Grade 1 Gliomas

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12.1 Introduction

Central nervous system (CNS) gliomas are divided according to *St. Anne-Mayo* grading system into four grades based on morphology, the criteria being: cellular atypia, mitoses, microvascular (endothelial) proliferation, and necrosis. Further description is provided in the chapter on pathology of gliomas.

Grade I gliomas do not satisfy any of these parameters. They have a slow growth rate, are considered benign and have a long-term survival.

Grade II gliomas have cellular atypia but none of the other criteria. They also have a slow growth rate but may recur as high grade gliomas (HGG) later. Clinical behavior may be variable—benign or malignant.

Together, grade I and II tumors comprise low-grade gliomas (LGGs).

As per World Health Organization (WHO) 2016 CNS classification, LGGs may be either astrocytic or mixed neuronal-astrocytic tumors [1].

The various tumors described as LGGs are noted in Table 12.1.

12.2 Epidemiology

The term LGG includes tumors of varied origins but with relatively indolent behavior. They usually present in children or young adults, possess a slow growth velocity, but may be locally invasive. Occasionally they may undergo secondary transformation to HGGs. Grade 2 gliomas commonly affect the age group 35–44 years, are usually supratentorial, and may arise in the eloquent cortex. They represent nearly 10% of newly diagnosed tumors that originate in the brain.

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Table 12.1 WHO 2016 CNS classification of low-grade gliomas/mixed/neuronal-glial tumors

	Grade 1	Grade 2
Astrocytic tumors		
Diffuse astrocytic and oligodendroglial tumors	–	• IDH mutant diffuse astrocytoma • IDH mutant and 1p19q co-deleted ODG • IDH wild-type diffuse astrocytoma
Other astrocytic tumors	• Pilocytic astrocytoma • SEGA	• Pleomorphic xanthoastrocytoma
Other gliomas	• Angiocentric glioma	• Chordoid glioma of third ventricle
Neuronal and mixed neuronal-glial tumors	• DNET • Ganglioglioma • Gangliocytoma • Dysplastic gangliocytoma of the cerebellum • Desmoplastic infantile astrocytoma and ganglioglioma • PGNT • RGNT	• Central neurocytoma • Extraventricular neurocytoma • Cerebellar liponeurocytoma

DNET dysembryoplastic neuroepithelial tumor, *IDH* isocitrate dehydrogenase, *ODG* oligodendroglioma, *PA* pilocytic astrocytoma, *PGNT* papillary glioneuronal tumor, *PXA* pleomorphic xanthoastrocytoma, *RGNT* rosette-forming glioneuronal tumor, *SEGA* subependymal giant cell astrocytoma

The entities of pilomyxoid astrocytoma, protoplasmic astrocytoma, and oligoastrocytoma were listed as grade 2 in WHO 2007 classification but are no longer part of WHO 2016 classification

Pilocytic astrocytomas (PA) constitute the most common grade 1 LGGs, followed by other variants. In children, LGGs constitute the most common brain tumors (>20%) without any specific age predilection. The most common locations are the cerebellum, visual pathways, and diencephalon. The group encompasses several histologies with differing biological origins. Most childhood LGGs are sporadic in origin but may have an association with familial cancer predisposition syndromes, or neurocutaneous syndromes. Children with neurofibromatosis 1 (NF-1) have a higher risk of developing gliomas involving optic pathways and other locations [2]. Children with tuberous sclerosis may have a high risk of developing subependymal giant cell astrocytoma (SEGA) [3].

