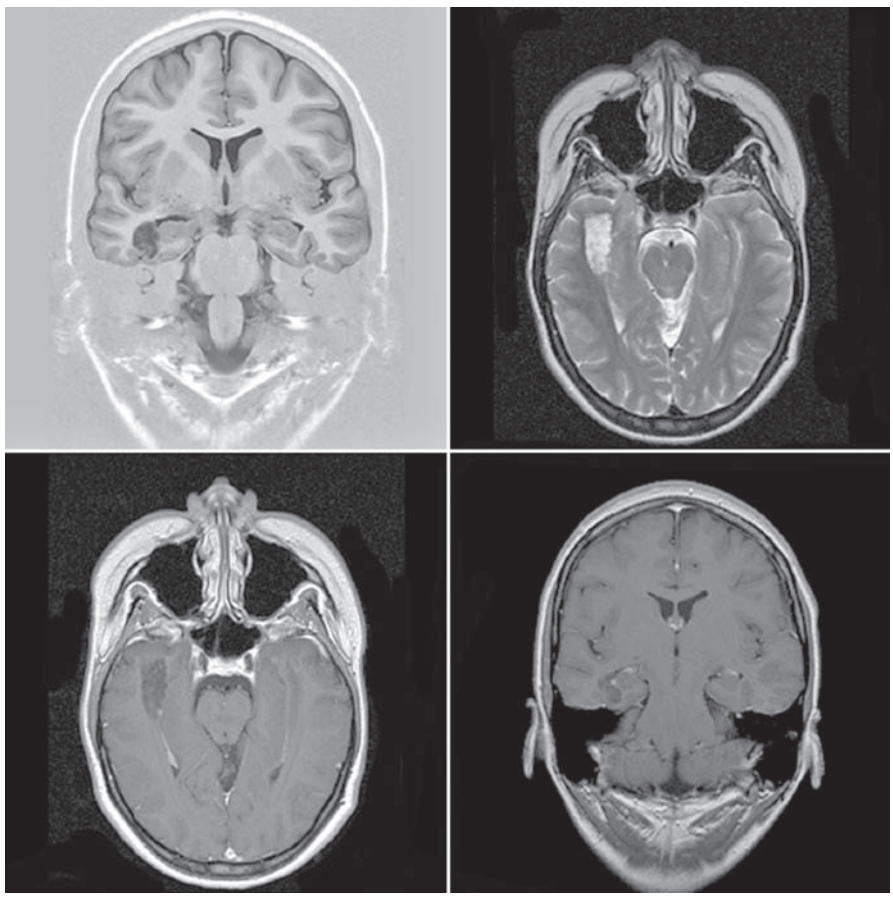

Fig. 11.2 Dysembryoplastic neuroepithelial tumor of the right temporal lobe. The tumor is hypointense on inversion recovery (*upper left*), as well as on T1-weighted images (*lower left* and *right*). There is no contrast enhancement (*lower left* and *right*). On T2-weighted images, the tumor is hyperintense (*upper right*). The tumor appears to be multinodular on all sequences. There is no notable mass effect or peritumoral edema

transformation [13]. In our experience, hemorrhage and calcifications occur significantly more often in the complex form of DNT. CT shows a usually hypodense mass without contrast enhancement. Calcifications occur in 20–30% of the cases. Erosions of the adjacent skull are observed in 50–70% of patients with DNT of the cerebral convexities [52].

11.6.4 Staging and Classification

The histological hallmark of DNT is its unique glioneuronal element composed of bundles of axons oriented perpendicularly to the cortex and surrounded by small oligodendroglia-like cells. Cytologically normal neurons appear to float in the matrix surrounding theses bundles. Foci of cortical dysplasia are associated with the tumor. The complex form of DNT is characterized by additional glial nodules resembling a glioma. Clinical behavior does not differ between both DNT forms. Tumors with a similar benign clinical course, cortical location, and neuroimaging findings, but lacking the specific glioneural element and glial nodules, have been referred to "non-specific" DNT. "Non-specific" DNTs are histologically often indistinguishable from astrocytoma, oligodendroglioma, and oligoastrocytoma. The concept of "non-specific" DNT is controversial [13].

DNTs correspond to WHO grade I. Their histological characteristics and clinical behavior suggest a dysembryoplastic origin [13].

11.6.5 Treatment

Surgery. Intraoperatively, DNTs are of soft, nodular consistency and are well delineated from the surrounding brain tissue. Since these tumors almost always manifest with chronic epilepsy, the principles of epilepsy surgery have to be applied. The rate of complete tumor resection has been reported to be 60–90%, with low perioperative morbidity and mortality [12, 32]. Recurrence/progression rates of DNT are very low.

