Review

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Future NEUROLOGY

Glioneuronal tumors: clinicopathological findings and treatment options

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Glioneuronal tumors are very rare CNS neoplasms that demonstrate neuronal differentiation, composed of mixed glial and neuronal cells. The majority of these lesions are low grade and their correct classification is crucial in order to avoid misidentification as 'ordinary' gliomas and prevent inappropriate aggressive treatment; nevertheless, precise diagnosis is a challenge due to phenotypic overlap across different histologic subtype. Surgery is the standard of therapeutic approach; literature concerning the benefit of adjuvant treatments is inconclusive and a globally accepted treatment of recurrence does not exist. Targetable mutations in the genes *BRAF* and *FGFR1/2* are recurrently found in these tumors and could take a promising role in future treatment management.

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Glioneuronal tumors are a heterogeneous group of CNS neoplasms with neuronal differentiation, exhibiting a pure neuronal pattern or a mixed glial and neuronal phenotype [1]. The revised fourth edition of the World Health Organization (WHO; Geneva, Switzerland) Classification of Tumors of the Central Nervous System, published in 2016, is both a conceptual and practical revolution in brain tumor classification systems, introducing for the first time molecular biology in addition to histology in order to define many tumor entities, according to the era of personalized therapies [2]. According to the 2016 WHO classification, the group of neuronal and mixed glioneuronal neoplasms currently includes dysembryoplastic neuroepithelial tumor (DNET), ganglioglioma, anaplastic ganglioglioma, desmoplastic infantile ganglioglioma/gangliocytoma, central and extraventricular neurocytoma, paraganglioma, cerebellar liponeurocytoma, papillary glioneuronal tumor, rosette-forming glioneuronal tumor and primary diffuse leptomeningeal glioneuronal tumor (DLGNT) [2] (Table 1).

Though this latest version of the WHO classification is recent, in the last few years, many cases have been reported of glioneuronal neoplasms with distinctive morphological features that are still not formally included in any classification [3,4].

Gangliogliomas are the most common histologic subtype, characterized by genetic alterations of the MAP kinase pathway, in particular *BRAF* V600E mutation, other alternative *BRAF* mutations or fusions, *KRAS* mutations, *NF1* mutations or *FGFR* mutations or fusions [5]. *BRAF* V600E mutation represents a valuable diagnostic marker and constitutes a novel and promising therapeutic target for molecularly selected CNS neoplasms in a clinically meaningful way.

Currently the literature of neuroglial tumors is poor and limited to small case series; we thus provide a comprehensive review to summarize presenting symptoms, radiological findings, prognosis and treatment options.

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Table 1. Grading of neuronal and mixed neuronal-glial tumors according to the 2016 CNS WHO classification.

Neuronal and mixed neuronal-glial tumors	Grading
Dysembriplastic neuroepithelial tumor	I
Gangliocytoma	I
Ganglioglioma	I
Anaplastic ganglioglioma	III
Dysplastic cerebellar gangliocytoma	I
Desmoplastic infantile gangliocytoma and ganglioglioma	I
Papillary glioneuronal tumor	I
Rosette-forming glioneuronal tumor	I
Diffuse leptomeningeal glioneuronal tumor	I
Central neurocytoma	II
Extraventricular neurocytoma	II
Cerebellar liponeurocytoma	II
Paraganglioma	I

Ganglioglioma

Epidemiology

Ganglioglioma is a rare well differentiated glioneuronal neoplasm composed of a combination of dysplastic mature ganglion cells with neoplastic glial cells, representing approximately 0.4–1.7% of all brain tumors [6–10]. It is classified grade I by the 2016 WHO system and generally occurs in children and young adults before age 30 with a slight preponderance in males [11–13].

Clinicopathological & molecular findings

Gangliogliomas commonly occur in the supratentorial region, mostly in the temporal lobe (up to 85%), followed by the frontal lobe. It can occasionally develop also in the brainstem, cerebellopontine angle, thalamus, optic nerve and spinal cord [14].

Presence of a ganglioglioma in the temporal lobe is particularly epileptogenic; this in part explains the classical clinical presentation with a seizure disorder, generally with a long standing history of epilepsy that is difficult to control medically [6,13,15,16]. As reported by Pasquier *et al.* in a series of 327 patients with drug-resistant epilepsy, ganglioglioma was found to be the second most common diagnosis [17]. Others presenting symptoms include increased intracranial pressure, headache, nausea, vomiting, personality change, irritability and focal neurological deficit. Cerebellar lesions present with ataxia, headache and hydrocephalus.