12.3 Pathology

Gliomas were earlier categorized according to cell lineage, histology, differentiation, and proliferation. Of late, improved understanding of tumor genetics has changed the landscape of how these tumors are classified, prognosticated, and treated. WHO 2007 classification introduced immunohistochemistry (IHC) to confirm cell lineage and differentiate astrocytic versus oligodendroglial tumors. The

WHO classification in 2016 introduced a system of molecular classification whereby isocitrate dehydrogenase (IDH) mutation, alpha-thalassemia/mental retardation syndrome X-liked (ATRX) loss, and 1p19q codeletion assessment became key to establishing the diagnosis and prognostic group of a tumor. The newer classification aims to group together tumors with similar biology and clinical behavior, fine-tuning both the prognostic assignment and treatment intensity, in addition to making the diagnostic process more objective by giving more importance to genotype than histopathologic diagnosis. IDH mutations are rare among grade 1 gliomas. However, individual tumor types may have specific mutations such as BRAF mutations or fusions.

12.4 Clinical Presentation

Grade 1 gliomas may cause symptoms due to cortical irritation (seizures) or mass effect over ventricles or optic pathways, although they may also be incidentally diagnosed on imaging done for other indications such as head trauma. Neurologic deficits are remarkably less common than in HGGs. In children, the presentation will also depend on age. Focal symptoms may include seizures, ataxia, limb weakness, focal sensory changes, cranial nerve palsies, aphasia, vision loss or field defects, nystagmus, Parinaud's syndrome (pupillary abnormalities, paralysis of upward gaze, or convergence-retraction nystagmus, eyelid retraction), diabetes insipidus, or growth retardation. Diffuse symptoms may include headache, neck stiffness, vomiting, lethargy, behavior change, change in cognition, or increased irritability. In infants, raised intracranial pressure may manifest as fontanelle bulge, split sutures, increase in head circumference, and "setting sun" sign. The specific presentation, histopathologic appearance, and management differ by tumor type and are discussed under specific tumor types.

12.4.1 Other Astrocytic Tumors

12.4.1.1 Pilocytic Astrocytoma (WHO Grade I)

PAs constitute the most common gliomas in childhood and the second most common brain tumors after embryonal tumors. Cerebellum is the most common location followed by midline structures such as hypothalamus and optic pathways. Other locations such as cerebral hemispheres, brainstem, and spinal cord are less common. Presentation is dependent on site of origin. Cerebellar lesions present with ataxia or features of raised intracranial tension (ICT). Optic pathway tumors present with proptosis, diplopia, nystagmus, or gradual vision loss. Tumors close to fourth or third ventricle may cause hydrocephalus, causing headache, vomiting, increased head size, delayed milestones, or behavior changes. Hypothalamic lesions may cause short stature, precocious puberty or symptoms related to hydrocephalus. Tumors involving both optic chiasm and hypothalamus may produce the diencephalic syndrome consisting of severe weight loss, failure to thrive while having

normal or accelerated growth, hyperalertness, hyperkinesis, and mood elation. Tectal plate location is usually considered characteristically pilocytic histology and these tumors are treated without biopsy confirmation. These patients may have papilledema on examination or have Parinaud's syndrome.

Children having NF-1 are prone to develop optic pathway gliomas, nearly 15–20% develop the tumor before the age of 7 years [4]. Nearly 2% of brainstem lesions may have NF-1 association; patients with other stigmata of NF-1 should be identified.

PAs are well-circumscribed tumors, often consisting of a cystic lesion with a solid component, usually present as a characteristic mural nodule. On histology, they have a biphasic architecture with variable proportion of compact fibrillary component (bipolar piloid cells, eosinophilic Rosenthal fibers), intermixed with spongy microcystic element (loose stellate cells, microcysts, granular bodies). The piloid cells are glial fibrillary acid protein (GFAP) positive while the granular bodies show periodic acid–Schiff (PAS), alpha1-antitrypsin and alpha1-antichymotrypsin positivity. MIB-1 labeling index (MIB-LI) varies from 1% to 3%.

Magnetic resonance imaging (MRI) shows a well-defined cyst wall, with T2 hyperintensity but minimal edema. The mural nodule or solid component shows brilliant enhancement while the cyst wall may show variable enhancement. The cyst fluid is more proteinaceous than cerebrospinal fluid (CSF) and is T1 iso- to hypointense but T2/FLAIR hyperintense. Peripherally located lesions may occasionally cause skull bone thinning. These tumors are usually unifocal. Visual pathway tumors have less defined boundaries. Optic pathway tumors are T1 iso- or hypointense and T2 hyperintense. Only 50% show contrast enhancement. Variable degree of optic pathway involvement may be seen; sporadic lesions usually arise from chiasm while NF-1 related lesions more commonly arise from optic nerve.