Radiotherapy and Chemotherapy. There is no evidence supporting radio- and chemotherapy as adjuvant therapy, not even in incompletely resected DNT. Malignant DNT transformation following radio- and chemotherapy has been reported [49].

11.6.6 Prognosis/Quality of Life

Following surgery, 60–85% of patients are seizure-free [32]. In our experience, as in other patient series, incomplete resection of DNT is associated with persisting and recurring seizures [37]. Completely resected DNTs have a very low recurrence rate. Incompletely resected DNTs have a very low progression rate [13, 37]. Only two cases with malignant progression have been described [49]. Repeat surgery should be considered in cases with recurrent tumor.

11.7 Central and Extraventricular Neurocytoma

11.7.1 Epidemiology

Neurocytomas of the cerebral ventricles, termed central neurocytomas (CN), are very rare tumors. In our series of 254 neuronal and neuronal–glial tumors, CNs were diagnosed in 1.6% of the cases. They account for 0.25–0.5% of all intracranial tumors [15]. In our series of 4,076 intracranial tumors, CNs were diagnosed in 0.09% of the patients. The vast majority of patients with CN are diagnosed in their third and fourth decades of life. There is no gender predilection. Neurocytomas located within the cerebral hemispheres and the spinal cord (extraventricular neurocytoma) are encountered even less frequently than CNs [15].

11.7.2 Symptoms and Clinical Signs

CNs are almost always located in the supratentorial ventricles, with approximately two thirds of them in the anterior part of the lateral ventricles, near the foramen of Monro. The third ventricle is rarely involved, the fourth ventricle only in exceptional cases [15]. Thus, the clinical symptomatology is usually that of raised intracranial pressure due to hydrocephalus and is of short duration (a few months). When the third ventricle is involved, hypothalamic-hypophyseal dysfunction may occur. In the rare cases of extraventricular central neurocytoma, focal neurological deficits may occur [15].

11.7.3 Diagnostics

T1-weighted MRI studies show an iso- to hypointense heterogeneous mass. Tumors are iso- to hyperintense on T2-weighted images. Small tumor cysts may be present. Contrast enhancement is somewhat inhomogeneous and moderate to marked. CT features of CN resemble those of T1-weighted MRI. Calcifications are present in approximately 50% of the cases [52].

11.7.4 Staging and Classification

CNs consist of a neuronal tumor cell population of uniformly round shape, embedded in clusters in a variably developed fibrillary matrix. Other architectural patterns may also occur. The proliferation rate is low. CNs correspond to WHO grade II. Some CNs may disclose anaplastic features, such as increased mitotic activity (MIB-1 index >2%), microvascular proliferation, and necrosis. Shorter recurrence-free intervals are more likely to be associated with a MIB-1 labeling index >2% than with other anaplastic features. Extraventricular neurocytomas are often of a more complex appearance and have to be delineated from other extraventricular neoplasms that may contain neurocytic cells in addition to other tumor cells [15].

11.7.5 Treatment

Surgery. Complete tumor resections have been achieved in approximately 35% of published cases [43]. Five-year recurrence-free survival rates of 85% vs 46% have been reported in completely versus incompletely resected tumors. The degree of resection is also an important predictor of overall survival. Due to the intraventricular location and often large tumor size, operative morbidity and mortality may be quite high. Hydrocephalus, if present, must be treated adequately.

Radiotherapy and Chemotherapy. Radiotherapy should be prescribed to patients with incompletely resected CNs. Adjuvant radiotherapy improves the 5-year progression-free survival rate of incompletely resected tumors from 46% to 83%, in typical CN from 51% to 87–100%, and in atypical CN (MIB-1 index > 2%) from 7% to 70% [43–45]. Adjuvant radiotherapy also improves overall survival. It is not yet clear if radiotherapy should be instituted early following an incomplete tumor resection or if it should be delayed until tumor progression is diagnosed on follow-up MRI [15, 43]. Gamma-knife surgery can be effectively used for small tumor remnants early after surgery [4]. Adjuvant radiotherapy does not seem to improve recurrence-free survival in completely resected CN, whether atypical or not [43, 44].

Only limited data regarding adjuvant chemotherapy of CN are available. Chemotherapy should be reserved for tumors that cannot be controlled by surgery and radiotherapy alone.