Prognosis is favorable and the disease-free survival rate is 97% at 7.5 years for patients with supratentorial tumors [18] and 88% for those with spinal cord lesions [19]. However, despite often presenting as low-grade tumors, recurrence or anaplastic progression can occur. Gangliogliomas can develop malignant degeneration of the glial component, thus representing an anaplastic ganglioglioma, a distinct pathological entity corresponding to grade III of WHO classification.

The genetic landscape of ganglioglioma appears to be distinct from several glial and glioneuronal neoplasms and is defined by V600E mutation or alternative *BRAF* mutations or fusions, *RAF1* fusion, *KRAS* mutation, *NF1* mutation or *FGFR* mutations or fusions.

The activating *BRAF* V600E mutation is common and occurs approximately in 10–60% of gangliogliomas, with highest prevalence in cortical tumors and lower frequency in spinal cord tumors [20–26]. Conversely, *IDH* mutation or combined deletion 1p/19q exclude a diagnosis of ganglioglioma. However, *BRAF* V600E mutation is not exclusive to ganglioglioma and has been described also in DNET, pilocytic astrocytoma, pediatric *IDH*-wild-type astrocytoma, polymorphous low-grade neuroepithelial tumor of the young, pleomorphic xanthoastrocytoma and epithelioid glioblastoma [26,27].

Several cases of pediatric grade I gangliogliomas have been identified harboring both *H3* K27M and *BRAF* V600E mutations, characterized by a relatively indolent course compared with diffuse midline glioma *H3* K27M mutant [28,29]. While a subgroup of gangliogliomas harbor the well-known *BRAF* V600E mutation, other genetic alterations are poorly documented.

Pekmezci *et al.* performed next-generation sequencing on a cohort of 40 gangliogliomas to provide a comprehensive assessment of the genetic profile of this tumor entity [5]. Thirty-six patients harbored mutations in the MAP kinase pathway; out of these, 18 patients harbored a *BRAF* V600E mutation, five a different *BRAF* mutation and four had *BRAF* fusion. In the 13 cases lacking an identifiable *BRAF* alteration, several genetic mutually exclusive alterations involving *KRAS*, *NF1*, *FGFR1* and *FGFR2* were found. No *PRKCA*, *IDH1*, *IDH2*, *TP53*, *ATRX* and *TERT* mutations were identified, suggesting that the genetic landscape of ganglioglioma is unique and distinct from the majority of diffuse gliomas, papillary glioneuronal tumors and chordoid gliomas [30,31]. Gangliogliomas sometimes harbor the same *BRAF* mutations as pilocytic astrocytomas, such as the *KIAA1549-BRAF* fusion with the appearance of a pilocytic astrocytoma but with foci of gangliocytic differentiation [25].

The prognostic role of BRAF mutation in ganglioglioma is still under investigation.

Dahiya *et al.* observed that positive *BRAF* V600E staining is associated with shorter recurrence-free survival [22]. Furthermore, the association between *BRAF* V600E mutation and *CDKN2A* deletion may be associated with a worse outcome [32,33]. *CDKN2A* is a tumor suppressor gene and its loss acts as a 'secondary hit', which allows malignant behavior, especially when combined with *BRAF* mutations.

Radiological features

The neuroimaging appearance is variable, but gangliogliomas often display a mix of solid and cystic components. The computed tomography (CT) imaging of cerebral ganglioglioma is characterized by a nonenhancing cystic lesion, eventually with a ring enhancement or with an enhancing mural nodule. The presence of calcifications is usually extensive and is an important clue in diagnosing of ganglioglioma, especially in the case of small, solid nonenhancing tumors.

On MRI, this tumor usually appears as a solid mass or a mixed solid-cystic mass, iso- to hypointense and hyperintense on T1- and T2-weighted, respectively.

The differential diagnosis includes pleomorphic xantoastrocytoma, pilocytic astrocytoma and hemangioblastoma [34,35]. Although not common, ganglioglioma could be mistaken for a vascular malformation [36].

Treatment options

The current standard treatment of newly diagnosed gangliogliomas is complete surgical resection [18]. Preoperative and postoperative MRI are useful to define the exact extent of surgery. The tumor location affects the possibility of achieving radical surgery and impacts survival [37–39]. In particular, gangliogliomas of the midline present a poorer outcome, with a higher risk of recurrence and mortality [40]. When gross total resection is achieved and a grade I ganglioglioma is diagnosed, no adjuvant therapies are recommended. If resection is subtotal, a second surgical attempt should be considered, given the prognostic impact of complete resection.