Propensity for CSF dissemination is rare even if located close to the ventricles; it has been reported occasionally in de novo but largely in aggressive and recurrent tumors (3–5%). Even with leptomeningeal dissemination, median survival exceeding 5 years has been reported [5].

Several genetic pathways are associated with disease causation and progression. Causative factors include NF1 gene inactivation in neurofibromatosis 1 and BRAF gene overexpression/fusion/BRAF V600 E mutation in sporadic tumors, cause upregulation of MAPK/Erk pathway. KIAA1549-BRAF fusions occur more often in optic pathway lesions and cerebellum while BRAFV600E point mutation in supratentorial and diencephalic lesions [6].

Molecular alterations such as mammalian target of rapamycin (mTOR) or phosphoinositol 3 kinase (PI3K) pathway deregulation, or Matrilin 2 overexpression may lead to transformation into aggressive or recurrent disease [7]. Recurrent tumors treated with multiple lines of chemotherapy may have high CD133 and MDR1 expression that may act via PI3K-Akt-NF-κB signaling pathway and contribute to drug resistance [8].

Spontaneous regression is occasionally seen in these tumors. Surgical excision forms the mainstay of treatment and is curative if gross total resection (GTR) is achieved. A multicenter study on grade 1 gliomas showed better 5-year progression

free survival (PFS) with greater extent of resection in PA but not for ganglioglioma or dysembryoplastic neuroepithelial tumor (DNET) [9]. Temporal lobe tumors had better PFS than occipital/parietal lobe tumors. Intraoperative MRI may help improve surgical extent but not necessarily impact survival.

However, optic pathway gliomas are not resectable, even biopsy may cause vision loss. If associated with NF-1, they remain largely asymptomatic and do not need to be treated. Sporadic optic pathway gliomas in the absence of NF-1 may be more aggressive and require treatment.

Adjuvant radiotherapy (RT) after incomplete resection or biopsy in brainstem or spinal lesions may offer durable long-term control. It may also be offered in symptomatic sporadic visual pathway tumors and tumors refractory to chemotherapy or recurrent tumors that are not amenable to re-excision. Residual tumor seen on a recent T1 contrast MRI is marked as gross tumor volume (GTV). Clinical target volume (CTV) margin of 5–10 mm is generated around GTV respecting anatomic boundaries. A 3–5 mm planning target volume (PTV) is generated around CTV (depending on setup technique, imaging verification frequency, and institutional data) and a dose of 50.4 gray (Gy) in 28 fractions is planned using conformal techniques such as three-dimensional conformal radiation therapy. Other techniques such as intensity modulated radiation therapy with or without image guidance, volumetric modulated arc therapy, and proton therapy may be offered depending on proximity of tumor to critical normal structures. With adjuvant RT, long-term survival over 95% and event free survival between 70% and 90% is seen [10]. Not all patients with optic pathway PAs will have vision recovery. Children with NF-1 may be more prone to second cancers and vasculopathies with RT, where it should be avoided. However, in young children, chemotherapy consisting of vincristine-carboplatin may slow down progression and delay RT in residual, unresectable lesions [11].

Figure 12.1 shows the T1 contrast image (a) and adjuvant radiotherapy plan (b) of a large residual pilocytic astrocytoma involving brainstem in a young patient. A dose of 50.4 gray was planned to planning target volume.