11.7.6 Prognosis/Quality of Life

Following a complete tumor resection, a 99% (93% for atypical CN) 5-year survival rate for CN has been reported. Five-year survival rates of 86% (atypical CN: 43%) after incomplete resections without adjuvant radiotherapy, and 90% (atypical CN: 78%) with adjuvant radiotherapy have been observed [43–45]. Compared with other neuronal and glioneural tumors, the recurrence and survival rates of CN are relatively unfavorable. Therefore, long-term clinical and MRI follow-up of these patients is mandatory [7].

The clinical characteristics of extraventricular neurocytoma are not as well studied as those of CN. Extraventricular neurocytomas seem to behave similarly to CNs [9]

11.8 Cerebellar Liponeurocytoma

11.8.1 Epidemiology

Cerebellar liponeurocytoma (CLN) is a very rare tumor [1, 23, 39]. In our series of 4,076 successive intracranial tumors, including 254 neuronal and neuroglial tumors, no CLNs were diagnosed. The mean age of patients at diagnosis is 50 years. There is no obvious gender predilection [23]. Liponeurocytomas of the lateral ventricles have been described [27].

11.8.2 Symptoms and Clinical Signs

Due to the cerebellar location of CLN, the most frequent symptoms result from a posterior fossa mass effect, such as headaches, vomiting, and dizziness,

followed by cerebellar signs, such as ataxia, dysmetria, and nystagmus. At the time of diagnosis, patients have usually been symptomatic for anywhere in between several weeks to several years (with a mean of several months). Other focal neurological signs are rare. Occlusive hydrocephalus may be present [2, 39].

11.8.3 Diagnostics

On T1-weighted MRI, the tumors are hypo- to isointense. They contain irregular areas of hyperintensity due to tumor lipidization. Contrast enhancement is minimal or moderate and usually irregular. On T2-weighted images, CLNs are iso- to slightly hyperintense with irregular areas of hyperintensity due to tumor lipidization. Tumor cysts and hemorrhagic areas are rare. No or only minimal perifocal edema exists. The tumor may extend from the vermis or the cerebellar hemispheres into the subarachnoid cisterns. On CT, the tumor is hypo- to isodense and may disclose markedly hypodense irregular areas due to tumor lipidization. Contrast enhancement is minimal and irregular [2, 39].

11.8.4 Staging and Classification

CLNs consist of round isomorphic neoplastic cells with advanced neuronal differentiation. The histological appearance resembles that of CN. Focally, these tumor cells undergo lipomatous differentiation. The mitotic activity is low. Microvascular proliferation and necrosis are absent (but may be present in recurring tumors). Because of its clinical behavior, CLN is assigned to the WHO grade II [23].

11.8.5 Treatment

Surgery. Although CLNs are usually described as soft and well delineated from the cerebellum, complete resection of the often large tumors is not always possible, since they may extend into the subarachnoid space and encroach on cranial nerves. Operative morbidity and mortality are otherwise similar to that of other intra-axial cerebellar tumors.

Radiotherapy and Chemotherapy. There is no evidence supporting primary adjuvant radiotherapy. Following incomplete tumor resections, progression of residual CLN has been observed with or without additional radiotherapy [2, 21].

The role of adjuvant chemotherapy in CLN is unclear.

11.8.6 Prognosis/Quality of Life

In a review of 21 cases, 62% of the patients developed recurrences after a mean of 6.5 years following surgery. The 5-year survival rate was 48%. None of the recurrent cases disclosed histological features of malignant progression [1, 23]. One case of an unusually aggressive course with tumor recurrence 1 year after surgery has been reported by Jankinson et al. [21]. As in CN, the recurrence and survival rates of CLN are relatively unfavorable when compared with other neuronal and neuroglial tumors. Thus, long-term follow-up of patients with CLN is mandatory.

11.9 Rosette-Forming Glioneuronal Tumor of the Fourth Ventricle

11.9.1 Epidemiology

The rosette-forming glioneural tumor is a rare tumor of the posterior fossa. It is most often diagnosed in (young) adults. There may be a slight female predilection [18, 25, 41, 47].

11.9.2 Symptoms and Clinical Signs

Most patients have presented with signs and symptoms of obstructive hydrocephalus (mainly headache), vertigo, and ataxia [18, 25, 41, 47].

11.9.3 Diagnostics

MR imaging typically shows a relatively circumscribed, often cystic vermian or paramedian cerebellar mass with possible extension into the pons, midbrain, and even pineal region and variable (sometimes even

ring-like) contrast enhancement. Rosette-forming glioneural tumors are hypodense on CT. There is usually no or only minimal perifocal edema. Calcification may occur [3, 41, 47].