The role of adjuvant postoperative radiation therapy is undefined, it appears to reduce the relapse rate after incomplete resection of high-grade lesions though its benefit is highly debated in cases of total resection or partial removal of low-grade tumors [41–43]. In their retrospective study of 402 patients with ganglioglioma, Rades *et al.* concluded that gross total resection does not require adjuvant radiation treatment. If resection is subtotal, radiotherapy should be considered because it can improve local control, even if survival advantage at 10 years has not been observed [44]. Radiation therapy can also be considered as an option for 'salvage' treatment in cases of recurrent low-grade tumors [45,46]. Giving the usual young age and long-term survival of individuals with these tumors, before considering the patient for radiotherapy, it is important to weigh its specific long-term toxicity spectrum, in particular neurocognitive sequelae and focal deficits such as optic pathway injury.

The role of chemotherapy is still uncertain; it should be considered for patients with progressive tumors not susceptible to re-resection or reirradiation [47]; nitrosoureas, temozolomide, etoposide, cisplatin, carboplatin and cyclophosphamide have been reported to be effective.

Studies on progressive *BRAF* V600E-mutated melanomas have shown the effectiveness of the *BRAF* inhibitors dabrafenib or vemurafenib [48]. Experience with these agents in *BRAF* V600E-mutated gliomas is limited to case reports [49–55]. Rush *et al.* described the first case of a brainstem ganglioglioma harboring *BRAF* V600E mutation that was successfully treated with vemurafenib and vinblastine, achieving complete resolution of symptoms and significant overall decrease in the size of the lesion [49]. Starting from this first experience, other cases of ganglioglioma successfully treated with *RAF i*nhibitors have been accumulated, reinforcing the idea that MAPK pathway inhibitors can be considered as a potential target therapy for these tumors (Table 2).

Table 2. Positive responses to RAF or MEK/RAF inhibitors in ganglioglioma and anaplastic ganglioglioma.

Study (year)	Treatment	Best response	Ref.
Rush *et al.* (2013)	Vemurafenib + vinblastine (ganglioglioma one case)	Partial response	[49]
Del Bufalo *et al.* (2014)	Vemurafenib (ganglioglioma one case)	Partial response	[52]
Shih *et al.* (2014)	Dabrafenib + gemfibrozil (ganglioglioma one case)	60% overall reduction in tumor volume	[53]
Aguilera *et al.* (2015)	Vemurafenib (ganglioglioma one case)	>70% decrease in tumor size	[50]
Chamberlain *et al.* (2016)	Dabrafenib (ganglioglioma threecases)	Stable disease in two patients and a partial response in one patient	[51]
Garnier *et al.* (2019)	Vemurafenib (ganglioglioma one case)	Partial response manteined 21 months after treatment discontinuation	[54]
Pasqualetti *et al.* (2019)	Dabrafenib (ganglioglioma one case)	Major response	[55]
Lucas Jr. *et al.* (2014)	Vemurafenib (anaplastic ganglioglioma one case)	Partial response	[56]
Melatath *et al.* (2016)	Dabrafenib (anaplastic ganglioglioma one case)	Complete response	[57]
Beland *et al.* (2018)	Dabrafenib + trametinib (anaplastic ganglioglioma one case)	Complete response	[58]
Kaley *et al.* (2018)	Vemurafenib + cobimetinib (anaplastic ganglioglioma one case)	Partial response	[59]
Marks *et al.* (2018)	Dabrafenib/trametinib (anaplastic ganglioglioma 1 case)	Complete response	[60]
Kaley *et al.* (2018)	Vemurafenib (anaplastic ganglioglioma one case)	Partial response	[59]
Toll *et al.* (2019)	Dabrafenib/trametinib (anaplastic ganglioglioma one case)	85% decrease in tumor size	[61]

As expected from experience in other cancers, acquired resistance to *BRAF* inhibitors may invariably develop, as well as side effects, including skin rash, papillomas and squamous cell carcinomas. To date, there is no valid therapeutic option for patients who progress on vemurafenib or having poor tolerability profile. Studies in *BRAF* V600E-mutant melanoma showed that a subset of tumors develop resistance to *BRAF* inhibitors through molecular events reactivating the MAPK pathway, such as *NRAS*, *KRAS* or *MEK* mutations.