Since these tumors affect young children and have an excellent prognosis, adjuvant radiation is not offered even with incomplete resection unless there is neurological compromise due to mass effect from large residual component in locations such as brainstem. The risk of malignant transformation should be explained before offering RT for any low-grade tumors in children and young adults. In very young children, chemotherapy may have a role in slowing down disease progression in unresectable tumors. Adult PAs are highly vascular, show high vascular endothelial growth factor (VEGF) expression and may be responsive to antiangiogenic therapies such as bevacizumab in recurrent/unresectable/disseminated settings [12]. mTOR inhibitors, MEK inhibitors, and farnesyl transferase inhibitors may have a therapeutic role. Systemic agents such as dabrafenib and trametinib are being investigated for treatment of such aggressive tumors through inhibition of mitogen activated protein kinase (MAPK) pathway.

Survival is good and depends on age as well as tumor location. Overall survival (OS) at 10 years for children exceeds 95% while for adults >40 years, it is around 70%. Tumors that have a chance of GTR have a better survival than

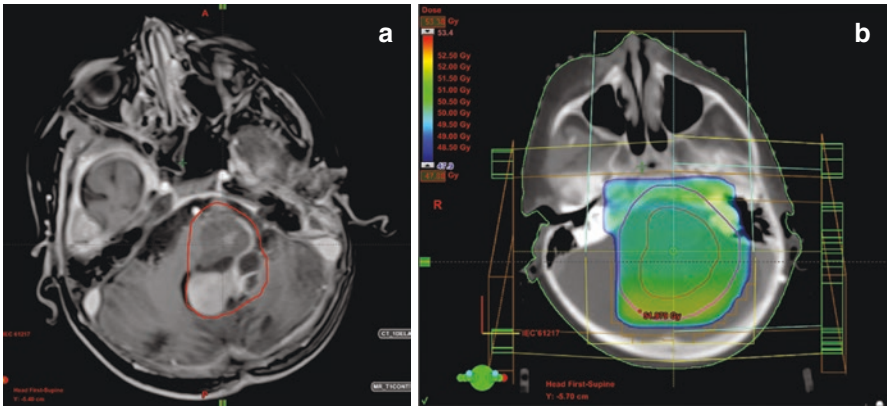

Fig. 12.1 (**a**) T1 Contrast enhanced axial section of magnetic resonance imaging showing a large residual tumor involving left half of brainstem and left cerebellar peduncle with solid and cystic areas, patchy enhancement, and mass effect over normal brainstem, fourth ventricle, and cerebellum. (**b**) Three-dimensional conformal radiotherapy plan for the same patient. A dose of 50.4 gray in 28 fractions is planned to planning target volume

unresectable tumors (brainstem, spine). Recurrence rates after GTR are under 5%, while nearly 50% after incomplete resection. Even with incomplete resection, it is reasonable to follow up and offer re-excision at progression for non-critical locations.

12.4.1.2 Subependymal Giant Cell Astrocytomas

SEGAs are slow-growing benign tumors arising primarily in periventricular region [13]. They are strongly associated with tuberous sclerosis, which is an autosomal dominant neurocutaneous disorder with TSC or TSC2 gene mutations, and the classic triad of *mental retardation, seizures, and multiple organ hamartomas*. SEGA was historically considered pathognomonic for tuberous sclerosis but rarely, instances of SEGA in absence of tuberous sclerosis are also reported although clinical features of the same may develop later in life [14]. There is a male predominance with a mean age of 11 years at diagnosis.

They typically originate from subependymal nodules in the region of foramen of Monro, and can be unilateral or bilateral. The only differentiation from subependymal nodules can be made with serial imaging showing growth or development of obstructive symptoms; even histopathology may be unable to distinguish SEGA from subependymal nodules. Rate of growth is slow, over weeks to months, although parenchymal invasion, perilesional edema, or atypical locations within hypothalamus or pineal are occasionally seen. For asymptomatic tumors, neuroimaging every 1–3 years is recommended. Symptoms may arise from acute or chronic obstructive hydrocephalus: vomiting, positional headache, diplopia or blurring of vision, new or worse seizures, and personality changes.

MRI shows T1 hypointense and T2/FLAIR hyperintense periventricular lesions, with only 10% showing contrast enhancement. Multiple cortical tubers/

subependymal nodules may be noted; only a serial change in size identifies a SEGA with certainty [15].