11.9.4 Staging and Classification

These tumors correspond to the WHO grade I. Multifocal tumor growth with involvement of the thalamus has been reported [18, 41, 47].

11.9.5 Treatment

Surgery. Patients usually require surgery for hydrocephalus control and tissue diagnosis. Tumor growth into the brain stem may limit the tumor's resectability.

Radiotherapy and Chemotherapy. There are no data supporting primary or adjuvant radiotherapy or chemotherapy. Radiotherapy has been administered to one patient after a partial resection, possibly resulting in brain stem radionecrosis and death [25].

11.9.6 Prognosis/Quality of Life

Survival even after subtotal resections is good. The only published fatality is a patient likely succumbing to radionecrosis rather than tumor progression [25]. However, due to the location of the tumors, postoperative neurological deficits are frequent. Pimentel et al. found a 56% rate of transient or permanent brain stem and cerebellar dysfunction among the 16 published cases for whom postoperative morbidity data are available [41].

11.10 Spinal Paraganglioma

11.10.1 Epidemiology

Paraganglioma of the cauda equina (PCE) is a rare neuroendocrine tumor. In our series of 254 neuronal and neuroglial tumors, PCEs were diagnosed in 3.9% of the cases. They account for 3.5% of all cauda equina tumors [35]. PCEs in other spinal locations (thoracic and cervical) are rare. Intracranial PCEs (parasellar region, pineal region, intracerebral, cerebellopontine angle) are extremely rare. In our series of 4,076 patients with intracranial tumors, no extraspinal paragangliomas were diagnosed. Most patients with PCE are in their fourth to seventh decades of life. Males are slightly more often affected than females [17, 35, 50].

11.10.2 Symptoms and Clinical Signs

Clinically, PCEs behave like other slow-growing tumors of the cauda equina. The mean duration of preoperative signs and symptoms is about 3–4 years. Major symptoms are low back pain (50–90%) and sciatica (20–70%). Sensory and motor deficits have been reported to occur in 35% and sphincter dysfunction in 15% of patients in one series, but in less than 5% in another. Paraplegia as well as a vasomotor amine syndrome (as in other paragangliomas) is very rare [17, 35].

11.10.3 Diagnostics

On T1-weighted MRI, PCEs are isointense. There is usually marked and homogeneous contrast enhancement. On T2-weighted images, the tumor is usually hyperintense. Serpiginous hypointensities are due to the usually rich vascularization. Signs of subacute hemorrhage and rarely tumor cyst formation may be present. Routine lumbar spine CT (without contrast administration) is of very limited value because the tumor can be completely missed when indirect signs of an intraspinal mass are absent [17, 35].

11.10.4 Staging and Classification

PCEs correspond to WHO grade I. Histologically, PCEs resemble paraganglia. They consist of uniformly round, so-called chief cells disposed in nests ("zellballen") and surrounded by an inconspicuous single layer of sustentacular cells embedded in a capillary network. Electron microscopy discloses neurosecretory granules in the

chief cells. In approximately 50% of these tumors, ganglionic cells or cells with a cytological appearance intermediate between chief cells and mature ganglionic cells are present ("gangliocytic paraganglioma," analogous to pheochromocytoma with neuronal differentiation). Several other histological variants of PCE have been described. Predicting the biological behavior of a PCE based on histological features is not possible. However, overtly anaplastic and metastasizing PCEs contain no or only few sustentacular cells [50].

11.10.5 Treatment

Surgery. The majority of PCEs are attached to the filum terminale. In 15% of the tumors, an infiltrative growth pattern is present. Complete tumor resection has been reported in 80–90% of the patients [17, 35]. Surgical complication rates are low.

Radiotherapy and Chemotherapy. Some authors recommend radiotherapy for incompletely resected tumors and in particular for recurrent PCE [35, 55].

The role of adjuvant chemotherapy in PCE is unclear.

11.10.6 Prognosis/Quality of Life

In contrast to some other paraganglioma locations, the prognosis of PCE is good. Following a complete tumor excision, recurrence rates of only 2% have been observed. After an incomplete resection, tumor regrowth is seen in approximately 10–20% of patients. Primary arachnoidal seeding or seeding at the time of recurrence is very rare [35, 50, 55]. Tumor recurrence may reportedly occur as late as 23 years following surgery. Hence, long-term follow-up of these patients is advisable.

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