This provided rationale for combined *BRAF*/*MEK* inhibition, which demonstrated superior outcomes in comparison with *BRAF* inhibitors monotherapy in *BRAF* V600E mutant melanoma. Supported by this evidence, several cases of gangliogliomas have been published in which combined treatment with vemurafemib and MEK inhibitor resulted in clinical benefit for patients. Marks *et al.* reported the case of an anaplastic ganglioglioma with an important skin rash reaction from vemurafenib, who experienced good tolerability and tumor response to the *BRAF*/MEK inhibitor combination dabrafenib plus trametinib [62]. Koelsche *et al.* observed that *BRAF* V600E-mutated gangliogliomas frequently show lymphocytic infiltrates [63], suggesting an immunogenicity of *BRAF*-mutated gangliogliomas and a potential role for immunotherapy in the future.

Certainly, targeted therapy is very promising in selected subsets of gangliogliomas and further studies are needed to legitimize the use of these novel agents in such a rare group of tumors.

Anaplastic ganglioglioma

Anaplastic ganglioglioma is a glioneuronal tumor composed of dysplastic ganglion cells and an anaplastic glial component with elevated mitotic activity. It is defined by a WHO grade III component and is associated with significantly worse local control rates, strong potential for distant relapse and short overall survival.

Epidemiology

The incidence of anaplastic gangliogliomas is very rare and estimated at 0.02 cases/million/year [64], therefore literature is limited to case reports and small retrospective case series.

Clinicopathological & molecular findings

Anaplastic ganglioglioma which most often affects children and young adults, is generally unifocal, highly epileptogenic and is known to arise from any part of the CNS, including the spinal cord as well as the cerebral ventricles, even though the temporal lobe is the most common location. Selvanathan *et al.* reported 27% of cases arising from temporal lobe, followed by 22% of cases in the frontal lobe [64]. Unlike gangliogliomas which almost always progress locally, anaplastic gangliogliomas often exhibit diffuse failure within the craniospinal axis and leptomeninges. In particular, in the case series reported by Lucas *et al.*, all three patients experienced leptomeningeal failure [56]. Most commonly the anaplastic transformation occurs in the glial component, resembling a high grade astrocytoma, while

the neuronal component is relatively benign, although there are reports of anaplastic cells exhibiting both neuronal and astrocytic features as well as sarcomatous differentiation [65].

Anaplastic gangliogliomas rarely occur as *de novo* tumors (cases not related to previous radiation therapy or prior diagnosis), but more often have been associated with previous subtotal resection or radiotherapy of a low grade ganglioglioma [66–71]. Literature review found only 31 anaplastic gangliogliomas not related to prior radiotherapy or previous diagnosis [72]. The main pathologic findings of anaplastic gangliogliomas include increased mitotic index, pleomorphism, microvascular proliferation, necrosis and gemistocytic differentiation pattern [73]. The *BRAF* V600E mutation has been identified in a number of cases of anaplastic ganglioglioma and the incidence of this mutation appears higher in pediatric population.

Radiological features

Radiological diagnosis is difficult due to the broad spectrum of solid and cystic lesions, the irregularity of contrast enhancement and the variability in the calcification pattern. On MRI, anaplastic gangliogliomas generally appear as a solid mass with a cystic component, hypointense on T1-weighted sequences and hyperintense on T2-weighted images with irregular enhancement after the administration of gadolinium. Proton magnetic resonance spectroscopy (^{1}H-MRS), performed to measure the levels of metabolites in the tumors, can reveal a high choline peak relative to a high N-acetylaspartate/creatine ration and increased lactate and lipid levels, which suggest anaplastic behavior [13].

Treatment options

Gross total resection is considered the standard of care for anaplastic gangliogliomas [64,74,75]. However, even after a complete surgical resection tumor recurrence can occur; thus, many centers recommend adjuvant radiotherapy or chemo-radiotherapy to improve tumor control and survival [64,74,75]. Even after adjuvant treatment survival is poor.

In a retrospective study from the the National Cancer Institute's Surveillance, Epidemiology and End Results database, Selvanathan *et al.* analyzed a cohort of 58 adult and pediatric anaplastic gangliogliomas [64]. The median overall survival was 28.5 months and univariate and multivariate analysis identified surgical resection and unifocal disease as prognostic factors that could impact survival. No statistically significant benefit was found in overall survival, but only a trend toward longer survival has been observed in patients who received adjuvant radiotherapy. As admitted by the authors themselves, however, in this study, the small sample size may have influenced statistical power and the information on tumor size, type of surgical resection and the use of radiotherapy or chemotherapy is limited.