A symptomatic (intractable seizures) or growing SEGA should be surgically excised to avoid complications from raised ICT. Early surgery is recommended to avoid hydrocephalus-related sequelae [16]. GTR is curative. If resection is incomplete, tumor growth may still continue. For larger tumors, surgery may have its attendant risk of hemiparesis, ventriculoperitoneal shunt dependence, stroke, transient memory impairment, etc., and in these situations, medical management may be considered to shrink or stabilize the tumor. mTOR is a protein kinase that is constitutively activated in tuberous sclerosis. mTOR inhibitors (rapamycin, everolimus) have been used successfully with significant tumor shrinkage and resolution of hydrocephalus; tumor regrowth may happen following interruption of the drug. There are complex interactions with anticonvulsants, in addition to the significant adverse effects such as thrombocytopenia, delayed wound healing, and immunosuppression, hence judicious use is recommended [17]. RT is usually not recommended; however, gamma knife (doses of 11–13 Gy at periphery) has been used for growing but asymptomatic tumors who were not candidates for surgery or medical management, with variable results [18].

A Surveillance, Epidemiology, and End Results (SEER)-18 database analysis of 226 cases over 10 years places the incidences at 0.027 per 100,000 person-years. Age younger than 18 years and surgery were both prognostic for survival while gender, tumor size, location, extent of surgery, and receipt of RT had no impact [19].

12.4.2 Other Gliomas

12.4.2.1 Angiocentric Glioma

Angiocentric glioma is a rare and new distinct tumor type of glial and possibly partial ependymal origin first defined in 2005, that forms one of the tumors constituting the group of drug-resistant long-term epilepsy associated tumors (LEAT). There is a slight male preponderance, with median age of 13 years at diagnosis [20]. Seizures start in childhood. Disease location is supratentorial, unilobar (most commonly in frontal lobe) with involvement of superficial cerebral cortex and extension to subcortical white matter. MRI shows rim-like T1 hyperintensities in cerebral cortex with stalk-like extension to ventricle on T2/FLAIR [21]. Lesions are usually well defined though diffuse change is also reported. Contrast enhancement is variable. Radiologic differential diagnoses comprise other LEAT associated lesions such as focal cortical dysplasias (FCD), ganglioglioma, or cortical tubers. On histology, typical features include monomorphous, bipolar tumor cells showing angiocentric arrangements and diffuse infiltration of cerebral cortex and focal subpial growth pattern. Proliferative activity is rare. IHC for GFAP, vimentin, S100B, and epithelial membrane antigen (EMA) is positive; p53, epidermal growth factor receptor (EGFR), neurospecific nucleoprotein (NeuN), smooth muscle actin (SMA), chromogranin A (CgA), microtubule associated protein 2 (MAP 2) and CD34 and CD99 are negative. Ki-67 is <5%, usually ~1%. Differential diagnoses include PAs,

Table 12.2 Differential diagnosis between AG and similar grade 1–2 gliomas

Tumor type (WHO 2016)	Age	Symptoms (in addition to epilepsy)	Location	MRI	Histopathology	IHC (in addition to GFAP)
Angiocentric glioma	Children and young adults	–	Supratentorial (frontal, temporal)	Small non-enhancing mass	Angiocentric growth pattern, monomorphous bipolar cells	S-100, vimentin, EMA
Ganglioglioma	Children and young adults	Raised ICT	Temporal lobe, cerebellum	Nodular, cystic, rim-like or solid, contrast enhancing	Both ganglion and glial cells	NF, NeuN
Diffuse grade 2 gliomas	Young adults	Focal neurologic deficits, neurocognitive dysfunction, raised ICT	Cerebral hemispheres	No or minimal enhancement	Diffusely infiltrating	S-100, Olig2, EMA, nestin