Another large series published is the French Brain Tumor Database study, which included 43 cases of anaplastic ganglioglioma [57]. In this series, the total resection was achieved in 58.8% of patients. Adjuvant radiotherapy with concomitant temozolomide – the standard Stupp protocol of combined chemo-radiotherapy for glioblastoma – was performed in approximately half of the patients. Adjuvant radiotherapy alone was administered in approximately 30% of patients and adjuvant chemotherapy alone without radiotherapy in 6% of patients. Tumor recurrence rate at 5 years was about 100% and median overall survival was 24.7 months. The subgroup with the best overall survival (37.3 months) was that of patients treated with gross total resection and adjuvant radio-chemotherapy [74].

Mallick *et al.* [75] performed a search of PubMed to find all the publications related to anaplastic ganglioglioma to establish the optimum treatment of this tumor type. A total of 40 publications with overall 69 patients were found eligible. It has been observed that patients undergoing a gross total resection have a significantly better overall survival compared with those with a subtotal resection, but neither adjuvant radiation, nor chemotherapy were found to have any impact on progression-free or overall survival. Also, this analysis failed to elicit any advantage of adjuvant radiation and chemotherapy and the authors concluded that the small sample and the heterogeneity of treatments may have affected the results. Therefore, they suggest, as reasonable approach, radiation for patients who received a gross total resection and adjuvant radiation or chemotherapy or a combination of both in case of subtotal resection or for disease at eloquent location. It is important to note that in all these large case series, median overall survival is poor and does not exceed 30 months.

Positive responses to targeted therapy with *RAF* inhibitor or MEK/RAF inhibitor combination therapy have been reported in anaplastic ganglioglioma refractory to other treatments (Table 2) [56,58,60,61]. Kaley *et al.* published the Phase II, histology-independent VE-BASKET trial for *BRAF* V600-mutant nonmelanoma patients. Patients with *BRAF* V600-mutant glioma received vemurafenib 960 mg twice per day until they experienced disease progression, unacceptable adverse effects or withdrew. Twenty-four patients with glioma, including malignant diffuse glioma

(n = 11; six glioblastoma and five anaplastic astrocytoma), pleomorphic xanthoastrocytoma (n = 7), anaplastic ganglioglioma (n = 3), pilocytic astrocytoma (n = 2) and high-grade glioma, not otherwise specified (n = 1), were treated. Objective response rate was 25% and the median progression-free survival was 5.5 months. In particular, one patient diagnosed with anaplastic ganglioglioma obtained a partial response and was treated for 13.8 months for a confirmed clinical benefit rate of 33% (95% CI: 4.3–77.7%) [59]. On the basis of this evidence, a larger prospective study is needed.

Dysembryoplastic neuroepithelial tumor

A DNET is a grade I mixed neuronal-glial tumor, causing drug-resistant epilepsy that occurs in the cerebral cortex of children and young adults with a predilection for the temporal lobe.

Epidemiology

The incidence of DNETs is 0,03 person-year per 100.000, with a peak in the range between 10 and 14 years.

Clinicopathological & molecular findings

It is characterized by multinodular architecture consisting of columns of oligodendroglial cells interspersed with a mucoid matrix with floating neurons [76,77]. Histological variants of DNET have been described, with additional glial cell component and a nodular appearance [78–81]; the simplest form, instead, consists of unique glioneuronal elements. DNET cells are positive for S100 protein, synaptofisin, neuronal nuclei, neurite outgrowth inhibitor OLIG2 and MAP 2, but negative for GFAP.

DNETs are stable or very slow growing and require no postoperative adjuvant therapy [82]. Long-term clinical follow-up usually demonstrates an extremely low rate of recurrence; however, the rare cases of recurrences and malignant transformations legitimize the need for MRI surveillance, mostly after incomplete resection.

DNETs share with gangliogliomas *FGFR1* and *BRAF* V600E mutations, the latter found in 27–51% of cases (3283). The prevalence of *BRAF* V600E mutations is higher in the complex type and in the extratemporal location (i.e., tumors in midbrain or brainstem). Prabowo *et al.* observed that the presence of *BRAF* V600E mutation is significantly associated with an mTOR pathway overactivation in ganglioglioma and DNET [32]. In ganglioglioma and DNETs, the presence of *BRAF* V600E mutation has been associated with the expression of phosphorylated ribosomal S6 protein (pS6), a marker of overactivation of the mTOR pathway and a key regulator of cell growth and proliferation. Interestingly, on the basis of this association, mTOR targeted treatment may be developed.

Radiological features

Cortical topography and the absence of edema and mass effect are the most important criteria for differentiating DNETs from diffuse gliomas. In conventional MRI, DNETs present as multiple or single cystic lesions, hypointense on T1-weighted and hyperintense on both T2-weighted and fluid attenuated inversion-recovery MRI. Noncystic tissue is hypointense on T1-weighted images and hyperintense on T2-weighted and fluid attenuated inversion-recovery images. On both CT and MRI, in approximately 20% to a third of the patients, a nodular, ring-like or heterogeneous contrast enhancement may be observed. The enhancement can also be observed during the follow-up in a previously nonenhancing tumor, these variations being usually considered ischemic and/or hemorrhagic changes rather than an expression of malignancy.

Fiber tractography is also important for the differential diagnosis versus low-grade glioma. In DNETs, a pattern of displacement of the fiber tracts is observed, while gliomas spread along white matter tracts.

Advanced MRI techniques – in other words, diffusion, perfusion and spectroscopy – may be useful in the differential diagnosis for DNET versus other low-grade gliomas. Unlike low-grade gliomas, on diffusion-weighted MRI, DNETs generally present a high apparent diffusion coefficient as the expression of low cellular density; such values range between 2.38 and 2.78. On perfusion-MRI, DNETs have a lower relative cerebral blood volume value than diffuse gliomas (range 0.66–0-99), due to the presence of 'floating neurons' and high-water content. Proton magnetic resonance spectroscopy profile is characterized by a not decreased N-acetyl-aspartate/choline (NAA/Cho) ratio, when compared with diffuse gliomas and a high myoinositol/creatine ratio, which ranges between 0.19 and 0.57. Identification of *FGFR1* and *BRAF* V600E mutations limits the risk of misdiagnosis [83,84].

Treatment options

Complete tumor resection leads to a long-term seizure control [85–87], with 70–90% of resected patient seizure free.

Central neurocytoma & extraventricular neurocytoma

Epidemiology

Central neurocytomas (CNs) represent about 0.1–0.5% of all brain tumors. CNs are more frequent among young adults, with an incidence peak at about 30 years [88–93]. In several studies, it has been observed that there is a higher incidence of CNs in Korea, Japan and India, which may be attributable to genetic interracial differences [94–97].

Clinicopathological & molecular findings

CN is composed of uniform round cells with neuronal differentiation and low proliferation index and it corresponds histologically to grade II. It is usually supratentorial, occurring in the lateral ventricles or in the third ventricle, especially in the region of the foramen of Monro. Attachment to the septum pellucidum seems to be a feature of the tumor. CN may manifest as obstructive hydrocephalus with signs of increased intracranial pressure or with distinct focal deficit.

The MIB-1 Labeling Index (MIB-1 LI) is an important prognostic tool for CN and is an accurate indicator of tumor relapse and tumor grade. Imber *et al.* analyzed progression-free survival and overall survival in a cohort of 28 patients and found that low MIB-1 LI (<4%) correlates with longer progression-free survival and overall survival [98]. Similarly, Chen *et al.* found that a MIB-1 LI >2% may indicate a more aggressive disease course [99].

Many types of genetic mutations have been associated with CNs, in particular overexpression of *N-MYC*, *IGF2*, *PTEN*, *PDGF-D* and *NRG-2* [100].

Radiological features

The radiological features of CN are nonspecific; CT scans usually demonstrate a hyperdense mass in the lateral ventricles. MRI shows a peri-ventricular mass, hypointense or isointense on T1-weighed images and isointense or hyperintense on T2-weighed. Contrast enhancement can be variable, generally moderate-to-strong [91,101–103].

Treatment options

The gold standard of treatment is gross total resection, which often allows for a very high rate of tumor control and long-term survival. In case of subtotal resection and/or an elevated MIB-1 LI, there may be an indication for adjuvant radiotherapy. The use of chemotherapy is debated; the literature is limited to case reports and is very heterogeneous with regard to scheme of chemotherapy and timing of initiation – upfront versus salvage treatment. Brandes *et al.* reported three cases of neurocytoma treated with chemotherapy. Disease progressed in two patients after surgery and adjuvant radiotherapy and in one patient after surgery. The treatment regimen included etoposide, cisplatin and cyclophosphamide. Disease stabilization was observed in two patients and complete response occured in one patient with long maintenance of the response [104]. Johnson *et al.* reported the case of a young woman successfully treated with temozolomide. The patient had a recurrence 6 years after initial treatment with gross-total resection, this recurrence was treated with repeat surgery followed by temozolomide and concurrent radiation for 5 weeks. Fourteen years after the first diagnosis and 6 years 9 months after the recurrence, the patient was clinically stable [105].