AG angiocentric glioma, *EMA* epithelial membrane antigen, *GFAP* glial fibrillary acidic protein, *ICT* intracranial tension, *IHC* immunohistochemistry, *MRI* magnetic resonance imaging, *NF* neurofilament, *NeuN* neurospecific nucleoprotein, *NSE* neurospecific enolase, *Olig2* oligodendrocyte transcription factor-2, *WHO* World Health Organization

gangliogliomas, and ependymomas, but they are differentiated based on morphology and IHC. Table 12.2 lists important differences between angiocentric gliomas and other LGGs. Some angiocentric gliomas have loss of chromosomal bands 6q24-q25 (PLAGL1/ZAC1 gene) and gain on 11p11.2 (PTPRJ gene, CD148) and these may have pathobiological relevance. GTR is the treatment of choice, with most patients relieved of epilepsy. Clinical course is long and indolent. There are occasional reports of recurrence after incomplete resection with histologic signs of malignant change at progression. Since this is a relatively new entity with limited reports, long-term follow-up information is not available.

12.4.3 Neuronal and Mixed Neuronal-Glial Tumors

12.4.3.1 Dysembryoplastic Neuroepithelial Tumor (WHO Grade I)

The entity of DNET was first described in 1988. It comprises benign cortical tumors, mostly in supratentorial location. Presentation is with refractory seizures; other neurologic signs are usually absent. DNET is one of several LEATs; others being angiocentric glioma, ganglioglioma, pleomorphic xanthoastrocytoma (PXA), and isomorphic astrocytoma.

Both DNET and ganglioglioma have common characteristics of young age of presentation (childhood and adolescence), tumor location in temporal lobe, benign behavior and chronic epilepsy (starting before the age of 20 years) due to cortical involvement. Both are also tumors related to abnormal proliferation of neuronal and glial elements and are associated with FCD and hemimegalencephaly [22].

On imaging, DNETs appear as intracortical tumors without any mass effect or perilesional edema. Nearly half the patients have overlying skull deformities. Computed tomography (CT) shows a hyperdense lesion, occasionally with calcific changes. On MRI, lesions are T1 hypointense and T2 hyperintense, well demarcated, multilobulated or gyriform. Presence of contrast enhancement as multiple rings is seen in only one-third, but when present, it should raise suspicion of DNET (vs. HGGs) especially when mass effect and edema are absent. High choline peaks on MR spectroscopy, high apparent diffusion coefficient (ADC) on diffusion weighted MRI sequences, lack of high methionine uptake on PET with ^{11}C-methionine may help distinguish DNET or ganglioglioma from FCD [23].

On histopathology, glial nodules, cortical dysplasia, and glioneuronal elements are seen. Nearly 40% DNETs have cystic change; other forms may include single or multiple nodules or diffuse change. Nearly 30% have FCD. Oligodendroglioma (ODG)-like areas may also occur with corresponding myelin oligodendrocyte glycoprotein (MOG) expression on IHC and need to be distinguished from pure ODGs by presence of neuronal elements with a columnar appearance perpendicular to cortical surface, FCD, and a myxoid matrix. It may be difficult to distinguish from extraventricular neurocytoma, other LGGs and ODG. 1p19q codeletion is absent in DNET.

Genome sequencing shows an increased propensity to alteration of FGFR1 gene (duplication or point mutation), but rarely BRAF alterations [24].

With small tumors, complete excision may be possible (often with a rim of surrounding dysplastic tissue) and is curative, also treating the epilepsy. However, cortical location may preclude complete excision in others. Usually, rate of regrowth is slow, and most tumors do not need re-treatment even after incomplete excision. Due to frequent diffuse brain involvement, there may be relapse of epilepsy despite no disease recurrence. DNET does not adversely impact survival. RT and chemotherapy have no role.

12.4.3.2 Ganglioglioma (WHO Grade I)

Grade 1 ganglioglioma consists of mixed neuronal and glial elements. They represent less than 1% of CNS tumors. Median age of diagnosis is 12 years with a male preponderance [25]. Temporal lobe is the most common location and seizures the most common presentation.