Imber *et al.* analyzed a cohort of 28 patients treated at their institution between 1995 and 2014. In their case series, four patients with recurrent CN received salvage chemotherapy. One patient, treated with CCNU, had significant radiographic response with subsequent disease stabilization. Two patients, treated with temozolomide, experienced 3 years of tumor stabilization followed by tumor progression in one case and slow progressive tumor despite chemotherapy in the other case, respectively [98].

Occasionally, neurocytoma occurs outside the ventricles and is called extraventricular neurocytoma, an atypical form that arises in the spinal cord or cerebellum. It is associated with worse outcome due to a higher proliferative index and recur within a relatively short period of follow-up [106–109].

Diffuse leptomeningeal glioneuronal tumor

DLGNT is a new entity which has been included in the 2016 update of the WHO classification, characterized by predominant and widespread leptomeningeal growth and an oligodendroglial-like cytology with elements of neuronal differentiation. It has been described a high rate of *KIAA1549-BRAF* gene fusion or 1p/19q co-deletion in the absence of *IDH* mutation. Due to the limited cases in literature, the WHO classification has not been assigned, to date, a grade to this tumor entity.

Clinicopathological & molecular findings

DLGNT was first described in 2010 [110], prior to that it was reported as 'disseminated oligodendroglial-like leptomeningeal tumor of childhood' [111]. The cellular origin is unclear; the absence of brain parenchymal lesions suggests an origin from neuroepithelial cells scattered in the meninges. The wide spectrum of histological and radiological features can make this tumor entity difficult to diagnose. This tumor is characterized by diffuse leptomeningeal growth, often without a recognizable parenchymal lesion (commonly in the spinal cord), with an incidence peak in children and young adults. Histology demonstrates a monomorphic clear cell glial morphology, reminiscent of oligodendroglioma, with immunostaining positivity for GFAP, OLIG2, S100 and synaptophysin and negativity for IDH1. Microscopic cerebral fluid examination demonstrates elevated protein levels although cytology is often negative.

A newly recognized entity is the multinodular and vacuolated pattern, a low-grade purely neuronal tumor affecting adults, situated in the cerebral hemispheres, most often in the temporal lobe, composed of tumor cells exhibiting nuclear immunolabeling for the HuC/HuD neuronal antigens and expression of other neuronal markers, in particular synaptophysin and neurofilament while chromogranin is variable [112]. This tumor commonly harbors *BRAF* fusions as well as 1p/19q co-deletion, 1p or 19q solo deletion [113]. *IDH* mutation is absent.

The prognosis is variable, with a majority of low-grade tumors showing relatively slow progression and a subset of tumors with a more aggressive course, that shows features of anaplasia. Studies have indicated that 1p/19q co-deletion or 1p/19q solo deletion demonstrate a more aggressive biological behavior and are sensitive to chemotherapy, especially temozolomide [114].

Radiological features

The MRI findings show two distinct patterns: one of diffuse leptomeningeal enhancing, the second of 'small cysts' implants scattered all over the brain and spinal cord, especially along the surface of the posterior fossa and basal brain regions, giving the distinctive neuroimaging profile of a diffuse 'microcystic meningoencephalopathy'.

Treatment options

Complete surgical resection is difficult; radiotherapy and chemotherapy are valid option most notably in more aggressive DLGNTs with high ki67 rate. Chemotherapy regimens include carboplatin and vincristine, temozolomide, etoposide and bevacizumab [114].

Rosette-forming glioneuronal tumor

Rosette forming glioneuronal tumor is a grade I neoplasm that has biphasic cytoarchitecture with two elements: neurocytes forming rosettes/perivascular psuedorosettes and astrocytic cells resembling pilocytic astrocytoma [115–117].

Epidemiology

The incidence rate is not yet available, with about 100 cases reported in literature.

Clinicopathological & molecular findings

The term rosette-forming glioneuronal tumor was used for the first time by Komori *et al.* in 1998 [118]; it most commonly occurs in young adults, occupying the fourth ventricle. Until the description of two cases in the optic chiasm [119] and spinal cord [120], respectively, these tumors were believed to originate only in the posterior fossa. To date, rare locations in the pineal region, cerebellar vermis, pons and septum pellucidum have also been observed [121,122].

The spectrum of clinical symptoms is wide, including headaches, visual disturbances, nausea and vomiting, vertigo, ataxia, cervical pain and neck rigidity [123].