Histopathology shows mature neoplastic astrocytes admixed with variable proportions of atypical large binucleate neurons with prominent nucleoli. Nearly 75% have alterations of BRAF gene (BRAF V600E or other mutations, BRAF fusion) [25]. Other mutations include RAF, NF1, KRAS, or FGFR1/2 alterations. MRI shows a T1 iso- to hypointense and T2 hyperintense solid-cystic or solid mass, most commonly in temporal lobe. Contrast enhancement, if present, may be solid or nodular rim. Extensive calcification may be seen. Mass effect and perilesional edema are usually not seen. Surrounding cortical dysplasia may be noted in the form of cortical thickening, abnormal gray and white matter signals, localized cortical volume loss, etc.

Complete resection is usually possible in more than two-third cases, and is curative. They have a favorable prognosis. Age less than 1 year at diagnosis and tumor origin in brainstem are associated with poor OS. SEER database results from pediatric ganglioglioma/gangliocytoma suggest that nearly 2/3 have complete resection; non-brainstem lesions had an excellent 5-year OS of 96.6%. Gangliogliomas have some malignant potential especially in recurrent situations, though rarely in children [26]. RT is rarely needed, for inoperable primary or recurrent tumors, largely in brainstem location.

12.4.3.3 Gangliocytoma

Gangliocytomas are clinically, radiologically, and histologically similar to gangliogliomas, but represent just 1% of gangliogliomas. They present in children and young adults with prolonged epilepsy. Most tumors are cerebral in location, most common location being temporal lobe. They may occasionally occur in pituitary gland in association with pituitary adenomas [27]. They are not distinguishable from ganglioglioma on imaging but sometimes have a dural tail. They are purely neuronal differentiated neoplasms. They are CD34 negative, comprise primarily of dysplastic neurons in a background of non-neoplastic glial cells, without almost any proliferation activity. Complete surgery is curative. These tumors are not known to have any malignant change on follow-up. No long-term follow-up information is available since they are largely clubbed with gangliogliomas [28]. It is not certain if these constitute a distinct tumor entity despite inclusion in all WHO CNS

classifications till date. They may possibly represent dysplastic or malformative lesions [29].

12.4.3.4 Dysplastic Gangliocytoma of the Cerebellum

Dysplastic gangliocytoma of the cerebellum (Lhermitte–Duclos disease) was first described in 1920. There is no predilection for any gender. Presentation is most often in young adults (third to fourth decade). The mean age of presentation is 4.3 years in children and 42.5 years in adults.

It manifests as a slowly growing cerebellar cortical mass, and may have a syndromic association and association with congenital malformations like polydactyly, cutaneous or mucosal lesions, gigantism, megalencephaly, and hemihypertrophy [30]. Patients have a long history of vague symptoms related to raised ICT, brainstem compression or cerebellar involvement, including headache, gait ataxia, and cranial nerve palsies. Sudden neurologic deterioration from acute or decompensation of chronic hydrocephalus may happen. An association with Cowden disease (an autosomal dominant neoplastic-hamartomatous disorder) is also reported, with multiple hamartomas and high incidence of malignancies of breast, endometrium, thyroid, and genitourinary systems. PTEN mutations have been identified in these patients [31].

On histology, the granular, Purkinje, and glial cells are present, loosely mimicking the architecture of cerebellar cortex but in a disorganized manner. Ki67 is low. Histopathology shows widened molecular layer, absent Purkinje cell layer and hypertrophic granule cell layer. Whether the origin is hamartomatous or neoplastic is still not clear.

MRI may show enlargement of cerebellar cortical folia with non-enhancing gyriform pattern. Lesions are well circumscribed, T1 hypointense, T2 hyperintense with a striated pattern (interspersed bands of isointensity, also known as tiger stripes), with minimal or no contrast enhancement.