They are low-grade tumors with lack of atypia and low Ki67 labeling indices [124]. Molecular studies of rosette-forming glioneuronal tumors are few and have revealed only two recurrent genetic alterations; *PIK3CA* or *FGFR1* mutations. *IDH1/2* mutation and 1p/19q co-deletion are absent. In particular, *PIK3CA* mutations are missense mutations in exon 20 (nucleotide 3140 A[G, H1047R) and in exon 9 (nucleotide 1624 A[G, E542K), while *FGFR1* mutations have been found in two patients: the *FGFR1* N546K mutation (AAC->AAG, Asn->Lys) was found in a 27-year-old woman and the K656E (AAG->GAG, Lys->Glu) in a 12-year-old boy. The presence

of *FGFR1* mutations in rosette-forming glioneuronal tumors may suggest a molecular similarity with pilocytic astrocytoma [125,126].

Radiological features

These tumors are relatively circumscribed, with calcifications and a ring-shaped contrast enhancement, hypointense on T1 and hyperintense or isointense on T2-weighted MRI sequences [123].

Treatment options

Management is usually through surgery with gross total resection providing better prognosis. Nevertheless, tumor location and its frequent extension within the adjacent structures does not always permit a total resection without surgical morbidity or neurological dysfunction. Due to their indolent nature, a subtotal removal is also considered acceptable, whereas an aggressive approach can increase morbidity. In this tumor type, the recurrence rate is extremely low, with only four cases of recurrence reported as of now [124,125,127].

Conclusion & future perspective

Glioneuronal tumors represent a heterogeneous group of neoplasms that exhibit neuronal differentiation, with a pure neuronal differentiation pattern or with a mixed glial and neuronal phenotype [1]. The numerous new entities recently described in the literature suggests that the wide spectrum of neuronal and glioneuronal neoplasms is far from being exhaustively documented. Given the rarity of these neoplasms, the benefit of various management

Executive summary

Epidemiology & pathology of neuronal & glioneuronal tumors

- Neuronal and glioneuronal tumors are a heterogeneous group of CNS neoplasms that demonstrate neuronal differentiation, with either a pure neuronal or a mixed glial and neuronal phenotype.
- Compared with other brain tumors they are very rare and therefore not well characterized; they mainly occur in children and young adults, predominantly have a low-grade histology, with an indolent course and long-term survival after surgical resection.
- Onset symptoms depend on tumor location, the most common being pharmacoresistant seizures, followed by intracranial hypertension and focal deficits.
- Within this group, ganglioglioma is the most common histologic subtype and consequently also the best studied, whose molecular biology is well known, which paves the way for new target therapies.
- The excellent prognosis and the malignant transformation potential of the glial component are the two most remarkable findings in ganglioglioma.
- Radiological diagnosis presents a challenge due to the overlap of imaging features across different histotypes, which complicates diagnosis.
- The MRI appearance of glioneuronal tumors could be very variable across the diverse histotypes but these tumors, expecially WHO grade I, most often demonstrate similar neuroradiological findings: a solid-cystic mass with enhanced peripheral ring and diffuse pattern of calcification.

Treatment options

- The conventional treatment for low-grade tumors involves surgical resection.
- Adjuvant treatments, though their exact role is unknown, may be considered individually based on pathological subtypes and a proper assessment of risks and benefits. Adjuvant radiotherapy, in particular, may be recommended in case of incomplete surgical resection and high proliferative index.
- The role of chemotherapy is unclear and generally reserved for savage therapy, with a vast heterogeneity of schemes across the diverse histotypes but also within the same type of tumor.
- In case of disease progression, despite aggressive treatment with radiation and chemotherapy, *BRAF* and MEK inhibitors represent a promising therapeutic option that may improve the disease course of glioneuronal tumors in a clinically meaningful way.

Future perspective & conclusion

- Due to the rarity of these neoplasms, available studies comparing the benefit of various management strategies are few. Thus, the level of evidence of recommendations is low.
- Identification of the molecular basis of this niche diseases is a challenge; prospective clinical studies with BRAF-MEK inhibitors should be conducted, not only in patients who have already failed the radiotherapy and chemotherapy, but also in the adjuvant setting where traditional therapies are associated with acute and long-term toxicities, shifting the therapeutic algorithm toward an earlier integration of molecularly targeted agents.

strategies is not clearly established and the level of evidence of recommended treatments is low. Currently the interest in this class of brain tumors is high, thanks to the increasing knowledge of molecular biology and the remarkable responses to targeted therapies observed, especially in those with *BRAF*-mutated tumors.

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