Tumor growth is slow but there may be rapid deterioration with mass effect in some. Surgical excision is the treatment of choice. Residual or recurrent lesions have not demonstrated malignant change in any reports. RT and chemotherapy have no role. Due to the association with Cowden disease, these patients need long-term follow-up after treatment to help early detection of other associated cancers and genetic counseling.

12.4.3.5 Desmoplastic Infantile Astrocytoma and Ganglioglioma

These are tumors of newborns or infants, usually presenting in first 18 months of life. Presentation may be with increased head size, seizures, and focal neurologic signs. MRI shows a typically supratentorial tumor with more than one lobe involved, with T2 heterogeneity (hyperintense cystic component and hypointense solid component). The solid component enhances with contrast. Superficial cerebral cortical and leptomeningeal involvement with dural attachment with a desmoplastic reaction are characteristic. MRS shows high choline/N-acetylaspartate (NAA) ratio, perfusion studies show increased perfusion, and diffusion studies show low ADC values [32]. Histology shows mixed ganglionic and astrocytic cells. Presence of

primitive cells may be indicated by a high number of mitosis and these may mimic malignant astrocytomas in appearance.

BRAF mutations are occasionally found. Complete surgical resection is curative although possible in only 1/3 cases. Challenges to surgery include young age with low weight, large size of tumor with hypervascularity. Even after partial resection, these tumors merit observation only. Chemotherapy may be appropriate for recurrent disease after a second look surgery. Long-term prognosis is excellent. Midline (hypothalamic) tumors have more aggressive course [33].

12.4.3.6 Papillary Glioneuronal Tumor

Papillary glioneuronal tumor (PGNT) are rare tumors of younger population, with mean age of presentation at 27 years. Clinical features include symptoms due to raised ICT, seizures, focal neurologic changes as per tumor location (hemiparesis, dysphasia, vision changes). MRI shows a cystic lesion (hypointense on T1, iso- to hyperintense on T2) with a solid component or mural nodule in supratentorial location, often frontal and occasionally temporal or parietal [34]. The solid component or nodule is contrast enhancing. A possible origin from subependymal plate explains their close proximity to ventricles. On histology, the tumor is low grade, biphasic with papillary and solid parts containing neurocytic and glial elements. Sometimes, ODG-like cells or mini-gemistocytes may be seen. GTR is curative, and extent of resection and Ki-67 are prognostic factors for local control (5-year PFS 91.9% with GTR vs 46.7% with partial resection) [35]. Recurrences may happen following partial resections especially in parietal location (due to proximity to eloquent cortex, basal ganglia, or internal capsule). Efforts should be made to remove as much of solid part as possible. RT is reserved for aggressive lesions that are not candidates for re-surgery.

12.4.3.7 Rosette-Forming Glioneuronal Tumor

Rosette-forming glioneuronal tumor (RGNT) is a rare tumor predominantly affecting females with a mean age of 31.8 years at detection. The tumor is most often located in relation to fourth ventricle (~60%), extending to cerebellar vermis or thalamus [36]. Presenting symptoms may include headache, gait imbalance, vertigo, or vision problems. MRI may show a mass (average size 3 cm) spanning cortex and underlying white matter with solid, cystic or mixed features. The solid areas show T1 iso- to hypointensity and T2 hyperintensity with focal contrast enhancement. Hydrocephalus may be seen in nearly half of them. Nearly one-fourth may show calcification. Histopathology shows a biphasic tumor with neuronal (neurocytic rosettes and perivascular pseudorosettes) and glial (spindled astrocytic cells, elongated nuclei, slender bipolar processes, similar to PA) elements without mitotic activity, necrosis, or vascular endothelial proliferation [34]. IHC shows synaptophysin, neuron specific enolase (NSE), neurofilament protein (NFP) positivity in neuronal component and GFAP in glial component, with low Ki-67 index. PIK3CA gene mutations are seen. GTR is the goal; however, often only partial resection is possible due to intimate relationship with neural structures of cerebellum. Most patients do well despite partial resection. Risk of postoperative neurologic deficits (ataxia, cranial nerve palsies) may be considerable.

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